Premotor and prefrontal contributions to modulating upper limb somatosensory input into non-primary motor areas

by

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Authour's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

I, Matt Brown, contributed to the majority of research design, data collection, data processing, data analysis, data interpretation and writing of the thesis.

Dr. Rich Staines was the co-authour with myself, Matt Brown, of two published manuscripts entitled “Modulatory effects of attention and movement sequence preparation on somatosensory input into non-primary motor areas” and “Somatosensory input to non-primary motor areas is enhanced during preparation of cued contralateral finger sequence movements” that form the basis of Chapters 2 and 3 in the thesis, respectively.

Abstract

Upper limb motor control requires the use and integration of afferent somatosensory input from peripheral receptors to help plan and prepare movements. Cortical surface electroencephalography can be used to measure the earliest relay and processing of mixed somatosensory input in primary (SI) and secondary somatosensory (SII) cortices using parietal somatosensory evoked potentials (SEPs) that occur 20 to 100 milliseconds (ms) after median nerve stimulation. Moreover, somatosensory input into non-primary motor areas, such as premotor cortex (PMC) and supplementary motor area (SMA), can be measured by frontal N30 and N60 SEPs. Therefore, frontal N30 and N60 SEPs may provide an important neurophysiological link between somatosensory processing and upper limb motor control. Both PMC and SMA have intracortical connections with primary motor cortex (M1) and prefrontal cortex (PFC) as well as intercortical connections with their contralateral representations. However, it is not fully understood how somatosensory input in non-primary motor areas, represented by frontal SEPs, are modulated in the cortex by contralateral PMC and ipsilateral PFC. A modulatory role of contralateral M1 but not contralateral premotor areas on somatosensory input into non-primary motor areas has been established through contralateral movement paradigms. Furthermore, a modulatory role of the ipsilateral PFC on somatosensory input into non-primary motor areas has been identified through prefrontal lesion patients but it is unclear how PFC functionally modulates this somatosensory input during movement.

Thus, the current thesis aimed to evaluate the contributions of the ipsilateral PFC as well as contralateral PMC on somatosensory processing in non-primary motor areas as well as SI/SII. SEP modulations were examined using experimental manipulations of top-down attention and

cued contralateral movements to evaluate PFC and PMC contributions, respectively. In addition, continuous theta burst stimulation, a specific type of inhibitory non-invasive transcranial magnetic stimulation technique, was applied over PMC and PFC to evaluate their specific contributions to modulating somatosensory input into non-primary motor areas and SI/SII during a cued movement task. Understanding frontal SEP modulations and their association with upper limb motor control will have important applications for understanding dysfunctional upper limb motor control in various neurological disorders such as Parkinson's disease (PD) that are known to have irregular frontal SEPs.

The main findings from Chapters 2 and 3 revealed that frontal N30 and N60 SEPs were decreased during early response selection and increased during the late stages of preparing finger sequences to attended somatosensory input. In contrast, SI/SII input represented by parietal P50 and P100 SEPs were increased with attention. The main results of Chapter 4 showed that N30 and N60 SEPs were decreased and increased after transiently decreasing excitability in left PMC and right PFC, respectively. Collectively, the results of this thesis revealed temporally-specific modulations of somatosensory input into non-primary motor areas during contralateral upper limb movements that are a result of changes in activity in a network that includes the right PFC and left PMC.

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List of Key Terms

Bottom-up – Flow of information from lower-order to higher-order subcortical or cortical areas such as bottom-up attention from temporoparietal junction to ventral frontal cortex.

Centrifugal gating – Efferent information from motor areas, involved in preparing and executing a movement, inhibits somatosensory input at cortical or subcortical levels.

Centripedal gating - Afferent input from joint, cutaneous or muscle spindles caused by movement causes an interference and reduction on somatosensory input.

Contralateral movements –movements that are executed with the opposite limb as measured somatosensory input.

Erb's point – meeting point of several nerves located at the upper trunk brachial plexus, 2-3 cm above the clavicle.

Far-field somatosensory evoked potentials (SEPs) – recorded from the cortical surface but do not represent SEPs generated in underlying cortex but rather from the periphery, spinal cord or subcortical relays; these potentials can be recorded from the periphery as early as 7 ms at Erb's point until about 18 ms in the thalamus after MN stimulation.

Ipsilateral movements –movements within the same as limb as measured somatosensory input.

Motor threshold – generally speaking, the minimum intensity level of output from a magnetic or electrical stimulation device to elicit a muscle response after application over the cortex or peripheral nerve.

Motor hot-spot – area in the primary motor cortex where magnetic or electrical stimulation evoke the largest and most reliable muscle activity for a given muscle.

Near-field somatosensory evoked potentials (SEPs) – recorded from the cortical surface and represent relay and processing in cortical areas.

Sensory gating (or gating) – in EEG literature often referring to the reduction or attenuation of sensory input such as reduction in amplitude of SEPs. However, in its truest sense, gating refers to mechanisms that either increase or decrease the flow of sensory input.

Short-latency somatosensory evoked potentials - generally refers to somatosensory input that reaches the cortex before 50 ms; although, other studies have suggested before 100 ms. For the current thesis, short-latency will refer to before 100 ms.

Top-down – the flow of information from higher-order to lower-order cortical or subcortical areas such as top-down attention from prefrontal cortex to parietal cortex.

List of Abbreviations

AMT Active motor threshold

A-P Anterior-posterior

APB Abductor pollicis brevis

BOLD Blood-oxygen-level dependent

cTBS Continuous theta burst stimulation

D-wave Direct wave

DLPFC Dorsolateral prefrontal cortex

EEG Electroencephalography

EMG Electromyography

FDI First dorsal interosseous

fMRI Functional magnetic resonance imaging

Hz Hertz

iTBS Intermittent theta burst stimulation

I-wave Indirect wave

L-M Lateral-medial

M1 Primary motor cortex

M-L Medial-lateral

MEP Motor-evoked potential

MN Median nerve

ms Milliseconds

N Negative

P Positive

P-A Posterior-anterior

PD Parkinson's disease

PET Positron emission tomography

PFC Prefrontal cortex

PMC Premotor cortex

PMd Dorsal premotor cortex

rCBF Regional cerebral blood flow

RMT Resting motor threshold

rTMS Repetitive transcranial magnetic stimulation

SI Primary somatosensory cortex

SII Secondary somatosensory cortex

SEP Somatosensory-evoked potential

SMA Supplementary motor area

TBS Theta burst stimulation

TMS Transcranial magnetic stimulation

µV Microvolts

VibT Vibrotactile

Chapter 1 - Introduction

1.1. Thesis Overview

Chapter 1 states the general thesis objectives followed by a comprehensive review of relevant literature. The literature review focused on a) functional neuroanatomy of sensory-motor interactions, b) somatosensory processing measured by short-latency somatosensory evoked potentials (SEPs) and their modulation by movement and attention, and c) transcranial magnetic stimulation (TMS) and its use as a method to evaluate neural areas in SEP modulation. Chapter 1 is concluded with the thesis research objectives, specific research questions and hypotheses. Chapters 2 and 3 provide original research examining SEP modulation with manipulations of attention and movement. Chapters 4 and 5 also provide original research examining SEP modulation after the use of repetitive TMS to transiently inhibit activity in premotor areas and PFC. Finally, Chapter 6 is a general discussion of the findings of this thesis followed by limitations and future directions.

1.2. Problem Statement and General Thesis Objectives

Somatosensory input from peripheral receptors in the upper limbs is necessary for upper limb motor control. Somatosensory information that inputs directly into non-primary motor areas, rather than somatosensory cortices, offers a unique opportunity to evaluate somatosensory input into the same neural areas that are involved in movement preparation. Abnormal somatosensory input into non-primary motor areas has been documented in a variety of neurological disorders such as Parkinson's disease (PD) and this abnormality has been associated with sensorimotor deficits. Thus, it is important to understand how this somatosensory input into

non-primary motor areas is modulated and the functional significance of these modulations to upper limb motor control. As outlined in detail below (see section 1.3), there is currently limited understanding of how and when several neural areas that contribute to the planning and preparation of upper limb movements, including prefrontal cortex (PFC) and premotor cortex (PMC), modulate somatosensory input into non-primary motor areas. Therefore, determining the temporal relationship of cortical somatosensory modulations by specific cortical areas, such as PMC and PFC, will provide insight into the temporally-specific neural mechanisms involved in somatosensory processing and potential association to sensorimotor deficits that could occur in neurological disorders that affect these given areas.

The general objective of this thesis is to understand how and when upper limb somatosensory input is differentially modulated in non-primary motor areas and SI/SII by prefrontal and premotor cortices. Furthermore, it is also a thesis objective to investigate the temporal aspects of prefrontal attentional and motor system modulations to upper limb somatosensory input as well as the functional significance of SEP modulations for upper limb motor control.

1.3. Literature Review

1.3.1. Cortical representations of upper limb somatosensory input

Somatosensation in the upper limbs occurs through a variety of peripheral receptors, such as Golgi tendon organs (GTO), muscle spindles or cutaneous receptors, to detect limb position or objects in the environment (Lynn, 1975; Proske & Gandevia, 2009, 2012). Afferent somatosensory information from peripheral receptors ascends into the dorsal horn of the spinal cord and ascends in the spinal cord as the posterior column (Canedo, 1997; Chapman, 1994;

McGlone & Reilly, 2010). In the caudal medulla, these posterior column fibers synapse and form the dorsal column nuclei (DCN) (Canedo, 1997; McGlone & Reilly, 2010). After synapsing in DCN, the ascending posterior column fibers of somatosensory input (ex. cuneothalamic fibers) cross the midline and ascend rostrally through brainstem (rostal medulla, midbrain and pons) as the medial lemniscus pathway where they synapse on ventral posterolateral (VPL) (for body inputs) and ventral posteromedial (VPM) (for face inputs) nuclei in thalamus (Canedo, 1997; McGlone & Reilly, 2010).

Primary afferent ascending somatosensory information is relayed from the VPL/VPM nuclei in the thalamus to its given somatotopic area within SI (Canedo, 1997; McGlone & Reilly, 2010). SI can be further divided into different sub-regions that receive the majority of specific afferent information. Muscle afferents primarily project to area 3a, slow-adapting cutaneous afferents to area 3b (i.e. Merkel or Ruffini-like endings), fast-adapting cutaneous afferents (i.e. Meissener or Pacini endings) to area 1 and joint receptors to area 2 (Allison et al., 1989; Johansson & Flanagan, 2009; Zilles et al., 1995). In addition, SI sends projections to the SII located in the superior bank of the lateral sulcus (McGlone & Reilly, 2010). In addition, SII also projects to the somatic area in the insular cortex (McGlone & Reilly, 2010) and the posterior parietal cortex (BA 5 and 7) receive somatosensory inputs (McGlone & Reilly, 2010).

Evidence in both humans and animal research supports that somatosensory information also inputs to primary motor cortex (M1), premotor cortex (PMC) and supplementary motor area (SMA) (Chouinard & Paus, 2006; Dum & Strick, 2005; Geyer, Matelli, Luppino, & Zilles, 2000; Picard & Strick, 2001; Raos, Franchi, Gallese, & Fogassi, 2003; Strick & Preston, 1978; Strick, 1975; Wiesendanger, Hummelsheim, & Bianchetti, 1985). The PMC and SMA have been separated into 6 different functional sections that include the rostral SMA (pre-SMA), caudal

SMA (SMA-proper), rostral dorsal premotor area (pre-PMd), caudal dorsal premotor area (PMd-proper) as well as superior and inferior ventral premotor cortex (PMv) (Barbas & Pandya, 1987; Chouinard & Paus, 2006; Geyer et al., 2000; Hoshi & Tanji, 2004a, 2004b, 2007; Picard & Strick, 2001; Schubotz, Anwander, Knösche, von Cramon, & Tittgemeyer, 2010; Tanji, 1994). The functional organization of both the SMA and PMd is relevant for the current discussion as both of these areas have been associated with early somatosensory input (i.e. frontal SEPs) in humans (Barba, Valeriani, Colicchio, & Mauguière, 2005; Kaňovský, Bareš, & Rektor, 2003).

PMd is highly active after arbitrary sensory stimuli or spatial cues to initiate a motor response (Chouinard & Paus, 2006). Strick and Picard (2001) found that pre-PMd, which has dense connections with the PFC, is involved in cognitive demanding visuo-motor associations, response selection and motor imagery. In contrast, PMd-proper, which contains dense connections with M1 and pyramidal tract neurons, is primarily activated by movement preparation and execution (Picard & Strick, 2001). However, using a voxel-based meta-analysis Chouinard and Paus (2006) found an area close to the intersection between the pre-PMd and PMd-proper that was activated by sensory stimuli cueing a motor response. In contrast, an area in the caudal PMd (i.e. PMd-proper) was activated during the execution of simple responses (Chouinard & Paus, 2006). Raos *et al.* (2003) revealed about half the neurons that were tested (40%) within the PMd-proper in monkeys (F2 area in primates) were activated by peripheral somatosensory stimulation; approximately 70% of these neurons to proprioceptive compared to 20% to tactile stimuli. Furthermore, most of the neurons tested (84%) were activated during active movements whereas a smaller but significant portion (43%) could elicit movements after microstimulation (at a threshold above neurons in M1). A medial-lateral somatotopic organization was revealed with neurons active during movements and during peripheral

somatosensory stimulation. For example, trunk movements and stimulation were more medial while hand activated neurons were in the lateral sector. Arm movements and stimulation activated neurons in both the medial and lateral portions of the PMd (Raos et al., 2003). Based on these findings, it appears that the functional distinction between pre-PMd and PMd-proper as it relates to somatosensory-guided movements are not as clear as its anatomical cytoarchitecture since both subdivisions of the PMd receive somatosensory input and are involved in using the sensory stimuli during response selection.

The pre-SMA, which has dense connections with the PFC, is activated during sensory-motor associations but is sensory modality and motor effector independent (Picard & Strick, 2001). In contrast, the SMA-proper, which contains dense connections with M1 and pyramidal tract neurons, is primarily activated by movement preparation (Picard & Strick, 2001). As reviewed by Geyer *et al*. (2000), microstimulation of the majority of neurons (80%) tested in the SMA-proper in monkeys (F3 area in monkeys) can elicit movements whereas only a small portion (20%) can evoke movements in the pre-SMA (F6 area in monkeys). In contrast, neurons in the pre-SMA respond to visual stimuli whereas neurons in the SMA-proper respond to somatosensory stimuli. Pre-SMA neuronal activity occurs almost exclusively before the onset of movement and when needed to develop a new motor plan. Alternatively, the SMA-proper demonstrated phasic activity associated to the onset of movement (Geyer et al., 2000). Thus, there is much clearer functional organization between the pre-SMA and SMA-proper as it relates to somatosensory-guided movements; SMA-proper is more involved in receiving somatosensory input and using this information for planning movements.

Neurophysiological tools such as EEG combined with neuroimaging and TMS have provided critical information on how, when and where somatosensory input is processed and

modulated within the human cerebral cortex. The rest of the current literature review will focus on how somatosensory input is recorded on the scalp using EEG to record frontal and parietal SEPs. In addition, the current review will examine how SEPs are modulated by movement, attention and TMS. The use of neurophysiological techniques such as EEG and TMS can help to identify both the temporal and spatial neural mechanisms that may be involved in modulating somatosensory input once it reaches the cerebral cortex.

1.3.2. Short-latency frontal and parietal SEPs

N20-P20 SEPs

The earliest near-field short-latency scalp potentials recorded from the cortical surface following median nerve (MN) stimulation are the parietal N20 and frontal P20 SEPs (Allison, McCarthy, Wood, & Jones, 1991; Allison, Wood, McCarthy, & Spencer, 1991; Allison et al., 1989; Deiber, Giard, & Mauguière, 1986; McCarthy, Wood, & Allison, 1991). Scalp topography and direct intracerebral recordings have revealed that parietal N20 and frontal P20 peaks are generated by a dipole source tangent to the scalp surface across the central sulcus near the medial portion of the hand area of area 3b of SI (Allison et al., 1989; Balzamo, Marquis, Chauvel, & Régis, 2004; Buchner et al., 1995; Goff, Matsumiya, Allison, & Goff, 1977). N20 and P20 peaks were absent during passive finger movements supporting that these reflect cutaneous rather than joint afferent input (Desmedt & Ozaki, 1991). In addition, excision of the hand area of the SI but not M1 in humans and monkeys abolishes the N20 and P20 peaks (Allison, Wood, et al., 1991). Based on this evidence, N20 and P20 peaks likely reflect responses of neurons in the hand representation of area 3b to cutaneous afferent input where one dipole is recorded with electrodes over parietal areas and the other dipole is recorded with frontal electrodes.

P27-N30 SEPs

Parietal P27 SEPs, sometimes referred to as parietal P30 or late parietal P25 peaks, have been shown to reflect activity in the lateral contralateral hand area of area 1 in SI based on scalp topography and intracranial recordings (Allison, McCarthy, et al., 1991; Allison et al., 1989; Balzamo et al., 2004; Goff et al., 1977; Rossini, Narici, et al., 1989). Magnetic recordings have also recorded activity in postcentral sensory regions around 30 ms following contralateral MN stimulation (Narici, Romani, Traversa, & Rossini, 1989; Rossini, Narici, et al., 1989). However, dipole modeling (following MN stimulation) has found conflicting evidence that an independent dipole source is active at the latency of the parietal P27 peak (Restuccia et al., 2002; Valeriani et al., 1998). The absence of parietal P27 peaks in some circumstances of MN stimulation could be explained by the proposed hypothesis that sequential activation in different areas of area 1 in SI are observed in both monkeys and humans after finger compared to MN stimulation (Allison et al., 1989; McCarthy et al., 1991). It should also be noted that intracranial recordings have identified a negative SEP peaking approximately 27.4 ms after contralateral MN stimulation (5.8ms later after ipsilateral stimulation) in the frontal suprasylvian opercular region caudal to the vertical anterior commissure (Barba, Frot, & Mauguière, 2002). In addition, N27 peaks may also be recorded in frontal regions representing a dipole of parietal P27 (or 'late P25' peak) across the central sulcus that is sometimes mislabeled as frontal N30 (Allison, McCarthy, et al., 1991; Allison et al., 1989; Rossini, Narici, et al., 1989). If present, frontal N27 (and frontal N25) peaks are visible as small notches on the negative slope of the frontal N30 peak (Delberghe, Mavroudakis, Zegers de Beyl, & Brunko, 1990; Garcia-Larrea, Bastuji, & Mauguière, 1992).

Thus, P27 and N27 peaks likely represent cutaneous afferent input in the hand area of SI that can be recorded by both parietal and frontal electrodes.

Frontal N30 SEPs, elicited from MN stimulation, are recorded from the contralateral hemisphere but spread over mid-frontal regions where they are recorded with their largest amplitude (Valeriani et al., 1998). Originally, it was argued that frontal N30 peaks reflect a dipole of parietal P27 peaks (Allison, McCarthy, et al., 1991) based on several findings: a) changing MN stimulation rates from 0.5 to 5 Hz equally decreased the amplitude of frontal N30 and parietal 27 peaks (Huttunen & Hömberg, 1991; Huttunen, 1994), b) intracranial recordings of the N30 peaks were largest over the hand area of M1 (Allison et al., 1989) and c) excision of the hand area of SI and not the hand area of M1 in humans and monkeys abolished both frontal N30 and parietal P27 (Allison, Wood, et al., 1991). However, it has since been argued that the sedatives used during intracranial recordings and excision in epileptic patients undergoing surgery and monkeys led to latency delays and subsequently, mislabeling of the frontal N30 peak in some earlier studies (Allison, McCarthy, et al., 1991; Allison, Wood, et al., 1991).

More recent evidence supports that separate neural generators are responsible for producing frontal N30 peaks (as compared to the parietal P27). Originally, dipole modeling revealed that the frontal N30 had a distinct neural generator from N20-P20, P22 and P27 peaks with a radial dipole potentially in area 2 of SI (Valeriani et al., 1998). More recent dipole modeling revealed that the radial dipole contributing to the frontal N30 peak was located at a medial fronto-central location (Restuccia et al., 2002). Additionally, decreased frontal N30 peak amplitudes have been revealed in patients with focal lesions in the frontal lobe, thalamus or internal capsule presenting with motor symptoms and normal sensation but parietal P27 peak amplitudes remain unaffected (Mauguière, Desmedt, & Courjon, 1983; Slimp, Tamas, Stolov, &

Wyler, 1986). In contrast, focal lesions of parietal cortex in patients presenting with astereognosis have shown reduced or abolished P27 peaks while frontal N30 peak amplitudes were normal (Mauguière et al., 1983). Decreasing the MN stimulation inter-stimulus interval from 4 to 1.4 s was shown to decrease the amplitude of the frontal N30 while leaving the parietal P27 amplitude unaffected (Tomberg, Desmedt, Ozaki, Nguyen, & Chalklin, 1989). Increasing the rate of MN or finger stimulation from 1.6 to 5.7 Hz was found to decrease the frontal N30 amplitude by 0.9 uV while the amplitude of the parietal P27 peak decreased in a divergent manner by 0.64 uV (Delberghe et al., 1990). Furthermore, frontal N30 peak amplitudes (P27 poorly identified even at low stimulation rates) were attenuated by nearly 40% when changing MN stimulation rate from 2 to 5 Hz and greater than 50% from 2 to 10 Hz leaving the peak indistinguishable in many individuals (Garcia-Larrea et al., 1992). Frontal N30 peak amplitudes have also been shown to decrease (or abolish) while parietal P27 peaks were unaffected under various circumstances including aging and Parkinson's disease (PD) (Bostantjopoulou et al., 2000; Desmedt & Cheron, 1980; Pierantozzi et al., 1999; Rossini, 1996; Rossini, Babiloni, et al., 1989; Ulivelli et al., 1999). Based on this evidence, it is clear that frontal N30 and parietal P27 SEPs have independent generators located in the medio-frontal cortex and hand area of SI, respectively. Importantly, the parietal P27 peaks can be recorded from both parietal and frontal electrodes unlike the frontal N30, which is recorded exclusively over fronto-central electrodes.

Cortical Generators of the Frontal N30

Direct intracerebral recordings in humans have found conflicting evidence on cortical generators of the frontal N30. Direct near-field recordings after transcutaneous MN stimulation have revealed activity dorsolaterally in BA 6 (representative of PMd) and medially in BA 6

(representative of the SMA) as well as in BA 8 in the latency of the frontal N30 peak (Kaňovský et al., 2003). However, intracortical recordings from pre-surgical epileptic patients did not identify N30 near-field potentials in the SMA-proper after contralateral MN stimulation (Barba et al., 2003; Barba, Frot, Guénot, & Mauguière, 2001; Barba et al., 2005). Furthermore, intracortical recordings using stereotactically implanted electrodes in the human pre-SMA did not record any clear near-field potentials before 50ms (only volume conducted potentials from superficial scalp) after contralateral or ipsilateral MN stimulation (Barba et al., 2003, 2001, 2005). Interestingly, intracranial recordings did identify a negative peak around 30 ms after contralateral MN stimulation localized to the lateral hand area of M1 (Balzamo et al., 2004). However, it was argued that this peak was likely a phase reversal of the parietal component rather than the frontal N30 (Balzamo et al., 2004). Based on these results, it is likely that there exist several neuronal populations within non-primary motor areas such as the PMd and SMA-proper that contribute to the generation of the frontal N30 but the extent of neuronal representation depends on the individual. Thus, frontal N30 peaks likely represent an independent input of somatosensory input into non-primary motor areas. As a consequence, it has been argued that the frontal N30 peaks supply non-primary motor areas with somatosensory input that is used in planning movement (Allison, McCarthy, et al., 1991; Kaňovský et al., 2003).

In conclusion, frontal P20, parietal N20, parietal P27 and frontal N27 peaks reflect the initial and propagation of afferent somatosensory input in SI. In contrast, frontal N30 peaks likely reflect direct activation of neurons responsive to somatosensory input within non-primary motor areas. The mechanisms that modulate frontal SEPs will be reviewed in the following section.

1.3.3. Modulation of afferent somatosensory input in non-primary motor areas

Once ascending afferent somatosensory input has reached non-primary motor areas, the sensory information may be modulated by a variety of complex mechanisms that include networks from SI, SII, PMC, SMA, PFC and M1 as well as subcortical structures such as the thalamus and basal ganglia (Gisiger & Boukadoum, 2011). Furthermore, intercortical networks originating from the contralateral hemisphere could also play a role in modulating somatosensory input in the cortex.

Centrifugal and centripetal mechanisms involved in modulating frontal SEPs

Two primary mechanisms have been proposed for modulating the amplitudes of scalp-recorded SEPs: centrifugal and centripetal gating mechanisms. Centrifugal gating refers to efferent signals, resulting from excitability changes in cortical motor areas, which modulate cortical somatosensory processing (Cheron & Borenstein, 1991; Jones, 1981; Kida, Wasaka, Nakata, & Kakigi, 2006). In contrast, centripetal gating refers to afferent activity from a resulting movement influencing the transmission and processing of ascending sensory information (Cheron & Borenstein, 1991; Jones, 1981; Kida, Wasaka, Nakata, & Kakigi, 2006). Studies investigating the effects of movement have found gating effects (i.e. decreased amplitudes) on frontal N30 peaks after movements in the same limb (i.e. ipsilateral) as MN stimulation (Böcker, Forget, & Brunia, 1993; Cebolla et al., 2009; Cheron & Borenstein, 1987, 1991). Importantly, these gating effects have been observed during movements (Cebolla et al., 2009; Cheron & Borenstein, 1987; Kida, Wasaka, Nakata, Akatsuka, & Kakigi, 2006b) and during movement preparation after a cueing stimulus (Böcker et al., 1993; Cohen & Starr, 1987; Kida, Wasaka, Nakata, & Kakigi, 2006), which would support a centrifugal gating mechanism. However, both

light and deep massage to the thenar eminence of the left thumb resulted in a significant decrease in frontal N30 peak amplitudes elicited by left MN stimulation (Cheron & Borenstein, 1991). Importantly, the gating effect observed on the frontal N30 by light and deep thenar eminence massage was less than half the amplitude modulation observed with rapid ipsilateral flexion and extension of the four digits (Cheron & Borenstein, 1991). In addition, mental simulation of a complex ipsilateral thumb to finger opposition sequence resulted in significant decreases in amplitude of frontal N30 and N23 peaks elicited through left MN stimulation (Cheron & Borenstein, 1992). Furthermore, mental simulation of the same complex sequence with the contralateral hand had no effect on frontal N30, N23 or P22 peaks (Cheron & Borenstein, 1992). Based on these results, a pure centrifugal gating mechanism was argued to be responsible for modulating the frontal N30 during ipsilateral movements by an inhibitory effect through a cortico(SMA/premotor)-striatal-ventrolateral thalamic pathway on motor neurons (Cheron & Borenstein, 1992). Thus, centrifugal gating mechanisms are suggested to be primarily responsible for gating somatosensory input during ipsilateral movements.

It has been proposed that centrifugal gating may be a result of cortico-cortical rather than subcortical inhibition from active motor neurons suppressing the activity of neurons involved in the generation of SEPs (Cohen & Starr, 1987). In most experimental designs, the somatosensory input from electrical peripheral nerve stimulation is irrelevant for planning the upcoming movement that results in the gating (Cheron, Dan, & Borenstein, 2000; Rushton, Rothwell, & Craggs, 1981). Animal studies have demonstrated subcortical gating of afferent somatosensory information during movement (Chapman, Jiang, & Lamarre, 1988; Ghez & Pisa, 1972) and after microstimulation of M1 (Canedo, 1997). However, human SEP recordings have consistently demonstrated that Erb's point peaks or far-field potentials representative of the afferent volley

ascending through the medial lemniscus pathway are not modulated by movement preparation, execution or imagination (Cheron & Borenstein, 1987, 1991, 1992; Cheron et al., 2000). Thus, it appears that the amplitude changes of frontal SEPs primarily represent modulations once they reach the cortex. This notion has been confirmed by Kaňovský, Bares, and Rektor (2003) who recorded significant modulatory effects on frontal N30 peaks in the SMA and PMd with intracranial recordings. Active movement (AM) and mental movement simulation (MMS) of a repetitive sequence of opposing movements with the thumb to ulnar fingers during the AM condition was shown to decrease the amplitude of the frontal N30 peaks in the SMA (~45%) but MMS of the same movement resulted in larger decreases in the N30 peak amplitudes (~63%) compared to AM in the SMA. In contrast, MMS also resulted in large decreases of frontal N30 peaks in the PMd (~47%) but AM resulted in the largest decrease in frontal N30 peak amplitude (~ 87%) and even abolishment in some cases (Kaňovský et al., 2003). These results support that centrifugal gating mechanisms are responsible for frontal N30 peak amplitude changes in both SMA and PMd generators with ipsilateral movements. However, it appears that neurons responsive to somatosensory input in PMd are more influenced by active movements as compared to neurons in SMA.

In contrast to gating mechanisms, selective enhancement of SEPs have been revealed with contralateral limb movements (Legon, Dionne, Meehan, & Staines, 2010; Legon, Meehan, & Staines, 2008; Rossini et al., 1997). Rossini *et al*. (1997) had participants perform a quick sequence of finger taps with their ulnar fingers and thumb or imagine the same movement with both hands during MN stimulation at the right wrist (0.1 ms at motor threshold). The peak amplitude of the N30 was decreased during the executed and imagined ipsilateral movements but increased in amplitude during the execution of contralateral movement (Rossini et al., 1997).

Furthermore, frontal N30 peaks were significantly enhanced during the execution of contralateral self-paced bulb squeezing (Legon et al., 2008). Legon, Dionne and Staines (2010) revealed that both right- and left-hand dominant individuals had larger N30 peaks during contralateral movements compared to during movement preparation with their non-dominant limbs. However, no significant enhancement effects were revealed for contralateral movement with the dominant limbs (Legon et al., 2010).

Thus, frontal N30 peak amplitudes can be decreased during the preparation, execution and imagination of movements ipsilateral to MN stimulation. Decreases in frontal N30 SEPs are likely mediated by centrifugal mechanisms that may originate in intracortical networks within PMC, SMA and/or from M1. In contrast, frontal N30 peaks may be enhanced during contralateral limb movements, particularly with movement of the non-dominant limb. It was argued that these facilitation effects from the contralateral hemisphere may be mediated by increased activity through intercortical networks from PMC, SMA and M1 as well as potentially subcortical networks from the basal ganglia areas that occur specifically during non-dominant limb movements (Legon et al., 2010). However, the mechanism for facilitating N30 peak amplitudes during contralateral limb movement is not currently understood. Consequently, one of the goals of the current thesis will be to investigate mechanisms that may contribute to the enhancement of frontal N30 peaks during contralateral movements.

Role of the prefrontal top-down attentional system on modulating somatosensory input in non-primary motor areas

The PFC may contribute to the modulation of somatosensory input through top-down attentional modulation of sensory information (Barbas & Zikopoulos, 2007). Top-down attention

refers to the use of knowledge, expectations and goals derived from previous experiences, instructions or cues to direct activity at an expected stimulus or parts of available sensory or motor information to facilitate its processing or response (Brunia, 1993; Corbetta & Shulman, 2002; Herrmann & Knight, 2001; Petersen & Posner, 2012; Posner & Petersen, 1990; Shulman et al., 1997). Consequently, covert spatial attention refers to knowledge of an expected sensory stimulus at a specific spatial location (i.e. finger) to facilitate its processing without overt eye movements. Corbetta and Shulman (2002) revealed two attention systems: 'top-down' and 'bottom-up' attentional networks. The 'bottom-up/stimulus-driven' attentional system involves the flow of sudden or distinctive stimuli from temporoparietal junction (TPJ) to ventral frontal cortex, predominantly in right hemisphere, that may not be initially influenced by cognitive factors (such as goals, expectations etc.) (Corbetta & Shulman, 2002). In contrast, the 'top-down' attentional system involves the flow of information bilaterally from PFC to intraparietal sulcus (IPs) (Corbetta & Shulman, 2002). However, it was argued that even sudden or distinctive stimuli that are typically not thought to rely on 'top-down' influences may still be highly influenced by behavioural relevance (Corbetta & Shulman, 2002). As a result, it was hypothesized that the 'bottom-up' system is in constant interaction with the 'top-down' attentional system (Corbetta & Shulman, 2002). The bilateral dorsal frontoparietal 'top-down' attentional network was shown to consist of the dorsal frontal cortex (at intersection of precentral gyrus and superior frontal sulci near frontal eye field (FEF)) and dorsal parietal cortex (along the intraparietal sulcus extending dorsomedially into the superior parietal lobule and anteriorly to the postcentral sulcus) (Corbetta & Shulman, 2002). The 'bottom-up' attentional system is analogous to the orienting network in other models of attention (Petersen & Posner, 2012; Posner & Petersen, 1990).

It has been proposed that attention directed to the right side of the body is strictly controlled by the left hemisphere top-down attentional network (Mesulam, 1999). In contrast, attention to the left side of the body is controlled by both the right and left hemispheres (Mesulam, 1999). Most models of the attentional system often include an 'alerting' network that acts to prepare frontal and parietal areas by norepinephrine (NE) release from locus coeruleus upon a warning signal (Petersen & Posner, 2012; Posner & Petersen, 1990). Furthermore, an updated model of attention by Petersen and Posner (2012) have also included an 'executive control' top-down network that includes two separate subsystems. One top-down subsystem involves sustained activity in medial frontal/cingulate cortex as well as bilateral anterior insula to monitor or maintain performance. In contrast, the second top-down subsystem involves transient activity in lateral frontal and parietal regions (frontoparietal network) at the beginning of trials, start cue initiation and during task switching within trials (Petersen & Posner, 2012). It is likely that these executive 'top-down' attentional systems are equivalent to the cognitive control network that have previously been reported (Badre, 2008; Fuster, 2004; Koechlin, Ody, & Kouneiher, 2003; Miller, 2000).

The PFC, particularly BA 9 and 46, are important for sustained and phasic attention to environmental stimuli but patients with prefrontal lesions also demonstrate problems with inhibitory control of sensory inputs (Knight, Staines, Swick, & Chao, 1999). Focal lesions in the PFC result in problems with inhibitory control of sensory inputs, deficits in selective attention, sustained attention and deficits in detecting new external stimuli (Knight et al., 1999). Dense contralateral neglect is seen after right PFC lesions (compared to left PFC lesions) suggesting it contributes to control of both ipsilateral and contralateral hemispheres (Knight et al., 1999).

Collectively these results suggest that the PFC is important for both inhibition of task-irrelevant stimuli and facilitation of task-relevant stimuli.

Electrophysiological studies have supported top-down attentional and inhibitory influences on parietal SEPs (such as the P50 and P100) via enhanced attended task-relevant stimuli and inhibition of unattended task-irrelevant stimuli (i.e. N130) (Adler, Giabbiconi, & Müller, 2009; Bolton & Staines, 2011; Desmedt & Tomberg, 1989; Eimer & Forster, 2003; Garcia-Larrea, Bastuji, & Mauguière, 1991; Giabbiconi, Dancer, Zopf, Gruber, & Müller, 2004; Michie, Bearpark, Crawford, & Glue, 1987; Zopf, Giabbiconi, Gruber, & Müller, 2004). Furthermore, lesions to the PFC were shown to remove attentional effects on P100 parietal SEPs to attended task-relevant tactile stimuli (Bolton & Staines, 2014) as well as reduce parietal P26 SEPs (equivalent to P27) at rest (Yamaguchi & Knight, 1990). In theory, it is plausible that the prefrontal top-down attentional system may contribute to modulations of somatosensory processing in non-primary motor areas (frontal SEPs) by a similar mechanism that has been demonstrated with parietal SEPs. However, a concentration task involving sequenced mental naming revealed no effects on frontal N30, N23 or P22 peaks supporting that sustained attention has no generalized effect on modulating these frontal SEPs (Cheron & Borenstein, 1992). Furthermore, frontal N30 peaks were unaffected by directing spatial attention to the same digit as electrical stimulation using simultaneous mechanical taps to the same digits (Garcia-Larrea et al., 1991) or by silently counting MN stimulations (Kida, Nishihira, Wasaka, Sakajiri, & Tazoe, 2004). Conversely, surface recordings of SEPs in unilateral PFC lesion patients (centered around BA 9 and 46) at rest have shown that frontal SEPs around 30 ms (frontal N28) as well as frontal P45 and N67 are increased in amplitude compared to control participants (Yamaguchi & Knight, 1990). These results suggest that the PFC (BA 9 and 46) may contribute to inhibitory modulation

of early somatosensory processing in motor areas (Yamaguchi & Knight, 1990). It is likely that previous studies have not been adequately designed to examine frontal SEP modulation by the prefrontal top-down attentional system, which may be related to the different functional organization of the PMC and SMA as well as the approach to measure top-down attentional effects on frontal SEPs.

Labelling techniques in rhesus monkeys have revealed that the PFC (BA 46, 8a, 9 and 11) project to the rostral part of the SMA (Bates & Goldman-Rakic, 1993). Similarly, labeling anatomical connections in monkeys found that the PFC (BA 46) was found to have strong input into the rostral SMA (pre-SMA) whereas no connections were discovered between PFC and caudal SMA (SMA-proper) (Luppino, Matelli, Camarda, & Rizzolatti, 1993). Furthermore, Barbas and Pandya (1987) examined anatomical connections within each of the subdivisions of the premotor areas. Rostral parts of the PMd were shown to have connections with the PFC (BA 46, 9 and 8), caudal PMd and SMA. In contrast, caudal PMd was primarily connected with M1, SMA and cingulate gyrus. In contrast, upper and lower parts of the PMv had widespread connections with PFC (BA 46 and 12), caudal area of M1, rostral PMd, SMA, SI (BA 3a, 1 and 2) and SII (Barbas & Pandya, 1987). Based on these animal-labeling studies, the rostral SMA (pre-SMA), rostral PMd (pre-PMd) and ventral premotor cortex (PMv) all appear to be connected with the PFC. In contrast, the caudal SMA (SMA-proper) and caudal PMd (PMd-proper) have dense connections with each other, M1 as well as PT neurons but minimal connections with the PFC.

In conclusion, the pre-SMA, pre-PMd and PMv are all connected to the PFC whereas the SMA-proper and PMd-proper have limited connections. Interestingly, both the pre-PMd and PMd-proper receive somatosensory input whereas only the SMA-proper receives somatosensory

input. Based on the anatomical and functional connectivity, it appears possible that the prefrontal cortex could directly influence somatosensory processing in the pre-PMd and subsequently, the pre-PMd could influence the somatosensory-cued movement through its connections with the PMd-proper. If this were true then modulations on frontal SEPs with changes in PFC excitability could be recorded representing modulations of somatosensory input in the pre-PMd and/or PMd-proper. It is possible that these effects may be small and subsequently, indistinguishable with cortical surface recordings of frontal N30 peaks since multiple generators within the SMA and PMd likely contribute to this SEP.

1.3.4. TMS and SEP modulation

TMS uses a magnetic coil tangential to the cortical surface to induce a brief (~100 μs) magnetic field perpendicular to the plane of the coil that can reach up to 2 Tesla (Hallett, 2007). In addition to the magnetic field, an electric field is induced perpendicular to the magnetic field that can activate and disrupt neuronal components through its current flow (Hallett, 2007). Physiologically, TMS has the ability to interact with cortical processing but the current understanding of the physiological effects are based primarily on TMS applied over M1. For example, when TMS is applied over M1 corticospinal excitability changes can be measured through peripheral muscle responses or motor-evoked potentials (MEPs) (Bestmann, 2007; Di Lazzaro, 2004; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Electrical stimulation over M1 by transcranial electric stimulation (TES) results in direct activation of descending corticospinal neurons via the direct (D) waves within a few ms after stimulation (Day et al., 1989; Di Lazzaro, Oliviero, et al., 1998; Hallett, 2007; Kaneko, Kawai, Fuchigami, Morita, & Ofuji, 1996; Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1996). However, TMS activates either

long polysynaptic networks or recurrent synaptic networks through indirect (I) waves rather than D waves resulting in indirect activation of corticospinal stimulation resulting in latency delays of MEPs (Day et al., 1989; Di Lazzaro, Oliviero, et al., 1998; Hallett, 2007; Kaneko et al., 1996; Nakamura et al., 1996). Other types of neuronal populations such as inhibitory interneurons are likely activated with any single TMS pulse (Hallett, 2007; Huang et al., 2005). Inhibitory networks are preferentially activated when the TMS pulses are below the threshold to evoke MEPs (Di Lazzaro, Restuccia, et al., 1998). This has been confirmed with paired-pulse TMS studies revealing a TMS pulse (conditioning stimulus) below motor threshold followed by a second TMS pulse (test stimulus) at motor threshold within 1-3 ms results in a reduction of the spinal cord volley and MEP to the test stimulus (Di Lazzaro, Restuccia, et al., 1998). However, since both excitatory and inhibitory networks can be activated with any single TMS pulse, this may result in competition between these neural networks and ultimately, result in some variability in measuring muscle responses (Huang et al., 2005). It should be noted that little is known about the physiological effects of a single pulse of TMS when applied over other areas of the cortex, such as PMC or PFC, in humans. However, investigations using repetitive TMS (rTMS) have provided some evidence for the physiological basis of TMS over other cortical areas.

rTMS and TBS

Repetitive TMS (rTMS) techniques apply regular repeated pulses to the same cortical area to induce neuronal excitability or inhibition plasticity-like changes that last beyond the period of stimulation. Importantly, the cumulative effects of rTMS on cortical excitability (i.e. increased excitability or inhibition) depend on the frequency, duration/number of pulses and

intensity of stimulation. In general, high-frequency rTMS above 5 Hz increases M1 excitability whereas low frequency rTMS (between 0.1 to 1 Hz) decreases M1 excitability as measured by changes in MEPs (Chen & Seitz, 2001; Fitzgerald, Fountain, & Daskalakis, 2006). However, there are variable effects in MEP amplitude changes with M1 rTMS when stimulation intensities vary between 80-200% of resting motor threshold (RMT) (Fitzgerald et al., 2006). In a review, 13 out of 19 studies demonstrated MEP size reduction after contralateral low-frequency rTMS (Fitzgerald et al., 2006). In contrast, several studies investigating high-frequency (5-20 Hz) contralateral M1 rTMS at intensities of 90-150 RMT have reported increases in MEP sizes but these effects are not universally found (Fitzgerald et al., 2006). Importantly, the reliability of both low-and high-frequency rTMS on reducing and increasing MEP amplitude appear to be dependent on the duration/number of pulses (Fitzgerald et al., 2006). However, there is a high degree of variability between-subjects as well as within-subjects across different sessions (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Pell, Roth, & Zangen, 2011; Ridding & Ziemann, 2010). One likely limitation of traditional rTMS studies is that these studies on humans use low-frequency of stimulation whereas animal studies investigating excitability changes have often used higher frequencies of stimulation (Huang et al., 2005). Theta burst stimulation (TBS) was developed for humans by applying high- rather than low-frequency stimulation (Huang et al., 2005; Huang & Rothwell, 2004).

In general, TBS methods developed by Huang *et al.* (2005) deliver a set of 3 pulses at high-frequency (50 Hz) at an intensity of 80% active motor threshold (AMT). AMT is determined by the minimum intensity required to produce MEP greater than 200 uV in 5 out of 10 trials while maintaining a 20% maximum voluntary contraction (MVC) at the motor hot spot in M1 of a given muscle. Intermittent theta burst stimulation (iTBS) delivers a 2 s train of TBS

repeated every 10 s for a total of 600 pulses over 190 s duration and increases MEPs when applied over the FDI motor hot spot up to 15 minutes. In contrast, cTBS delivers a continuous 40s train of TBS for a total of 600 pulses and was shown to suppress MEPs when applied to the motor hot spot of the first dorsal interosseus (FDI) for up to 60 minutes (Huang et al., 2005). Furthermore, Di Lazzaro *et al.* (2005) investigated the effects of cTBS on corticospinal volley using implanted electrodes in the cervical epidural space. It was revealed that cTBS preferentially decreased the I1 wave amplitude produced by single-pulse TMS over M1 whereas D waves and later I waves were unaffected. It was suggested that cTBS may function to produce long-term depression (LTD) at the excitatory synapse between I1 input and corticospinal neurons as well as on excitatory synapses of inhibitory interneurons (Di Lazzaro et al., 2005). In addition, both inhibitory effects of cTBS and facilitatory effects of iTBS were blocked after administration of memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist (Huang, Chen, Rothwell, & Wen, 2007). These results support that the long lasting effects produced through cTBS and iTBS likely occur through NMDA-dependent LTD-like and long-term potentiation (LTP)-like changes in synaptic plasticity. Altogether these results demonstrate the effectiveness and long-lasting effects of iTBS and cTBS in facilitating and suppressing cortical excitability in M1, respectively. Thus, the long-lasting synaptic plasticity changes, particularly the inhibitory effects of 40s/600 pulses of cTBS that lasts up to 60 minutes post-stimulation, may have worthwhile applications in behavioural or clinical research paradigms.

It should be noted that a recent review by Ridding and Ziemann (2010) suggests that the magnitude and direction of responses to M1 cTBS or iTBS are dependent on several factors including the history of cortical activation (including physical activity), and current state of the stimulated cortex (including attention state). In addition, individual factors like time of day

linked to diurnal factors such as variations in cortisol levels in afternoon compared to morning as well as age, sex, genetics (including BDNF polymorphisms) may all contribute to the plasticity changes induced during cTBS or iTBS (Ridding & Ziemann, 2010). Furthermore, Hamada *et al.* (2013) investigated whether variability to TBS can be explained by differences in intrinsic mechanisms of synaptic plasticity or different responses of cortical neurons in different people during different times. In a study of 52 young adults, significant facilitatory effects of iTBS and inhibitory effects of cTBS were not revealed. It was shown that participants who did respond to both cTBS and iTBS as expected (25%) were linked to differences in population of neurons that are activated with each TMS pulse. In addition, 31% of participants showed reversal effects of cTBS and iTBS while 17% showed inhibitory effects and 27% showed facilitatory effects regardless of TBS protocol (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013). Thus, responses to M1 cTBS and iTBS lead to a high degree of inter-individual variability. It is unclear if this variability holds true for TBS protocols when applied to areas outside M1 or whether this is unique to M1 TBS. Regardless, careful consideration needs to be taken when evaluating individuals that respond and non-responders during TBS protocols.

The physiological basis for TBS outside M1 is largely unknown but Bestmann *et al*. (2005) investigated the haemodynamic effects of 10 s trains of 3 Hz rTMS over the left PMd using fMRI. Results revealed increased BOLD responses in left PMd only when applying rTMS at 110% of RMT. However, increased BOLD responses were observed in other connected brain regions such as right PMd, bilateral PMv, SMA, SI, cingulate motor area, left posterior temporal lobe, cerebellum and caudate nucleus with rTMS applied at 110% and 90% RMT. It was concluded that short trains of TMS modify local haemodynamics through both cortical-cortical as well as cortical-subcortical connectivity (Bestmann, Baudewig, Siebner, Rothwell, & Frahm,

2005). Furthermore, cTBS applied over the right PFC was shown to decrease fMRI resting-state functional connectivity between right PFC (BA 46) and parietal (BA 40) cortices (Mastropasqua et al., 2014). Collectively, these studies provide evidence that premotor and prefrontal rTMS has the ability to influence haemodynamic responses in the area under stimulation as well as connected networks. It is likely that TBS influences neuronal function through similar changes in excitatory and inhibitory networks in PMC and PFC that have been observed in M1.

Effects of rTMS and cTBS to premotor areas, SI, M1 and PFC on modulating frontal SEPs

Limited research has evaluated the effects of rTMS on upper limb somatosensory processing, particularly using frontal SEPs. Legon, Dionne and Staines (2013) examined SEPs, MEPs and tactile sensory thresholds after SMA cTBS (over FCz electrode 3cm anterior to Cz on sagittal midline) at an intensity of 90% RMT determined for the right FDI in M1. Significant decreases in frontal N30 SEP amplitudes as well as increases in tactile detection thresholds for the right index finger were determined 30 min after SMA cTBS. However, no effects on other frontal (P18 or N60) SEPs, parietal SEPs or MEPs were found (Legon, Dionne, & Staines, 2013). These results supported that SMA is involved in the generation of frontal N30 SEPs and contributes to tactile detection.

Two studies have evaluated the effects of traditional rTMS on frontal SEPs (Hosono et al., 2008; Urushihara et al., 2006). Urushihara *et al.* (2006) investigated the effects of traditional inhibitory 0.2 Hz monophasic and 1 Hz biphasic rTMS on frontal (F3 electrode) and central (C3 electrode) SEPs elicited by right MN stimulation. 0.2 Hz rTMS was applied over left hemisphere PMC, M1 FDI motor hot spot, and SMA while 1 Hz rTMS was applied over PMC. In addition, regional cerebral blood flow (rCBF) was also examined using single photon emission computed

tomography (SPECT) after 0.2 Hz PMC rTMS. 0.2 Hz rTMS to PMC significantly increased N30 peak amplitude but not N60 peak amplitude or parietal SEPs when compared to M1 or SMA rTMS. In addition, 0.2 Hz rTMS to PMC resulted in significantly larger frontal N30 and N60 peak amplitudes compared to biphasic 1 Hz rTMS to PMC. SPECT revealed significant increases in rCBF in left middle frontal gyrus (BA 9), precentral gyrus (BA 6) as well as cingulate gyrus after 0.2 Hz rTMS (Urushihara et al., 2006). In a similar protocol by Hosono *et al*. (2008), 0.2 Hz monophosic rTMS was applied over left PMC and compared to 0.8 Hz monophasic rTMS, 0.2 biphasic rTMS and 1 Hz biphasic rTMS on frontal and parietal SEPs elicited by right MN stimulation. In addition, rCBF changes were measured using SPECT after monophasic 0.2 Hz rTMS and biphasic 1Hz rTMS. Results revealed that only N30 peak amplitudes at F3 electrodes were significantly enhanced immediately after monophasic 0.2 and 0.8 Hz rTMS while no significant differences were observed with biphasic 0.2 or 1 Hz rTMS. N30 peak amplitudes returned to baseline 30 minutes after 0.2 Hz rTMS. Increases in rCBF were observed in BA 6 and in left thalamus after 0.2 Hz rTMS. In contrast, biphasic 1Hz rTMS significantly increased rCBF in left occipital and right parietal lobes. The increased N30 peak amplitudes and rCBF in BA 6 were interpreted as N30 peaks reflecting summation of inhibitory activity in PMC and increases in rCBF result from increased inhibitory interneuron activities to decrease cortical excitability (Hosono et al., 2008). However, investigations of frontal SEPs after administration of tiagabine, a GABA reuptake inhibitor, revealed no effects on frontal N30 SEPs (Restuccia et al., 2002), supporting that N30 SEPs are not the summation of IPSPs. It is unclear why different effects of cTBS and rTMS have been revealed for frontal N30 peaks after SMA compared to PMC stimulation. It is plausible that 0.2 Hz rTMS stimulation used may have had excitatory rather than the expected inhibitory effects when applied to PMC in these rTMS studies

(Hosono et al., 2008; Urushihara et al., 2006). The results from these rTMS studies over SMA and PMC (Hosono et al., 2008; Legon et al., 2013; Urushihara et al., 2006) support intracranial recordings (Kaňovský et al., 2003) that the SMA and PMC are involved in the generation of the frontal N30 SEPs. However, these studies do not identify a functional role for the PMC (or SMA) in modulating afferent somatosensory input (i.e. SEPs) used in upper limb motor control as these studies were conducted while participants were at rest.

Ishikawa *et al.* (2007) investigated the effects of SI cTBS (2 cm posterior to M1 motor hot spot) as well as cTBS to M1 right APB motor hot spot on SEPs derived from MN stimulation. In addition, the effects on MEPs after cTBS to left SI (2cm posterior to M1 motor hot spot) and M1 of FDI motor hot spot were evaluated. Results revealed significant decreases in peak-to-peak amplitudes of parietal P25/N33 after SI cTBS for up to 13 minutes. In contrast, M1 cTBS significantly increased peak-to-peak amplitudes of parietal P25/N33 for up to 53 minutes post-stimulation. These effects were only revealed for right but not left MN stimulation. Frontal P22/N30 peak-to-peak amplitudes were influenced in a similar manner but this did not reach statistical significance suggesting these effects were unique to parietal but not frontal SEPs (Ishikawa et al., 2007). Based on these results, ipsilateral SI and M1 excitability differentially influences somatosensory input measured by the parietal P25/N33 peak-to-peak amplitudes; SI appears to have an excitatory role whereas M1 appears to have an inhibitory role.

Few studies have used rTMS methods to evaluate the role of the PFC in the context of upper limb somatosensory processing. Bolton and Staines (2011) evaluated the effects of right DLPFC cTBS (over F4 electrode at 80% of RMT for APB) on parietal SEPs to attended relevant and irrelevant tactile stimuli. cTBS to DLPFC was shown to increase P100 SEP amplitudes to irrelevant unattended stimuli (Bolton & Staines, 2011), suggesting the PFC has a role in

inhibitory control of irrelevant somatosensory input in SII. In addition, Bolton *et al.* (2012) evaluated modulations of SEPs elicited from MN after cTBS applied to the right DLPFC (over F4 electrode at 80% of RMT for APB) and M1 (motor hot spot of APB) during standing balance. P200 peaks recorded from FCz electrode were significantly larger in normal tandem stance compared to tandem stance with a sway-referenced touch after cTBS to M1. However, significant differences in P200 peak amplitudes were not observed after DLPFC cTBS. It was concluded that the PFC may be involved in gating irrelevant sensory information when balance is disturbed (Bolton, Brown, McIlroy, & Staines, 2012). Based on these studies, DLPFC may have a functional role in inhibiting irrelevant somatosensory input in both frontal and parietal areas.

1.4. Conclusions

Anatomically, prefrontal top-down attentional networks are connected directly (pre-PMd, pre-SMA, PMv) and indirectly (PMd-proper and SMA-proper) with non-primary premotor areas suggesting they have the ability to influence somatosensory input into these areas (i.e. frontal SEPs). Frontal SEPs are disinhibited in prefrontal lesion patients and parietal SEPs are often modulated by prefrontal top-down attention. However, there is limited understanding of the contribution of the prefrontal top-down attentional networks to somatosensory input modulation as it relates to non-primary motor area input and upper limb motor control. Specifically, it is not currently understood how and when frontal SEPs may be modulated by the PFC in healthy adults to explain the observations from prefrontal lesion patients. Furthermore, there is also conflicting evidence from contralateral movement paradigms, intracranial recordings and rTMS research of the role that the PMd, rather than SMA, has in frontal SEP generation and modulation of upper

limb somatosensory input. The following sections present the research objectives of the thesis including specific research questions and hypotheses.

1.5. Research Objectives, specific research questions and hypotheses

1.5.1. Research Objective 1

Does the PMd modulate afferent somatosensory inputs into contralateral non-primary motor areas or SI/SII? If so, when during a cued-movement does the PMd modulate this information?

Execution of contralateral repetitive hand movements, particularly with the non-dominant hand, but not preparation have been shown to enhance frontal N30 and N60 SEPs (Legon et al., 2010, 2008; Rossini et al., 1997), which could involve intercortical networks from SMA, M1 and subcortical areas such as basal ganglia (Legon et al., 2010). In contrast, parietal P27 and P50 SEPs were reduced during contralateral movements (Legon et al., 2010, 2008), which may have been caused by interhemispheric inhibition between SI and M1. However, it is currently unclear if the PMd may also be involved in frontal or parietal SEP modulation. Both left and right PMd are known to be involved in movement preparation, particularly to sensory stimuli that cue a motor response (Chouinard & Paus, 2006; Hoshi & Tanji, 2007; Picard & Strick, 2001; Raos et al., 2003). In addition, increased activity has been observed during neuroimaging in lateral premotor areas when preparing finger sequences of increased length or complexity (Bortoletto & Cunnington, 2010; Haslinger et al., 2002). Therefore, PMd may be particularly involved in SEP modulation during the preparation of cued-movements, particularly with more difficult movements such as finger sequences with increased length or complexitiy.

Specific Research Question 1

Do right (contralateral) cued finger sequence movements increase frontal SEPs generated by left MN stimulation?

Hypothesis: Frontal N30 and N60 peaks will be increased by cued finger sequence movements with the contralateral hand.

Specific Research Question 2

Do right (contralateral) cued finger sequence movements increase frontal SEPs generated by left MN stimulation differentially during preparation and execution?

Hypothesis: Frontal N30 and N60 peaks will be increased during preparation more than during execution of a cued finger sequence with the contralateral hand.

Specific Research Question 3

Does activity in the left PMd during right (contralateral) cued finger sequence preparation and execution contribute to frontal SEP modulations generated by left MN stimulation?

Hypothesis: Transiently decreasing activity in the contralateral (left) PMd with cTBS will reduce the enhancement of frontal N30 and N60 peaks during preparation of a cued finger sequence.

1.5.2. Research Objective 2

Do prefrontal top-down attentional networks differentially modulate somatosensory input into non-primary motor areas and SI/SII? If so, when during a cued-movement does the PFC modulate this information?

Prefrontal top-down attentional effects have been observed on parietal SEPs such as enhancements of P50 and P100 to attended task-relevant stimuli and inhibition of N130 SEP to unattended task-irrelevant stimuli (Adler et al., 2009; Bolton & Staines, 2011; Desmedt & Tomberg, 1989; Eimer & Forster, 2003; Garcia-Larrea et al., 1991; Giabbiconi et al., 2004; Michie et al., 1987; Zopf et al., 2004). Right PFC cTBS has been shown to increase P100 SEPs to unattended task-irrelevant stimuli (Bolton & Staines, 2011). In addition, prefrontal lesion patients do not demonstrate attention related enhancements of P100 SEPs to task-relevant tactile stimuli (Bolton & Staines, 2014) as well as have reduced parietal P27 SEPs at rest (Yamaguchi & Knight, 1990). In contrast, prefrontal lesion patients demonstrated increases in frontal N28, P45 and N67 SEPs at rest (Yamaguchi & Knight, 1990) but experimental manipulations of attention have not found modulatory effects on frontal N30 SEPs (Cheron & Borenstein, 1992; Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004). Anatomically, the PFC has connections with both rostral PMd and SMA (Barbas & Pandya, 1987; Bates & Goldman-Rakic, 1993; Luppino et al., 1993) where frontal N30 SEPs are likely generated (Balzamo et al., 2004; Barba et al., 2003, 2001, 2005; Hosono et al., 2008; Kaňovský et al., 2003; Legon et al., 2013; Urushihara et al., 2006). Functional imaging has revealed increased BOLD in the bilateral PFC when planning and executing finger sequences with increased length and complexity (Haslinger et al., 2002). In addition, the lateral PFC is particularly important for anticipatory attentional processes before an expected stimulus (Funderud et al., 2013; Haegens,

Händel, & Jensen, 2011). Therefore, the prefrontal top-down attentional networks may be involved in modulating frontal N30 SEPs when somatosensory input is task-relevant for planning and executing movements with increased complexity, particularly before an expected stimulus.

Specific Research Question 4

Are frontal SEPs increased by attending to somatosensory input at a spatial location that is either irrelevant for movement or required in the response selection of contralateral movements?

Hypothesis: Sustained attention to somatosensory information that is irrelevant for movement will not increase frontal N30 peaks. However, attending to somatosensory input at a spatial location that is relevant for response selection of a sensory-guided movement will increase frontal N30 and N60 peaks.

Specific Research Question 5

Are prefrontal attentional modulations of frontal SEPs greater before an expected stimulus that cues movement compared to during movement preparation or execution?

Hypothesis: Increases in frontal N30 and N60 peaks will be largest before an attended somatosensory movement cue at a spatial location that is relevant for response selection of a sensory-guided movement.

Specific Research Question 6

Does the right (ipsilateral) PFC contribute to modulations of frontal SEPs when attending to somatosensory input at the left hand that cues a movement?

Hypothesis: Transient inhibition of the ipsilateral (right) PFC with cTBS will reduce the enhancements of increased frontal N30 and N60 peaks when attending to somatosensory input that is relevant for planning a movement, particularly before an expected movement cue.

1.5.3. Research Objective 3

Can differences to single-pulse TMS over M1 be used as a predictor of the direction (i.e. inhibition or facilitation) of response to cTBS over PMd using frontal SEPs?

There is a large amount of variability in magnitude and direction (inhibition, excitation or no response) of MEP changes to most forms of rTMS (Fitzgerald et al., 2006) including cTBS when applied over M1 (Hamada et al., 2013; Ridding & Ziemann, 2010). History of cortical activation (including physical activity), current state of the stimulated cortex (including attention state), time of day (cortisol levels), age, sex, genetics (including BDNF polymorphisms) may all contribute to the differences in plasticity changes induced during cTBS (Ridding & Ziemann, 2010). It was recently shown that only 25% of 52 participants showed transient inhibition with M1 cTBS (and increasd excitatbility with iTBS) while 17% were inhibited (25% increased excitability) regardless of cTBS or iTBS as well as 31% demonstrated the opposite effects to iTBS and cTBS (Hamada et al., 2013). It is likely that this variability in response to cTBS (and iTBS) exists when applied over other cortical areas such as PMd or PFC, which could result in masking the true effects of transiently inhibiting or facilitating a given area.

It is well-documented that TMS activates either long polysynaptic networks or recurrent synaptic networks through indirect (I) waves rather than D waves resulting in indirect activation

of corticospinal neurons (Day et al., 1989; Di Lazzaro, Oliviero, et al., 1998; Hallett, 2007; Kaneko et al., 1996; Nakamura et al., 1996) resulting in latency delays of MEPs (Di Lazzaro et al., 1998; Hallett, 2007; Kaneko, Kawai, Fuchigami, Morita, & Ofuji, 1996; Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1996). Interestingly, MEP onset latency differences between MEPs elicited from M1 TMS with an A-P coil direction (I3 waves) compared to L-M coil direction (D waves) greater than 4 ms were significantly correlated with the expected response of transient inhibition with cTBS and facilitation with iTBS (Hamada et al., 2013). It was concluded that about 60% in the variation to TBS protocols is associated with efficiency of late I-wave recruitment associated with the population of neurons that is activated with each TMS pulse (Hamada et al., 2013). Functional imaging studies have revealed acute increased rCBF (using SPECT) (Hosono et al., 2008; Urushihara et al., 2006) and BOLD signals (using fMRI) (Bestmann et al., 2005) after PMd rTMS, supporting that neuronal haemodynamic activity is influenced by rTMS protocols over PMd. However, there is currently no method for objectively determining the magnitude or direction of response to rTMS protocols, specifically cTBS, when applied over PMd.

Intracortical recordings (Kaňovský et al., 2003) and previous rTMS (Hosono et al., 2008; Legon et al., 2013; Urushihara et al., 2006) studies measuring SEPs time-locked to MN stimulation have associated the generation of frontal N30 peaks to PMd as well as SMA, yet there is conflicting evidence for the latter (Balzamo et al., 2004; Barba et al., 2003, 2001, 2005). Therefore, the frontal N30 SEP could potentially be used as an objective measure of activity into PMd. It is possible that the population of neurons that are activated by TMS pulses over M1 are associated with the type of neurons activated by TMS over PMd. If this were true, measuring

MEP onset latencies with M1 TMS with different coil orientations could be used to predict the direction of PMd cTBS response (inhibition or facilitation) on frontal N30 SEPs.

Specific Research Question 7

Does the right PMd contribute to generation or modulation of frontal N30 SEPs from left or right MN stimulation at rest?

Hypothesis: cTBS to the right PMd will reduce the amplitude of frontal N30 from the left MN stimulation.

Specific Research Question 8

Does an onset latency greater than 4 ms between MEPs elicited by M1 TMS with A-P compared to L-M coil orientations correlate with decreases in frontal N30 SEPs to left MN stimulation after right PMd cTBS?

Hypothesis: Latency differences greater than 4 ms between A-P and L-M coil orientations after M1 TMS will not be correlated to frontal N30 peak modulations after right PMd with cTBS.

Chapter 2 – Modulatory effects of attention and movement sequence preparation on somatosensory input into non-primary motor areas

Adapted from:

Brown, M.J.N., and Staines, W.R. Modulatory effects of movement sequence preparation and covert spatial attention on early somatosensory input in non-primary motor areas. *Experimental Brain Research*, 233(2), 503-17

Chapter Research Objectives

This chapter aimed to answer specific research questions 1 and 4 (see section 1.5).

2.1. Abstract

Early frontal somatosensory evoked potentials (SEPs) (i.e. N30) are known to be modulated by movement. Furthermore, individuals with prefrontal lesions have enhanced early frontal SEPs. However, it is currently unclear through what mechanism the prefrontal cortex may modulate early frontal SEPs. The current study investigated whether prefrontal modulatory effects on frontal SEPs may depend on the relevancy of somatosensory input for movement (i.e. interaction with motor areas). Two experiments were conducted to determine whether selective spatial attention alone (*Experiment 1- Attend and Mentally Count*) or when using attended somatosensory input in the preparation of finger sequences with the limb contralateral to

somatosensory stimulation (*Experiment 2 – Attend for Movement Preparation*) could modulate SEPs. In Experiment 1, SEPs elicited by median nerve (MN) stimulation at both wrists were measured in trials when individuals attended and mentally counted vibrotactile (VibT) input at either index finger. In Experiment 2, SEPs elicited by MN stimulation at the left wrist were measured in trials when individuals used attended VibT input at the left index finger to prepare finger sequences that were contralateral to MN stimulation. In both experiments, control conditions were performed where participants received passive VibT and MN stimulation. Results from Experiment 1 confirmed that selective spatial attention alone does not modulate frontal N30 peak amplitudes. However, Experiment 2 revealed that frontal N30 peak amplitudes were decreased (i.e. gated) when individuals used attended VibT input at the left index finger to prepare contralateral finger sequences. These results support a role of sensory gating of early frontal SEPs during finger sequence preparation of the limb contralateral to MN stimulation that may result from increased activity in prefrontal, motor preparatory areas and basal ganglia.

2.2. Introduction

Intracerebral neurophysiological recordings performed in both humans (Balzamo et al., 2004; Kaňovský et al., 2003) and primates (Wiesendanger et al., 1985) show that ascending somatosensory information from the upper limbs reaches primary and non-primary motor areas during early sensory-motor processing. The cortical motor areas to which this somatosensory information projects include the primary motor cortex (M1), premotor cortex (PMC) and supplementary motor area (SMA) (Balzamo et al., 2004; Kaňovský et al., 2003; Wiesendanger et al., 1985). Furthermore, surface recordings of somatosensory evoked potentials (SEPs) over non-primary motor areas in humans have commonly recorded a negativity peaking around 30 ms

after peripheral nerve stimulation known as the frontal N30 (Cheron & Borenstein, 1987, 1991, 1992; Cohen & Starr, 1987; Legon et al., 2010, 2008; Rossini et al., 1996, 1997, 1999; Starr & Cohen, 1985; Tapia, Cohen, & Starr, 1987; Waberski et al., 1999). Although the origin of the frontal N30 is still debatable, it appears that this SEP is generated from neuronal populations within non-primary motor areas (i.e. SMA and PMC) (Barba et al., 2003, 2005; Kaňovský et al., 2003). Consequently, it is important to understand the mechanisms involved in modulating somatosensory input to the non-primary motor areas as it can provide important insight on the role of sensory gating in movement control.

Importantly, several factors have been shown to modulate frontal N30 peaks. Transcranial magnetic stimulation (TMS) over M1, SMA and PMC (Hosono et al., 2008; Ishikawa et al., 2007; Legon et al., 2013; Urushihara et al., 2006) as well as movement preparation, execution and imagination (Cheron & Borenstein, 1987, 1991, 1992; Cohen & Starr, 1987; Legon et al., 2010, 2008; Rossini et al., 1996, 1997, 1999; Starr & Cohen, 1985; Tapia et al., 1987; Waberski et al., 1999) have been shown to modulate frontal N30 peaks. For example, enhanced frontal N30 SEPs have been revealed during execution of repetitive hand movements contralateral to the limb receiving median nerve (MN) stimulation (referred to herein as contralateral movements) (Rossini et al. 1997; Legon et al. 2008, 2010). In addition, surface recordings of SEPs in unilateral prefrontal lesion patients (centred around Brodmann's areas 9 and 46) at rest have revealed enhanced frontal SEPs around 30 ms (frontal N28) compared to age-matched controls, suggesting that the prefrontal cortex may contribute to inhibitory modulation of early somatosensory processing in non-primary motor areas (Yamaguchi & Knight, 1990). However, the mechanism of how the prefrontal cortex may interact to modulate

processing of early somatosensory input in non-primary motor areas represented by frontal N30 peaks is currently unclear.

It is well-established that the prefrontal cortex is part of the top-down attentional system, in combination with parietal areas, that is involved in directing resources to facilitate sensory processing of stimuli with a previously established goal or at an expected location (Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Johansen-Berg, Christensen, Woolrich, & Matthews, 2000). Thus, one possible way to understand the role of the prefrontal cortex in modulating somatosensory input in non-primary motor areas is through the manipulation of spatial attention. To date, experimental evidence in healthy adults using behavioural manipulations to direct spatial attention to somatosensory stimuli have not supported that attentional processes can modulate somatosensory information in non-primary motor areas as early as the frontal N30 (Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004). For example, frontal N30 peaks were unaffected by directing spatial attention to the digit on the same hand receiving electrical stimulation using simultaneous mechanical taps (Garcia-Larrea et al., 1991). In addition, silently counting MN stimulations did not modulate N30 peaks (Kida, Nishihira, Wasaka, Sakajiri, et al., 2004).

One potential limitation of these studies is that attention was directed to peripheral stimulation that had no relation to movement (see Garcia-Larrea et al., 1991). This is an important consideration since it has been hypothesized that the frontal N30 peak represents somatosensory input into non-primary motor areas that is used to plan and perform movements (Kaňovský et al., 2003). Furthermore, imaging research has revealed increased blood flow in motor areas such as the rostral SMA (i.e. pre-SMA) and ipsilateral M1 as the complexity of movement increases during the execution of movement sequences (Boecker et al., 1998). In

addition, increased blood flow has been observed in the dorsolateral prefrontal cortex (Brodmann's areas 9, 10 and 46) when healthy older adults self-initiated finger extensions compared to auditory-cued movements (Jahanshahi et al., 1995). Similarly, increased activity has been observed in the medio-orbital frontal cortex (including Brodmann's areas 10 and 46) when there was an increased demand on timing the initiation of finger sequences (Bortoletto & Cunnington, 2010). Thus, another potential limitation of previous experiments investigating prefrontal modulatory effects on N30 peaks was that the somatosensory input was used to cue a simple movement without a strong demand on the complexity of movement or movement initiation. Thus, the modulatory effects of the prefrontal cortex on somatosensory input in non-primary motor areas (i.e. frontal N30) may depend on three important factors: a) somatosensory input is relevant to a movement, b) the movement is complex rather than simple (i.e. finger sequence vs. finger extension), and c) there is a significant demand on timing the initiation of the movements.

Two studies were completed to examine the modulatory effects of specific behavioural manipulations on early somatosensory input into non-primary motor areas (i.e. frontal N30). SEP modulation was evaluated when individuals attended to and mentally counted vibrotactile (VibT) stimuli without any movement requirements (*Experiment 1- Attend and Mentally Count*). In contrast, SEP modulation was examined when individuals attended to VibT stimuli and used this to prepare and execute a finger sequence with the hand contralateral to stimulation (*Experiment 2 – Attend for Movement Preparation)*. In the present experimental designs, electrical stimulation of the MN at the wrists was used as a probe for somatosensory input into non-primary motor areas but was irrelevant for the behavioural aspect of the task. However, covert spatial attention and movement sequences were cued by VibT stimuli to the index finger

innervated by the same MN. This experimental design allowed the manipulation of vibration amplitude to increase the complexity of the task by having multiple response choices while maintaining consistent amplitudes of MN stimulation. It was hypothesized that directing and sustaining attention alone while only required to mentally count index finger vibrations (*Experiment 1-Attend and Mentally Count*) would not influence the amplitude of the frontal N30. However, it was also hypothesized that the amplitude of the frontal N30 (i.e. excitability of somatosensory input in non-primary motor areas) would increase when attention was directed to index finger VibT stimuli that were relevant for planning and executing finger sequences (*Experiment 2-Attend for Movement Preparation*).

2.3. Methods

2.3.1. Participants

Electroencephalography (EEG) was collected from 13 self-reported right-handed healthy participants. Eight participants were included in Experiment 1 (five males and three females, aged 27.2 +/- 5 years old; range 22-38 years old) and ten participants in Experiment 2 (five males and five females, aged 27.2 +/- 5.1 years old; range 20-38 years old). Five participants were included in both experiments. All participants provided written informed consent and all experimental procedures were approved by the University of Waterloo Office of Research Ethics.

2.3.2. Experimental Task

For both experiments, the general behavioural task required participants to detect standard, high or low amplitude VibT stimuli (constant at 25 Hz) at two spatial locations (i.e.

fingers). If participants perceived stimuli as high or low targets at the attended location, they would either mentally count (*Experiment 1-Attend and Mentally Count*) or perform a pre-matched finger sequence movement with the hand contralateral to VibT stimulation (*Experiment 2-Attend for Movement Preparation*) corresponding to the perceived high or low VibT stimuli. In contrast, participants were not required to perform any task to standard VibT stimuli or VibT stimuli to the unattended location. It should be noted that electrical stimuli were also provided throughout each experimental trial to the median nerve (MN) at the wrists but were irrelevant for the behavioural task.

In each trial, VibT stimuli were randomly presented one at a time to the fingertips with varying amplitudes. The frequency of VibT stimulation at the different amplitudes used in both experiments was similar to oddball paradigms using frequent (75%) non-targets (either standard amplitude or stimuli to unattended location) and infrequent (25%) targets (high and low amplitude). To determine appropriate VibT stimulation amplitudes, five participants were evaluated for sensory thresholds of both right and left index fingers by repeating random patterns of high, low and standard VibT stimulation amplitudes until participants could accurately detect five consecutive high and low stimuli. Standard amplitudes were the same for all participants but small variations in low and high amplitudes occurred based on each participant's sensory threshold. The high and low sensory thresholds were set at a minimum of 170 and 30 (% of standard) after determining these values as inclusive values for the participants evaluated for sensory thresholds. All participants had at least two practice trials detecting VibT stimuli before testing sessions began in both experiments; this also allowed verification of appropriate sensory thresholds for each participant.

Experimental Design- Experiment 1: Attend and Mentally Count

Participants were instructed to perform one of four experimental conditions in pseudo-randomized trials while receiving both VibT and MN stimulation. VibT stimulation occurred one at a time to either the left or right index fingers (average ISI= 4 s) at standard, high (170% of standard) or low (30% of standard) amplitudes. The first experimental condition, *No Task*, had participants visually fixating forward while receiving VibT and MN randomly to the right or left index finger without any behavioural requirements. The second experimental condition, *Count*, participants mentally counted backwards by seven (i.e. serial 7's) from a randomly determined number under the same visual fixation and stimulation parameters as the *No Task* condition. At the end of each *Count* trial, participants reported the number they had reached. Experimental condition three, *Attend Right*, instructed participants to mentally count high and low VibT stimuli to the right index finger under the same fixation and stimulation parameters as the *No Task* condition. For experimental condition four, *Attend Left*, participants were instructed to mentally count high and low VibT stimuli to the left index finger under the same fixation and stimulation parameters as the *No Task* condition. Participants reported the amount of high and low VibT stimuli to the attended finger at the end of each trial in both *Attend Right and Left* experimental conditions.

The testing session consisted of at least six trials of the four different experimental conditions. Each trial consisted of approximately 25 VibT and 150 MN stimulations lasting approximately ninety seconds for a total testing duration of approximately two hours including set-up.

Experimental Design – Experiment 2: Attend for Movement Preparation

Participants performed one of 3 experimental conditions in pseudo-randomized trials while receiving both VibT and MN stimulation. VibT stimulation occurred one at a time to either the left index or pinky (D5) finger (average ISI= 3.75 s) at standard, high (180% of standard) or low (30% of standard) amplitudes. The first experimental condition, *No Task*, had participants visually fixating forward while receiving VibT stimuli randomly to left index or little fingers with MN stimulation ~ 250 ms after VibT without any behavioural requirements. The second experimental condition, *Attend Index and Move*, instructed participants to detect high and low VibT stimuli to the left index finger and produce a pre-matched button-press sequence with the right hand (i.e. contralateral hand to MN stimulation) under the same fixation and stimulation parameters as the *No task* condition. The pre-matched button-press sequences were produced with digits two through five of the right hand on a commercially available button-press device (Compumedics Neuroscan, Charlotte, NC, USA). The movement sequences included seven sequential button-presses in accordance with digits two through five: 2-2-3-4-4-4-5 or 5-5-4-3-2-2-2. Each button-press sequence was pre-matched before experimental testing began and randomized for low and high VibT targets across participants. Each participant practiced at least four trials of the movement sequences without VibT or MN stimulation then at least two practice individual trials with VibT stimuli. For experimental condition three, *Self-initiated Movement*, participants were instructed to randomly produce one of the two button-press sequences approximately every 5 seconds under the same fixation and stimulation parameters as the *No task* condition.

The testing session consisted of at least three trials of the three different experimental conditions. Each trial consisted of approximately 75 VibT and MN stimulations lasting

approximately 280 seconds for a total testing duration of approximately two hours including set-up.

2.3.3. Stimulation and Recording

Participants were seated in a sound-attenuating booth with their arms resting on plexiglass platforms placed on the surface of a table that held custom-made VibT stimulation devices. VibT stimulation was delivered to the fingertips using a smooth plastic dowel (1 cm diameter) attached to a ceramic piezo actuator (Noliac North America Inc., Alpharetta, Georgia, USA). VibT stimulation devices vibrated at various amplitudes (see above) to change the force on the fingertips by passing fluctuating current via 25 Hz sine waves through the piezo actuator to the plastic dowel through analog speaker connections; each vibration lasted for 125 ms. VibT stimulation was controlled by digitally generated waveforms that were converted to an analog signal (DAQCard 6024E, National Instruments Corporation, Austin, Texas, USA) and then amplified (Bryston 2B-LP, Peterborough, Ontario, Canada). Changes in the forces on the fingertips were produced through variations of the amplitudes of the driving voltage using the waveforms generated in a custom software program (LabVIEW 8.5, National Instruments Corporation, Austin, Texas, USA). All participants were given earplugs attached to a computer producing 70 dB whitenoise from commercially available software (STIM2, Compumedics Neuroscan, Charlotte, NC, USA) throughout all experimental conditions to prevent auditory perception of VibT stimuli.

MN stimulation was delivered using two separate stimulation units (GRASS, S88X stimulator with SIU5 stimulus isolation unit or SD9, West Warwick, Rhode Island, USA) that delivered square wave pulses of 0.2 ms duration through surface electrodes with the anode distal

and fixed over each MN. In Experiment 1 *(Attend and Mentally Count)*, MN stimuli were delivered randomly during the experimental conditions at an average rate of 2 Hz (ISI range 0.4-0.8 s) to either the left or right MN. In Experiment 2 (*Attend for Movement Preparation*), MN stimuli were delivered to the left MN time-locked an average of 250 ms after the onset of each VibT stimulation (range 230-270 ms) during each experimental condition. The time-locking of MN stimulation to VibT stimulation in Experiment 2 *(Attend for Movement Preparation)* was used to capture the period close to VibT stimulation where attentional and movement preparation processes would be active. The voltage of MN stimulation was set before experimental testing as the smallest voltage sufficient to elicit a visible thumb twitch (i.e. motor threshold) individually for each the left and right MN.

SEPs were elicited from electrical stimulation of the MN at both left and right wrists randomly in Experiment 1 *(Attend and Mentally Count)* and left wrist in Experiment 2 *(Attend for Movement Preparation)*. Eleven electrode sites (FP1, FP2, FPZ, FCz, FC4, FC3, FZ, CZ, CPZ, CP4, CP3) of a 64-channel EEG cap (Quick- Cap, Neuroscan, Compumedics, USA) were used to measure the electrical activity from the surface of the scalp in accordance with the international 10-20 system for electrode placement referenced to linked mastoids. Impedances were below 5 kOhms and continuous EEG data was amplified (40, 000x), filtered (2-100 Hz) and digitized at 500 Hz (Neuroscan 4.3) before being stored on a computer for offline analysis.

2.3.4. Data Analysis

SEP data analysis

SEPs were extracted from continuous EEG data by averaging epochs time-locked to either the left or right MN stimulation (-50 to 200 ms). Individual traces were baseline corrected

(based on pre-stimulus period -50 to 0 ms) then visually inspected for artifacts including eye blinks, eye movements, muscle activity or alpha activity. Epochs that were contaminated by artifacts were eliminated before averaging.

Experiment 1 – Attend and Mentally Count

In Experiment 1, epochs were averaged based on experimental condition (one through four) and side of MN stimulation (left or right wrist). Two-way analyses of variance (ANOVAs) were performed separately for each frontal SEP amplitude and latency with factors experimental condition (*No Task, Count, Attend Right, Attend Left*), and side of MN stimulation (*Right or Left*) at their maximum amplitude electrode site, FCz. In contrast, one-way ANOVAs were used to measure parietal SEP amplitudes and latencies with factors experimental condition (*No Task, Count, Attend Right, Attend Left*) at CP3 electrode location that was maximal after *Right* MN stimulation and at CP4 electrode location that was maximal after *Left* MN stimulation.

Experiment 2- Attend for Movement Preparation

In Experiment 2, epochs were averaged based on experimental condition (one through three), target amplitude (high, low and standard) and site of finger stimulation (index or little finger). In Experiment 2, epochs where MN stimulation occurred after high or low VibT stimuli when responses were made were included in analyses. It should be noted that epochs where responses were made to standard amplitude VibT were also included but VibT stimuli (either low, high or standard) where no responses were made were excluded from these analyses. Furthermore, SEPs in Experiment 2 were separated into periods of movement and movement preparation during the *Self-Initiated Movement* condition. Due to the low number of stimuli

available during movement in these trials, these were eliminated from analyses. Thus, SEPs used in analyses from *Self-Initiated Movement* represent only SEPs collected during periods without any movement (i.e. movement preparation). Peak latencies and amplitudes relative to baseline were measured for the frontal P20, N30, N60 and parietal N20, P27, P50, P100 peaks using averaged epochs for each participant from the electrode sites that displayed the maximal amplitudes for frontal and parietal SEPs, FCz and CP3/CP4, respectively.

In Experiment 2, one-way ANOVAs were performed separately for each SEP amplitude and latency with factors experimental condition (*No Task, Attend Index and Move, Self-initiated Movement)* during index finger VibT and left MN stimulation at their respective electrodes; FCz for frontal SEPs and CP4/CP3 electrode for parietal SEPs. In addition, a separate secondary one-way ANOVA evaluated peak amplitudes and latencies with the factor experimental condition (*Attend Left Index and Move, No Task)* to evaluate MN stimulations that occurred after unattended little finger (D5) VibT stimulation. Tukey's post hoc comparisons were used to evaluate significant effects. An alpha level of 0.05 was used to define statistical significance for any effects.

Behavioural data analysis

Experiment 1- Attend and Mentally Count

In Experiment 1, the accuracy of detection was calculated by comparing the difference between reported and actual targets (high and low VibT stimuli) to the attended fingers in each of the Attend Right and Attend Left experimental conditions. A two-way ANOVA was performed with factors experimental condition (Attend Right, Attend Left*)* and VibT Target

Amplitude (High, Low) to determine if there were differences in the perceptual ability to detect and mentally count high or low targets between the left and right index fingers when attending to the digit. Error rate was calculated by dividing the total amount of errors by the actual amount of targets then multiplied by 100.

Experiment 2- Attend for Movement Preparation

In Experiment 2, for the *Attend Index and Move* condition, the amount of target misses were calculated by subtracting the actual amount of high and low VibT by the amount of responses made by each participant to high and low targets. The amount of false positives were calculated by summing the amount of responses to standard and index finger VibT non-targets. The total number of errors for each participant was calculated by summing the amount of target misses (for both high and low VibT targets) and false positives (for both standard and little finger VibT non-targets). The error rate for each participant was calculated by subtracting the amount of errors by the total # of VibT and multiplying by 100 (see Table 2.2).

Furthermore, reaction time (RT) and movement time (MT) were calculated for the *Attend Index and Move* condition in Experiment 2. RT was calculated for high targets, low targets and responses to standard non-targets as the time between the presentation of a VibT stimulus and first response made on the button-press device. MT was calculated as the total duration of button-presses made in sequence before the presentation of the next VibT stimulus. Response times (RespT) were calculated by summing RT and MT (see Table 3). A one-way ANOVA was performed for dependent measures RT and MT with the factor VibT target amplitude (High, Low, Standard) to determine if there were differences in the speed to detect VibT stimuli then respond to high or low targets compared to responses to standard non-targets.

2.4. Results

2.4.1. Experiment 1-Attend and Mentally Count

SEPs

No significant main or interaction effects were revealed for either of the frontal SEPs (N30 or P20) peak amplitudes or latencies ($p>0.05$) at FCz. Furthermore, no main effects between conditions were revealed for parietal SEPs (N20, P27, P50 or P100) peak amplitudes or latencies ($p>0.05$) at either CP3 (for right MN stimulation) (see Figure 2.1) or CP4 (for left MN stimulation) electrode locations).

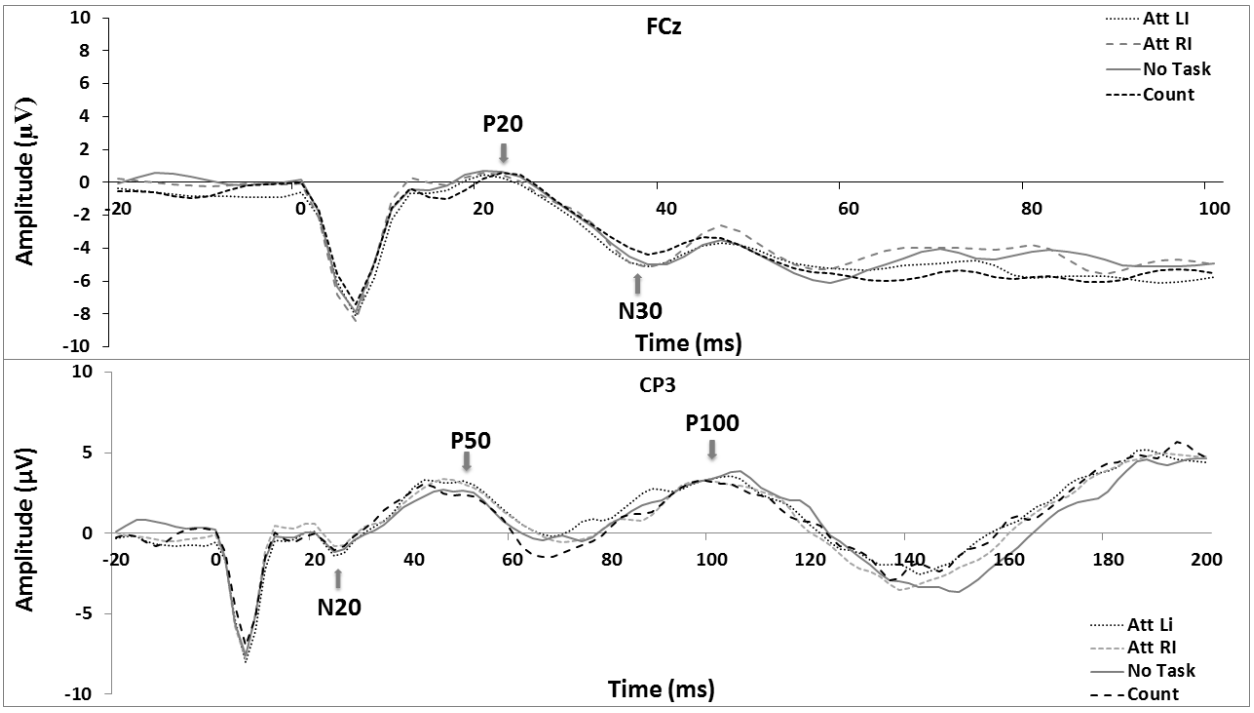

Figure 2.1 – Grand-averaged (n=8) waveforms (microvolts, uV) at (*Top)* FCz electrode and (*Bottom)* CP3 electrode comparing the effects between *Attend Right, Attend Left, Count* and *No Task* conditions after right MN stimulation for frontal and parietal SEPs, respectively.

Behavioural Data

The average error rate for participants was 20.6% (range 9-51.1%). No significant differences in the accuracy of detection was revealed between limb (left vs. right) or target amplitude (high vs. low) ($F(1,9)= 0.1$, $p=0.8$) (see Table 2.1).

Table 2.1 – Average and standard deviation of errors for high and low amplitude vibrotactile (VibT) targets determined by the difference between actual and reported amount of targets for participants (n=8) in the *Attend Left and Attend Right* conditions

Condition	Actual High VibT Targets	Reported High VibT Targets	Actual Low VibT Targets	Reported Low VibT Targets	Total Errors for High Targets	Total Errors for Low Targets
Attend Left	19 (+/- 5.3)	21 (+/- 7.9)	19.3 (+/- 5.6)	19.4 (+/- 8.9)	10.6 (+/- 7.6)	7.7 (+/- 4.7)
Attend Right	19.9 (+/- 5.9)	26.9 (+/- 7.3)	14.3 (+/- 5.7)	19.8 (+/- 9.9)	11.7 (+/- 7.1)	10 (+/- 7.9)
TOTAL	389	479	336	392	223	177

2.4.2. Experiment 2- Attend for Movement Preparation

Frontal N30 and N60

A significant main effect of condition was revealed for N30 peak amplitudes ($F(2,18)= 5.2$, $p=0.02$). Tukey's post hoc analysis revealed that N30 peak amplitudes were significantly suppressed (i.e. less negative) during the *Attend Index and Move* compared to the *No Task* condition ($p=0.02$). In addition, N30 peak amplitudes were approaching significantly smaller in *Attend Index and Move* compared to *Self-Initiated Movement* condition ($p=0.057$) (Figure 2.2). No significant difference in peak latency was observed for N30 peaks between conditions ($p>0.05$).

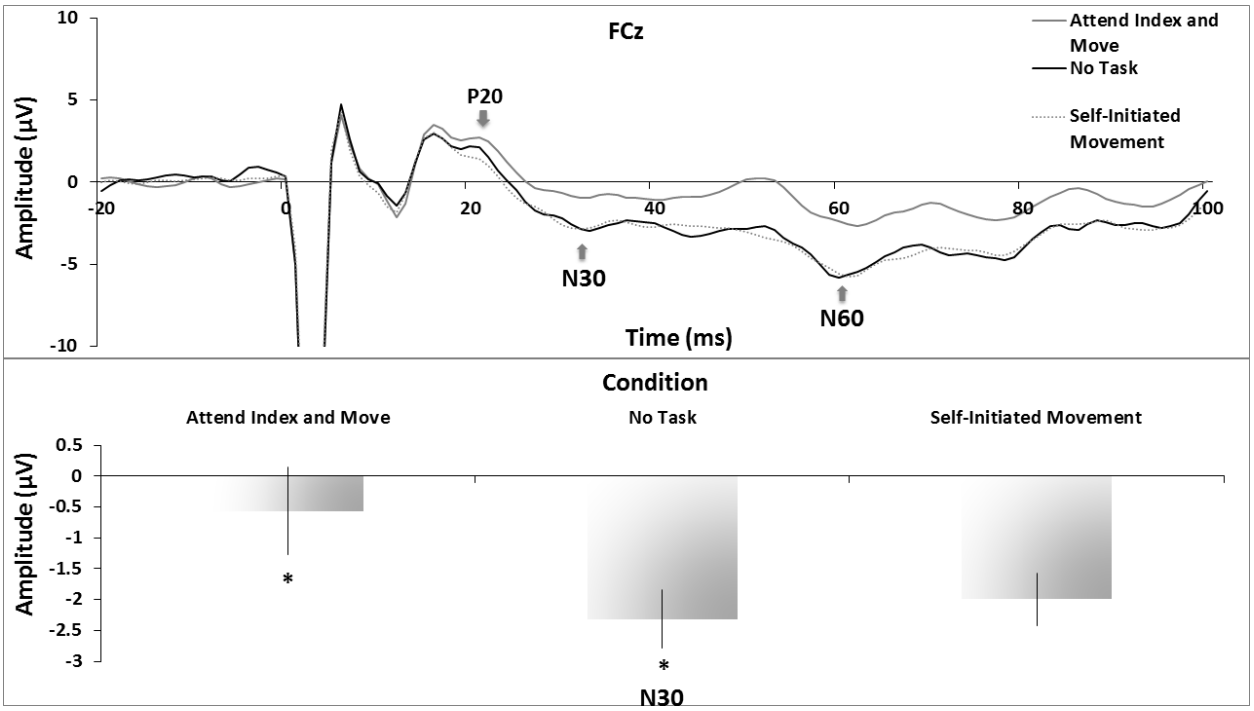

Figure 2.2 – (Top) Grand-averaged (n=10) waveform (microvolts, uV) of frontal SEPs and (Bottom) N30 mean peak amplitudes (with standard deviation) at FCz electrode comparing the effects of Attend Index and Move, Self-Initiated Movement and No Task conditions. Asterisks denote significant differences between conditions.

A significant main effect between conditions was revealed for the frontal N60 peak amplitude at FCz ($F(2,18)=22.8$, $p=0.000001$). Tukey's post hoc analysis revealed that frontal N60 peaks were significantly gated (less negative) during the *Attend Index and Move* condition compared to either *No Task* or *Self-Initiated Movement* conditions.

Frontal P20, parietal N20 and parietal P27

There were no significant differences between conditions for P20, N20 or P27 peak latencies or P20, N20 peak amplitudes ($p>0.05$). A significant main effect of condition was

revealed for P27 peak amplitude ($F(2,18)=3.9$, $p=0.04$). However, Tukey's post hoc analysis did not confirm any significant differences between conditions ($p>0.05$).

Parietal P50 and P100

Significant main effects of condition were revealed for P50 peak amplitudes ($F(2,18)= 9.9$, $p=0.001$) and peak latency ($F(2,18)= 5.3$, $p=0.02$) (see Figures 2.3 and 2.4). Tukey's post hoc revealed that P50 peak amplitudes were significantly larger during the *Attend Index and Move* condition compared to *No Task* or *Self-initiated Movement* conditions ($p<0.05$). Furthermore, Tukey's post hoc analysis showed that P50 peaks were significantly later during the *Attend Index and Move* condition compared to *No Task* or *Self-Initiated Movement* conditions at CP4.

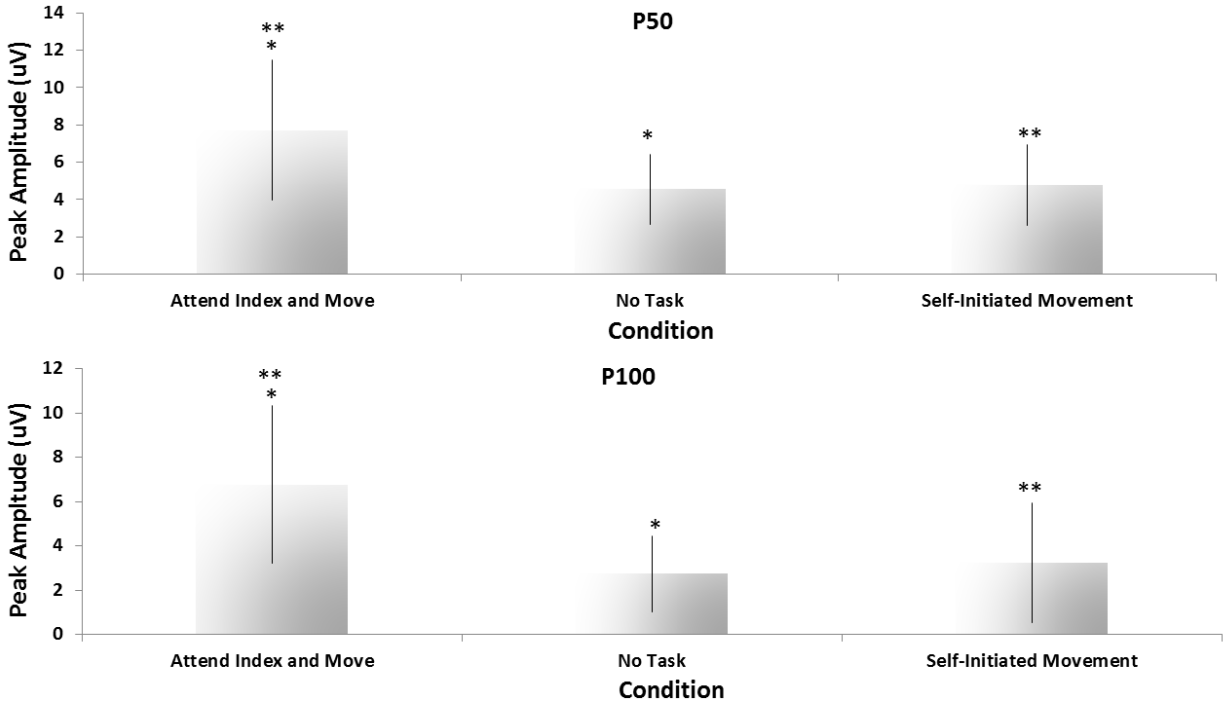

Figure 2.3 – Comparison of mean (n=10) peak amplitudes (with standard deviation) of (*Top)* P50 and (*Bottom*) P100 contralateral parietal SEPs at CP4 electrode after left MN stimulation between *Attend Index and Move, Self-Initiated Movement* and *No Task* conditions. Asterisks denote significant differences between conditions.

A significant main effect of condition was revealed for P100 peak amplitudes ($F(2,18)=14.7$ $p=0.0002$) (Figure 4). Tukey's post hoc analysis confirmed that P100 peak amplitudes were significantly larger during the *Attend Index and Move* condition compared to either *No Task* or *Self-Initiated Movement* conditions (see Figure 3 and 4). No significant differences were observed for the P100 peak latency between conditions at CP4 ($p>0.05$).

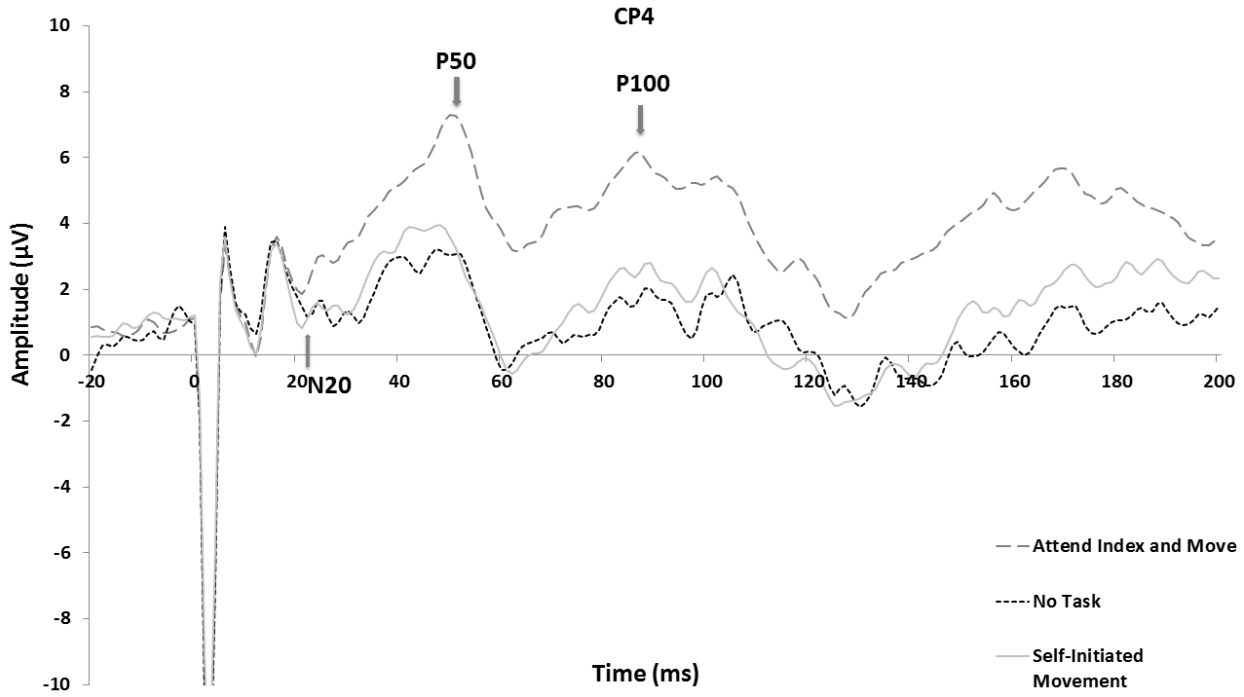

Figure 2.4- Grand-averaged (n=10) waveforms (microvolts, uV) of contralateral parietal SEPs at CP4 electrode comparing the effects of *Attend Index and Move*, *Self-Initiated Movement* and *No Task* conditions.

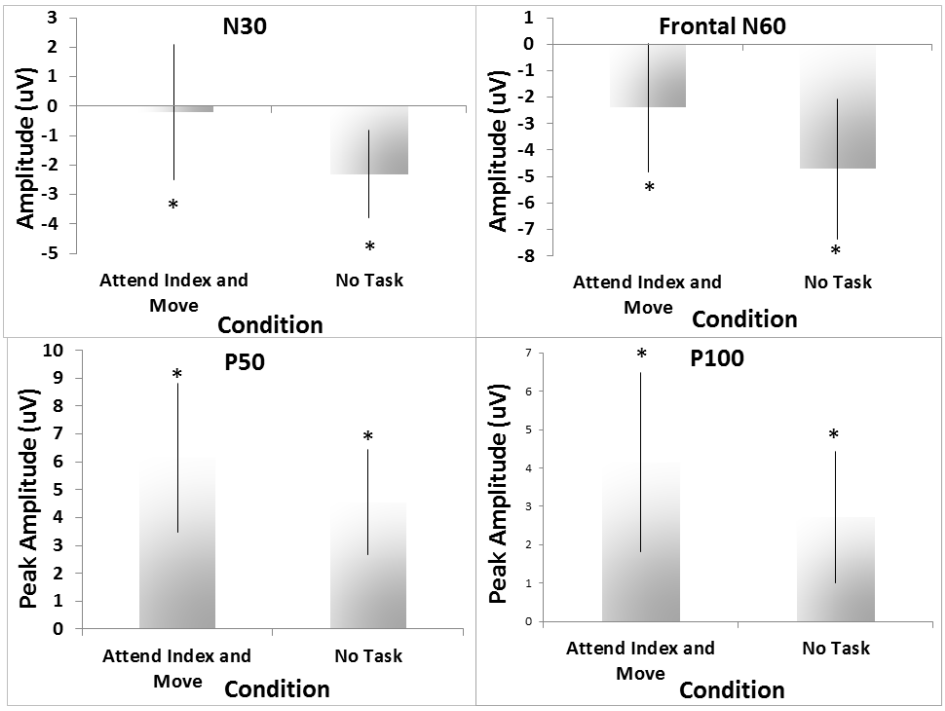

Figure 2.5 – Mean (n=10) peak amplitude (with standard deviation) of (*Top Left)* N30 and (*Top Right*) N60 peaks at FCz electrode as well as (*Bottom Left)* P50 and (*Bottom Right*) P100 peaks at CP4 electrode with left MN stimulation after unattended little finger (D5) stimulation in *Attend Index and Move* compared to *No Task* condition. Asterisks denote significant differences between conditions.

SEPs after little (D5) finger VibT stimulation

In the secondary analysis, frontal and parietal SEPs were evaluated when MN stimulation occurred after unattended little (D5) finger VibT stimulation in either the *Attend Index and Move* or *No Task* conditions (see Figure 2.5). No significant main effect of condition was revealed for peak latency of any peak (N30, P20, N60, N20, P27, P50 and P100). A significant main effect of condition was determined for N30 peak amplitude at FCz ($F(1,9)=34.16$, $p=0.0002$). As demonstrated in Figure 2.5, N30 peak amplitudes were significantly gated (i.e. less negative) in the *Attend Left Index and Move* compared to *No Task* condition. There was also a significant

main effect of condition for frontal N60 peak amplitude at FCz ($F(1,9)= 21.0$, $p=0.001$) which revealed frontal N60 peaks were significantly suppressed (less negative) in the *Attend Index and Move* compared to *No Task* condition.

In addition, a significant main effect of condition was revealed for P50 peak amplitudes at CP4 ($F(1,9)=11.9$, $p=0.007$) demonstrating that P50 peak amplitude was significant larger in the *Attend Index and Move* (6.2 μV) compared to the *No* Task (4.6 μV) condition. A significant main effect of condition was also revealed for P100 peak amplitude at CP4 electrode ($F(1,9)=11.3$, $p=0.008$). P100 peak amplitude was significantly enhanced in the *Attend Left Index and Move* compared to *No task* condition. No significant main effect of condition revealed for peak amplitude of frontal P20 or parietal N20, or P27.

Behavioural Data

The average error rate for participants was 19.1% (range 3.6-40.2%) (see Table 2.2). In the *Attend Index and Move* condition, significantly slower RT was observed to non-target standard VibT stimuli compared to low or high target VibT stimuli ($F(2,18)=21.4$, $p>0.0001$) (see Table 2.3). However, MT was significantly faster to standard non-target VibT stimuli compared to either high or low target VibT stimuli. Furthermore, MT was faster to high target VibT stimuli compared to low VibT stimuli ($F(2,18)=9.7$, $p>0.01$).

Table 2.2 – The average and standard deviation (n=10) of errors and error rate in the *Attend Index and Move* condition determined through target misses to target virbotactile (VibT) stimuli and false positives to non-target VibT stimuli

	Target Misses	False Positives	Total Errors	Error Rate (%)
	23.4 (+/- 13.1)	53.1 (+/- 43.5)	76.5 (47.4)	19.1 (+/- 12.0)
TOTAL	234	531	765	

Table 2.3 – Reaction time (RT), movement time (MT) and response time (Rest) (ms) measured for all participant's (n=10) responses to high target, low target and standard non-target vibrotractile (VibT) stimuli in the *Attend Index and Move* condition

	Reaction Time (RT) (ms)	Movement Time (MT) (ms)	Response Time (RespT) (ms)
High Targets	1051 (+/- 358)	1992 (+/- 332)	3042 (+/- 690)
Low Targets	1056 (+/- 371)	2063 (+/- 337)	3119 (+/- 708)
Standard Non-Targets with Response	1436 (+/- 518)	1846 (+/- 295)	3283 (+/- 814)

2.5. Discussion

The novel finding of the current study was that the frontal N30 peaks, elicited by left MN stimulation, were gated during the early stages of movement preparation (~250 ms after stimulus presentation) when individuals attended to VibT input that was relevant to plan and execute movement sequences with the dominant limb that was contralateral to MN stimulation. However, frontal N30 peak amplitudes were not influenced by covertly directing attention to a spatial location when individuals were only required to mentally count VibT input but no movement was planned or executed. Furthermore, significant enhancements in both P50 and P100 components as well as significant suppression of frontal N60 peaks were also revealed when individuals directed attention to VibT input that was relevant to plan and execute movement sequences. Interestingly, secondary analyses demonstrated the same significant modulation for all these peaks with unattended D5 stimulation but these effects were less than those observed when attention was directed towards the index finger.

2.5.1. Gating effects on frontal SEPs

There have been conflicting results as to the origin of the frontal N30 based on intracerebral recordings in humans. Direct near-field recordings after transcutaneous MN stimulation have revealed activity representative of the frontal N30 dorsolaterally (representative of dorsal premotor cortex, PMd) and medially in Brodmann's area 6 (representative of the SMA) (Kaňovský et al., 2003). However, intracortical recordings from pre-surgical epileptic patients only identified far-field N30 potentials in the SMA-proper from contralateral MN stimulation (Barba et al. 2003, 2005). Furthermore, intracortical recordings using stereotactically implanted electrodes in the human pre-SMA did not record any clear near-field potentials before 50 ms

(only volume conducted potentials from superficial scalp) after contralateral or ipsilateral MN stimulation (Barba et al. 2001, 2005). Recent research using repetitive TMS (rTMS) and continuous theta burst stimulation (cTBS) support that the SMA and premotor cortex (PMC) are involved in the generation of frontal N30 SEPs. cTBS over the SMA (i.e. over electrode FCz) resulted in gating of the frontal N30 but had no effects on parietal SEPs (Legon et al., 2013). Similarly, low-frequency (0.2 Hz) monophasic rTMS over the PMC increased N30 peak amplitudes that were associated with increased regional cerebral blood flow in both PMC and prefrontal cortex (Urushihara et al., 2006). However, increases in N30 peak amplitudes were not observed after rTMS to M1, SMA or after 1 Hz rTMS to PMC (Urushihara et al., 2006). It was argued that the differential effects after 1 Hz compared to 0.2 Hz rTMS may have resulted due to the use of monophasic compared to biphasic pulses (Urushihara et al., 2006). Furthermore, cTBS to the left M1 resulted in increases in the parietal P25/N33 peaks following right MN stimulation for 53 minutes whereas cTBS to a location 2 cm posterior (representative of SI) resulted in suppression of the same peaks for 13 minutes (Ishikawa et al., 2007). Interestingly, only small insignificant increases and decreases were observed on the P22/N30 peaks with left M1 cTBS and left SI cTBS, respectively (Ishikawa et al., 2007). Based on these findings, it is likely that there exist several neuronal populations within non-primary motor areas such as the PMd and SMA that contribute to the generation of the frontal N30 but the extent of neuronal representation depends on the individual.

Importantly, the contribution of the premotor areas to the generation of the frontal N30 SEP has been supported by evidence in the frequency domain. Research has demonstrated significant phase-locking (i.e. inter-trial coherence, ITC) as well as power enhancement (i.e. event-related synchronization, ERS) in the beta/gamma frequency band (25-35 Hz) peaking at a

frequency of ~30 Hz within the latency range of the frontal N30 component (Cheron et al., 2007). These results suggest that both phasic neuronal activation as well as phase resetting of ongoing neural beta/gamma oscillatory activity contribute to frontal N30 components. Cebolla et al., (2011), using an advanced dipole source localization method, determined that the frontal SEP in the time domain involved generators in M1 through the premotor cortex extending to the prefrontal cortex (BA 9). In the frequency domain, the beta/gamma power (ERS) increase involved M1 and premotor cortex while increased phase-locking (ITC) involved all 3 of these areas. It was argued that the frontal N30 may involve oscillatory generators in M1, PMC and prefrontal cortex that are involved in phase-locking the basal ganglionic-thalamo-cortical loop at beta/gamma frequency, in addition to phasic generators in M1 and PMC that are recruited after peripheral somatosensory stimulation (Cebolla, Palmero-Soler, Dan, & Cheron, 2011).

It has commonly been reported that N30 peaks are gated during preparation, execution or imagination of movements that are ipsilateral to MN stimulation (Starr and Cohen 1985; Cheron and Borenstein 1987, 1991, 1992; Cohen and Starr 1987; Tapia et al. 1987; Rossini et al. 1996, 1997, 1999; Waberski et al. 1999; Legon et al. 2008, 2010; Cebolla et al. 2009). For example, frontal N30 SEPs were gated following MN stimulation to left wrist 100 ms after EMG burst of a rapid self-initiated left digit flexion (Cheron & Borenstein, 1987). In contrast, previous research has revealed that frontal N30 peaks are enhanced during contralateral movements such as repetitive opposition movements with the ulnar fingers and thumb (Rossini et al., 1997) and repetitive non-dominant limb self-paced gripping movements (Legon et al., 2010, 2008). It was argued that enhancements of frontal N30 SEPs during repetitive self-paced gripping movements that were contralateral to MN stimulation may result due to increased activation in a network involving the basal ganglia, ipsilateral M1 and SMA (Legon et al., 2010).

Several differences in the current experimental task may provide an explanation of the different mechanism responsible for the current findings (i.e. gating of frontal N30) compared to previous work (Rossini et al. 1997; Legon et al. 2008, 2010). Traditionally, it has been proposed that gating effects on SEPs such as the frontal N30 are caused by cortical centrifugal mechanisms rather than subcortical or centripetal (i.e. peripheral) processes (Cheron & Borenstein, 1987; Cohen & Starr, 1987). Centrifugal gating effects may be caused by active motor neurons (that would be involved in the generation of the SEPs) inability to discharge to somatosensory input since they are already active for movement (Cohen & Starr, 1987). An alternative explanation may be that corticocortical inhibition results from active motor neurons that may suppress the activity of neurons involved in the generation of SEPs (Cohen & Starr, 1987). Thus, the gating effects of frontal N30s revealed during the current study when attending to VibT at the index finger to plan and execute finger sequence movements may involve centrifugal mechanisms originating from the SMA and/or PMd in the contralateral hemisphere that are active during the movement sequence preparation suppressing the generators of the frontal N30.

One possible explanation for the centrifugal mechanism contributing to the gating when individuals prepared contralateral finger sequences to attended VibT stimuli rather than enhancement of the frontal N30 during repetitive contralateral gripping may be associated with the increased activity related to complexity of preparing movement sequences. Imaging research has revealed increased blood flow in motor areas such as the rostral SMA (i.e. pre-SMA) and ipsilateral M1 as the complexity of movement increases during the execution of overlearned movement sequences (Boecker et al., 1998). Furthermore, increased blood flow was also correlated to movement sequence complexity in the basal ganglia including the bilateral globus

pallidus and putamen (Boecker et al., 1998). Interestingly, previous research has demonstrated that N30 peak amplitudes are significantly depressed and even sometimes absent in individuals with Parkinson's disease (Bostantjopoulou et al., 2000; Cheron, Piette, Thiriaux, Jacquy, & Godaux, 1994; Cheron, 1999; Garcia, Aminoff, & Goodin, 1995; Pierantozzi et al., 1999; Rossini, Bassetti, & Pasqualetti, 1995; Rossini, Babiloni, et al., 1989; Ulivelli et al., 1999) although movement gating effects are typically preserved (Cheron et al., 1994). Furthermore, apomorphine (dopamine-agonist) injection (Pierantozzi et al., 1999; Rossini et al., 1995; Ulivelli et al., 1999) as well as deep brain stimulation of the internal globus pallidus or subthalamic nucleus (Pierantozzi et al., 1999) increases N30 peak amplitudes. Altogether, these studies support that the basal ganglia have a modulatory role on the generators of the frontal N30. Thus, increased activity in neurons in pre-SMA or basal ganglia during preparation of movement sequences may have resulted in a reduction of activity in relation to somatosensory input and/or corticocortical inhibition on the generators of the frontal N30 in the SMA and PMd. This notion is supported by previous imaging research that revealed increased BOLD responses in the bilateral SMA when attending to tactile stimuli at the fingers compared to tactile stimuli at the unattended finger (Galazky et al., 2009). It was argued that somatosensory attentional effects are closely associated with movement preparatory processes (Galazky et al., 2009), which would be supported by the current results.

Importantly, investigation of gating effects on frontal N30 components in the frequency domain during finger movement of the same (ipsilateral) limb as median nerve stimulation would support a similar network. Cebolla and colleagues (2009) demonstrated that both phase-locking (ITC) as well as the power increase (ERS) of the beta/gamma band oscillatory activity (at 30 Hz) were reduced within the latency range of the frontal N30 peak amplitude. It was

concluded that decreases in N30 peak amplitude during ipsilateral movement may occur due to disrupted phase-locking and synchronization of neurons in the beta/gamma frequency that may result from increased excitation in premotor and motor areas in the same hemisphere (Cebolla et al., 2009). Furthermore, Cebolla *et al.* (2014) applied MN stimulation during the observation of another person's wrist movement and revealed increased frontal N30 peak amplitude that was accompanied by increased fronto-central alpha and fronto-parietal beta and frontal gamma power as well as fronto-central phase locking of alpha frequency. It was concluded that a complex network involving precentral, postcentral and parietal cortical areas can contribute to the modulation of activity at the latency of the frontal N30 component (Cebolla, Palmero-Soler, Dan, & Cheron, 2014). Thus, it is possible that the observed frontal N30 amplitude reductions when individuals attended to VibT stimuli that were used for preparing contralateral movements could reflect similar altered phase-locking and synchronization of beta/gamma or alpha oscillatory activity involving a network that includes premotor areas, M1 and prefrontal areas.

2.5.2. Effects of covert spatial attention and prefrontal activity on frontal and parietal SEPs

It is well-established that the prefrontal cortex is part of the top-down attentional system in combination with parietal areas that are involved in directing resources to stimuli to facilitate sensory processing when there is a predetermined goal or at an expected location (Corbetta & Shulman, 2002; Hopfinger et al., 2000; Petersen & Posner, 2012; Staines, Graham, Black, & McIlroy, 2002). As revealed in Experiment 1 (*Attend and Mentally Count)*, no effects on frontal N30 SEPs were revealed when individuals selectively direct covert attention to somatosensory input at a spatial location in support of previous work (Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004). Garcia-Larrea et al. (1991) did not find an influence of

selective spatial attention on the frontal N30 using a paradigm that delivered mechanical taps to direct attention to the same index finger as electrical stimulation. Furthermore, no modulatory effects were revealed on the frontal N30 when directing attention to MN stimulation by having participants silently count the number of MN stimuli (Kida, Nishihira, Wasaka, Sakajiri, et al., 2004). Altogether, these results support that covertly directing attention to somatosensory stimuli at a specified location does not enhance afferent somatosensory input into non-primary motor areas when no movement is involved.

The prefrontal cortex is also actively involved in the suppression of non-attended and distracting stimuli (Bolton & Staines, 2011; Knight et al., 1999). It was previously shown that patients with unilateral lesions to the prefrontal cortex (centered around Brodmann's areas 9 and 46) demonstrated increased frontal SEPs around 30 ms (frontal N28) at rest compared to control participants (Yamaguchi & Knight, 1990). It was suggested that the prefrontal cortex (Brodmann's areas 9 and 46) may contribute to inhibitory modulation of somatosensory processing in non-primary motor areas (Yamaguchi & Knight, 1990). Interestingly, significant gating of the frontal N30 was revealed in the secondary analysis in Experiment 2 when MN stimulation followed vibrations to the left pinky (D5) finger when attention was directed towards the index finger (compared to passive stimulation in the No Task condition). This evidence supports an active role of the prefrontal cortex in suppressing early somatosensory stimuli in the non-primary motor areas at an unattended location. Anatomically, the dorsal premotor cortex (PMd) and ventral premotor cortex (PMv) have dense connections with the prefrontal cortex (Barbas & Pandya, 1987; Chouinard & Paus, 2006; Selemon & Goldman-Rakic, 1988). Despite previous reports of connections between the supplementary motor area-proper (SMA) and prefrontal cortex (Goldman-Rakic, 1987; Selemon & Goldman-Rakic, 1988), retrograde labeling

in the macaque monkey have identified that only the rostral portion of the SMA (pre-SMA) have dense connections with the prefrontal cortex whereas the caudal portion of the SMA (SMA-proper) have limited connections (Luppino et al., 1993). Thus, it may be possible that increased activity in the prefrontal cortex through its connections with non-primary motor areas (i.e. PMd or pre-SMA) could contribute to gating N30 peaks that was observed in Experiment 2 *(Attend for Movement Preparation)* when individuals directed attention to VibT stimuli that was used to prepare and execute contralateral finger sequences.

The prefrontal cortex may also have a role in the gating observed in Experiment 2 when individuals attended to vibrations at the index finger in preparation of movement albeit through a different functional mechanism. Previous research has revealed increased blood flow in the dorsolateral prefrontal cortex (Brodmann's areas 9, 10 and 46) during movements that require greater decision-making such as self-initiated finger extensions compared to auditory-cued movements (Jahanshahi et al., 1995). Furthermore, recent imaging research also found that the medio-orbital frontal cortex (including Brodmann's areas 10 and 46) was particularly active when there was an increased demand on timing the initiation of a sequence of finger movements (Bortoletto & Cunnington, 2010). Thus, it is possible that the prefrontal cortex contributed to the modulation of sensory input in non-primary motor areas in the current task due to the increased activity related to the complexity of preparing movement sequences with a strict demand on initiating the movements before the subsequent VibT stimulus. A frontoparietal executive control system mediated by the lateral prefrontal cortex has been revealed to stimuli that cue the initiation or switching of tasks that is separate from the top-down system involved in the orienting of attention (Dosenbach et al., 2007; Petersen & Posner, 2012). This may be an additional explanation for the gating of frontal N30 SEPs revealed during the current study when

attending to somatosensory input that was used in a movement response compared to the enhancement of frontal N30 SEPs previously demonstrated with repetitive movements contralateral to MN stimulation (Legon et al. 2008, 2010).

Interestingly, the gating of frontal N30 peaks in Experiment 2 were found with parallel increases in the amplitudes of the P50 and P100 peaks when attention was directed to the VibT input at the index finger that was used in the preparation of contralateral finger sequences. Previous research has shown attentional effects on parietal SEPs while using tactile stimulation to the digits rather than MN stimulation at the wrist (Desmedt & Tomberg, 1989; Eimer & Forster, 2003; Garcia-Larrea et al., 1991; Schubert et al., 2008; Zopf et al., 2004). However, directing attention to electrical (rather than tactile) stimulation at the digits can increase the amplitude of several parietal SEPs including the P50 and P100 peaks in the hemisphere contralateral to electrical stimulation (Desmedt & Tomberg, 1989; Eimer & Forster, 2003; Garcia-Larrea et al., 1991; Schubert et al., 2008; Zopf et al., 2004). Imaging research has shown that increased amplitudes of SEP components (P50, N80 and P100) during spatial selective attention are mediated by increased BOLD signals in both SI and SII in the hemisphere contralateral to electrical finger stimulation (Schubert et al., 2008). Source analysis using magnetoencephalography (MEG) have revealed that the brain response peaking 80 ms after stimulus onset was localized over a lateral region of the parietal cortex in the area SII (Bauer, Oostenveld, Peeters, & Fries, 2006). Thus, the enhancement of P50 and P100 peak amplitudes in the hemisphere contralateral to MN stimulation that was applied following vibration to attended index finger in Experiment 2 were typical of attentional enhancement of afferent input in SI and SII.

In the secondary analysis, enhancement of P50 and P100 SEPs was revealed when MN stimulation followed pinky (D5) finger VibT stimulation when attention was directed towards the index finger. Imaging research has identified that activations in SII are observed to non-attended somatosensory stimuli regardless of location of attentional focus (Galazky et al., 2009; Meador, Allison, Loring, Lavin, & Pillai, 2002). Furthermore, increased P100 SEPs to unattended vibrotactile stimuli have previously been demonstrated after application of inhibitory cTBS over the dorsolateral prefrontal cortex (Bolton & Staines, 2011). The increased P50 and P100 SEPs elicited by MN stimulation after unattended pinky (D5) finger vibrotactile stimulations could represent a decreased ability of the prefrontal cortex to filter out this sensory information in SI and SII, respectively. This effect cannot be explained by automatic orientation to the MN stimulation driven by the bottom-up attentional system that is lateralized to the right hemisphere (Corbetta & Shulman, 2002; Petersen & Posner, 2012). Enhancements in P100 SEPs have been demonstrated after electrical stimulation of the digits when stimuli are presented infrequently against a silent background supporting a potential role of bottom-up orienting of attention during active attention tasks (Kida, Nishihira, Wasaka, Nakata, & Sakamoto, 2004; Kida, Wasaka, Nakata, Akatsuka, & Kakigi, 2006a). However, the same bottom-up system would be active during the *No Task* condition suggesting that these effects are likely primarily caused by top-down attentional modulation mediated by the prefrontal cortex. Future research is needed to clarify the mechanisms to which the prefrontal cortex may have in filtering out unattended somatosensory input in SI and SII during active attention tasks.

2.6. Conclusion

Frontal N30 peaks were gated while parietal P50 and P100 were enhanced during early movement preparation when attending to VibT input that was relevant for planning and executing movement sequences with the dominant limb contralateral to MN stimulation. These same effects were not revealed when attending to VibT input that was irrelevant for movement. Based on these findings, increased corticocortical inhibition likely contributed to the reduction of somatosensory input in the non-primary motor areas (i.e. gating of N30 peaks) from increased neural activity in areas such as pre-SMA, PMC, basal ganglia and/or prefrontal cortex. If the prefrontal cortex contributes to gating N30 peaks, it is likely that this modulation occurs through its dense projections to the PMC and pre-SMA (Barbas & Pandya, 1987; Chouinard & Paus, 2006; Luppino et al., 1993; Selemon & Goldman-Rakic, 1988). In contrast, increased activity in the prefrontal cortex likely also contributed to corticocortical enhancement (via disinhibition or excitation) of the somatosensory input in SI and SII (i.e. P50 and P100 peaks).

Chapter 3 - Somatosensory input to non-primary motor areas is enhanced during preparation of cued contralateral finger sequence movements.

Adapted from: Brown, M.J.N., and Staines, W.R. (2015). Somatosensory input to non-primary motor areas is enhanced during preparation of cued contralateral finger sequence movements. *Behavioral Brain Research, 286, 166-174.*

Chapter Research Objectives

The goals of this chapter were to confirm results from Chapter 1 (specific research questions 1 and 4) as well as answer specific research questions 2 and 5 (see section 1.5) related to the temporal nature of SEP modulatory effects.

3.1. Abstract

Frontal N30 somatosensory evoked potentials (SEPs) represent early somatosensory input into non-primary motor areas. Importantly, modulations of frontal N30 SEPs can provide insight into the mechanisms involved in sensory processing for movement control. Enhancements of frontal N30 SEPs have been revealed during repetitive but not during the preparation of movements that are contralateral to median nerve (MN) stimulation (i.e. contralateral movements). Importantly, these enhancements during contralateral movements may be dependent on increased activity in several neural areas such as the primary motor cortex (M1),

supplementary motor area (SMA) and basal ganglia (BG). Furthermore, research has also shown that patients with prefrontal lesions have enhanced early frontal SEPs (i.e. N28) at rest supporting a role of the prefrontal cortex in inhibitory modulation of early somatosensory input. The current study evaluated whether differential modulations of frontal N30 SEPs occurred during different time periods when individuals prepared and executed contralateral (right) finger sequences to attended vibrotactile (VibT) stimuli at the left index finger. SEPs were measured to median nerve (MN) stimuli elicited at the left wrist and MN stimuli were time-locked in four different periods relative to VibT onset (during pre-stimulus, early response preparation, late movement preparation and movement execution). Results revealed that frontal N30 SEPs were significantly enhanced when MN stimulation occurred in the late preparatory and/or early movement execution period (~750 ms) after the attended VibT stimuli. This result supports that increases in frontal N30 amplitudes during contralateral movements are dependent on the complexity of preparing and executing finger sequences, which is associated with increased activity in several neural areas such as the non-primary motor areas, prefrontal cortex and BG. Furthermore, enhanced N30 SEPs during contralateral movement preparation and execution may be a necessary mechanism to decrease sensory gating to facilitate somatosensory processing in non-primary motor areas when there is a 'noisy' environment.

3.2. Introduction

Sensorimotor integration involves selective extraction of relevant sensory input and suppression of irrelevant or distracting information (i.e. sensory gating) to effectively plan and execute movements. Importantly, abnormal sensory gating has been associated to atypical movement control in various disorders including delayed response deficits in prefrontal lesion

patients (Knight et al., 1999) and slow, bradykinetic movements in basal ganglia disorders such as Parkinson's diseases (Abbruzzese & Berardelli, 2003). Thus, it is important to understand the mechanisms contributing to modulations of sensory input for movement control.

Frontal N30 somatosensory evoked potentials (SEPs) have frequently been recorded by surface electrodes over non-primary motor areas after transcutaneous electrical stimulation of the median nerve (MN) (Cheron & Borenstein, 1987, 1991, 1992; Cohen & Starr, 1987; Legon et al., 2010, 2008; Rossini et al., 1996, 1999; Starr & Cohen, 1985; Tapia et al., 1987; Waberski et al., 1999). It is well-established that the frontal N30 is gated during preparation, execution or imagination of movements to the same limb as MN stimulation (i.e. ipsilateral movements) (Cebolla et al., 2009; Cheron & Borenstein, 1987, 1991, 1992; Cohen & Starr, 1987; Legon et al., 2010, 2008; Rossini et al., 1996, 1999; Starr & Cohen, 1985; Tapia et al., 1987; Waberski et al., 1999). In contrast, previous research has also shown that N30 peaks are enhanced during the execution of contralateral repetitive finger-to-thumb opposition movements (Rossini et al., 1997) and during self-paced gripping (Legon et al., 2008). Furthermore, it was revealed that the facilitation of the N30 peaks occur predominantly during contralateral non-dominant rather than dominant limb self-paced gripping (Legon et al., 2010). It was hypothesized that these facilitatory effects on N30 peaks during non-dominant hand movements resulted from increased activity in supplementary motor area (SMA), primary motor cortex (M1) and basal ganglia (BG) (Legon et al., 2010). However, it is currently unclear if this mechanism (i.e. increased activity in SMA, M1 and/or BG) is responsible for facilitating N30 peaks.

One way to investigate this hypothesis is through the evaluation of SEP modulation during the preparation and execution of movements that are known to recruit and increase activity in these neural areas. Previous imaging research has identified increased blood flow in

several neural areas including the rostral supplementary motor area (pre-SMA), ipsilateral primary motor cortex (M1) and basal ganglia when preparing and executing movement sequences with increased complexity (Boecker et al., 1998). Thus, it appears that the frontal N30 peaks could be modulated by the preparation and execution of sequential finger movements compared to repetitive contralateral movements. In addition to motor areas, imaging research has also identified increased activity in the prefrontal cortex (Brodmann's areas 9, 10 and 46) during movements that require greater executive control such as timing the initiation of movements or more difficult sequential movements (Bortoletto & Cunnington, 2010; Jahanshahi et al., 1995). Furthermore, the prefrontal cortex has also been linked to both the extraction of relevant and inhibition of distracting sensory stimuli (Knight et al., 1999). Interestingly, previous research demonstrated that amplitude of frontal SEPs around 30 ms (frontal N28) increased in unilateral prefrontal lesion patients (involving Brodmann's areas 9 and 46) at rest compared to control participants (Yamaguchi & Knight, 1990). These findings suggest that the prefrontal cortex may be involved in inhibitory modulation of early somatosensory processing in non-primary motor areas (Yamaguchi & Knight, 1990). However, previous manipulations of selective spatial attention have not revealed amplitude modulations of frontal N30 SEPs (Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004). Thus, it is currently unclear what role the prefrontal cortex has in modulating frontal N30 peaks in healthy adults.

The current study investigated amplitude modulations of frontal N30 peaks during contralateral (right) finger sequences that were cued by somatosensory input at an attended location. The current experimental paradigm measured SEPs to MN stimulations that were elicited during four different periods (pre-stimulus, early response selection, late movement preparation and movement execution) during the vibrotactile cued response task. This

experimental protocol was different compared to previous SEP gating experiments since index finger vibrations were used to direct attention and cue movement rather than the MN stimuli themselves or alternatively, epoching MN stimulation during self-paced movements. The current paradigm provided two major advantages compared to previous protocols of SEP gating: 1) experimental manipulations of attention to index finger vibrations (rather than MN stimuli themselves) allowed investigating the timing of attentional and movement-related modulatory effects but maintained spatial attention to somatosensory input to the left hand MN representation, and 2) the cued-response task allowed for attended somatosensory input to be relevant for movement that would not be possible when epoching MN stimulation during self-paced movement. Thus, the time-locking of MN stimulation during the cued response task allowed the investigation of SEP modulation that would be associated with different neural activity in particular regions during each period: a) prefrontal mediated activity during pre-stimulus anticipatory period (Funderud et al., 2013; Haegens et al., 2011), b) increased activity in prefrontal (Pleger et al., 2006) and non-primary motor areas during early response selection and late movement preparation (Cunnington, Windischberger, & Moser, 2005; Ikeda et al., 1999), and d) in primary motor cortex during movement (Cunnington, Windischberger, Deecke, & Moser, 2002). It was hypothesized that the amplitude of frontal N30 peaks would be modulated in each period as follows: a) enhanced during anticipatory period as a result of disinhibitory attentional effects, b) gated during early response selection and late movement preparation mediated by widespread increased activity in both prefrontal and non-primary motor areas associated with the executive control and planning of movements and c) enhanced during movement execution as a result of increased activity in the contralateral primary motor areas.

3.3. Methods

3.3.1. Participants

Ten right-hand dominant healthy adults (five males, aged 27 +/- 3.6 years old; range 21-33 years old) were recruited and provided written informed consent to participate in the experiment. The University of Waterloo Office of Research Ethics Board approved all experimental procedures used in the current study.

3.3.2. Experimental Task

The behavioural task required participants to detect vibrotactile (VibT) stimuli at an attended (i.e. left index finger, D2) or ignore distracting stimuli to an unattended location (i.e. left pinky finger, D5) and determine whether attended VibT stimuli were standard, high or low amplitude. If participants perceived VibT stimuli as low or high amplitude at the attended D2 (i.e. targets), they would execute a pre-matched finger sequence movement with the contralateral (right) hand corresponding to the perceived high or low stimuli. In contrast, if participants perceived standard amplitude VibT or VibT stimuli to the unattended D5 location no response was required. Overall, the VibT stimulation paradigm applied frequent non-targets (65%) (standard amplitude to attended location and stimuli to the unattended D5) and infrequent targets (35%) (high and low amplitude to attended D2) during the experimental conditions. Furthermore, transcutaneous electrical stimulation of the median nerve (MN) at the left wrist occurred throughout the experiment, but was irrelevant for the behavioural aspect of the task.

3.3.3. Experimental Design

Participants were instructed to perform one of two experimental conditions in pseudo-randomized trials while receiving both VibT and MN stimulation. The first experimental condition, *No Task*, had participants visually fixating forward while receiving VibT randomly to left D2 or D5 fingers with time-locked MN stimulations (see below) without any required behavioural response. In the second experimental condition, *Attend Index and Move*, participants were instructed to detect high and low VibT stimuli to left D2 and respond with a pre-matched finger sequence with the right hand (i.e. contralateral hand) under the same fixation and stimulation parameters as the *No Task* condition. The pre-matched finger sequences were produced with digits two through five of the right hand on a custom-made response device. The response device consisted of four separate force-sensing resistors (FSRs) placed and secured on plexiglass in accordance with the position of the participant's digits. The finger sequences included seven sequential finger taps in accordance with digits two through five: D2-D2-D3-D4-D4-D4-D5 or D5-D5-D4-D3-D2-D2-D2. Each finger sequence was pre-matched before experimental testing began and randomized for low and high VibT targets across participants. Each participant practiced at least four trials of the finger sequences without VibT or MN stimulation then at least two practice trials with VibT stimuli.

The testing session consisted of at least eight trials of the two different experimental conditions. Each trial consisted of approximately 75 VibT and 150 MN stimulations and lasted about 280 seconds for a total testing duration of approximately two hours including set-up.

3.3.4. Stimulation and Recording

Participants were seated in a sound-attenuating booth while receiving VibT stimulation one at a time to the fingertips of either D2 or D5 using a smooth plastic dowel (1 cm diameter) attached to a ceramic piezo actuator (Noliac North America Inc., Alpharetta, Georgia, USA). VibT stimulation devices vibrated at various amplitudes (see below) to change the force on the fingertips by passing fluctuating current via 25 Hz sine waves through the piezo actuator to the plastic dowel through analog speaker connections. VibT stimulation was controlled by digitally generated waveforms that were converted to an analog signal (DAQCard 6024E, National Instruments Corporation, Austin, Texas, USA) and then amplified (Bryston 2B-LP, Peterborough, Ontario, Canada). Changes in the forces on the fingertips were produced through variations of the amplitudes of the driving voltage at the stimulating frequency (25 Hz) using the waveforms generated in a custom software program (LabVIEW 8.5, National Instruments Corporation, Austin, Texas, USA). The amplitude modifications were achieved through the generation of random waveforms using the software program. The high and low sensory thresholds were set at 1.8 and 0.3 (% of standard) for participants. However, these sensory thresholds were still verified for each participant during practice trials. Each participant practiced at least two trials with both MN and VibT stimulation to verify their ability to detect the different amplitudes of VibT stimulation after amplitudes of high and low stimuli were set for each participant. All participants were given earplugs in both ears attached to a computer producing whitenoise from commercially available software (STIM2, Compumedics Neuroscan, Charlotte, North Carolina, USA) during all experimental conditions to eliminate auditory perception of VibT stimuli.

Somatosensory evoked potentials (SEPs) were elicited from electrical stimulation of the MN at the left wrist. MN stimulation was produced using a stimulation unit (GRASS SD9, West Warwick, Rhode Island, USA) that delivered square wave pulses of 0.2 ms duration through surface electrodes with the anode distal and fixed over each MN. Stimuli were delivered to the left MN time-locked to VibT stimulation at four time periods: (a) 250 ms (range 230-270 ms) before VibT stimulation, (b) 250 ms (range 230-270 ms) after VibT stimulation, (c) 750 ms (range 730-770 ms) after VibT stimulation and (d) 1250 ms (range 1230-1270 ms) after VibT stimulation. Two MN stimulations with (a)-(c) or (b)-(d) combinations were delivered for each VibT stimulation and the delivery of each combination was randomized by the software program during each experimental condition. The inter-stimulus interval (ISI) ranged from 960-1040 ms for both combinations of MN stimulation. The time-locking of MN stimulation to VibT stimulation was used to capture the different modulatory effects that may be present during each time period as follows: anticipatory pre-stimulus activity before VibT stimulus onset (~250 ms before), early stage of response selection (~250 ms after), late stage of movement preparation (~750 ms after) and during movement execution (~1250 ms after). The voltage of MN stimulation was set before experimental testing as the smallest voltage sufficient to elicit a visible thumb twitch (i.e. motor threshold) for the left MN. Surface electromyography (EMG) was recorded from the thenar musculature to record the M-wave (activity resulting from direct stimulation of motoneuronal axons serving the thenar muscle) to confirm consistent amplitudes of stimulus intensity. The unfiltered analog signal from finger responses was recorded from each of the four FSR's at 100 Hz in the software program and stored for off-line analysis.

Twelve electrode sites (FP1, FP2, FCz, FC4, FC3, Fz, F4, F3, Cz, Pz, CP4, CP3) of a 32-channel EEG cap (Neuroscan, Compumedics, Charlotte, North Carolina, USA) were used to

measure the electrical activity from the surface of the scalp in accordance with the international 10-20 system for electrode placement referenced to linked mastoids. Impedance was below 5 kOhms and continuous EEG data was amplified (20, 000x), filtered (DC-200Hz) and digitized at 1000 Hz (Neuroscan 4.3, Compumedics, El Paso, Texas, USA) before being stored on a computer for offline analysis.

3.3.5. Data Analysis

SEPs data analysis

SEPs were extracted from continuous EEG data by averaging epochs time-locked to the left MN stimulation (-50 to 400 ms) using commercially available software (NeuroScan 4.3, Compumedics, El Paso, Texas, USA). Individual traces were baseline corrected (based on pre-stimulus period -50 ms to 0 ms) then visually inspected for artifacts including eye blinks, eye movements or alpha activity. Epochs that were contaminated by artifacts were eliminated before averaging. Epochs from MN stimulation were averaged based on experimental condition (*Attend Index and Move* or *No Task*), target amplitude (high, low and standard), site of finger stimulation (D2 or D5) and time period of MN stimulation (-250, +250, +750, +1250 ms relative to VibT stimulation); only epochs where MN stimulation occurred either before or after high, low or standard VibT stimuli when responses were made were included in the primary analyses. Epochs for D5 VibT stimulation were included in separate secondary analyses. Latencies and amplitudes were measured using averaged epochs for each participant from the electrode sites that displayed the maximal amplitudes for frontal and parietal SEPs, FCz and CP4, respectively. Latencies of all components (frontal P20, N30 and parietal N20, P27, P50) were measured from

MN stimulus onset to the peak amplitude. Peak amplitudes were measured from the peak voltage relative to post-stimulus baseline.

Two-way analyses of variance (ANOVAs) were performed separately for each SEP amplitude and latency with factors experimental condition (*No Task, Attend Index and Move)* and time period of MN stimulation (-250, +250, +750, +1250 ms relative to VibT stimulation) during D2 VibT and left MN stimulation at their respective electrodes (FCz for frontal SEPs and CP4 for parietal SEPs). Tukey's post hoc comparisons were used to evaluate any significant interactions. Separate one-way ANOVAs were performed for each peak latency and amplitude with the factor experimental condition (*No Task, Attend Index and Move*) when MN stimulation occurred before or after D5 VibT stimulation. An alpha level of 0.05 was used to define statistical significance for any effects.

Behavioural Data

Finger sequences were quantified by peak detections for each FSR channel using a software program (LabVIEW 8.5); only peaks that exceeded five times the standard deviations of the average voltage for each FSR channel were included. Identification of peaks was necessary to appropriately classify SEPs when movement did or did not occur as well as for determining the onset and offset of movements for reaction time (RT) and movement time (MT) (see below).

For the *Attend Index and Move* condition, the number of target misses and false positives were calculated by comparing the responses to target and standard (non-target) stimuli. The accuracy for each participant was calculated by summing the amount of target misses (for both high and low VibT targets) and false positives (for both standard and D5 finger VibT non-

targets). The error rate for each participant was calculated by subtracting the amount of errors by the total # of VibT and multiplying by a hundred (see Table 3.1).

Furthermore, RT and MT was calculated for the *Attend Index and Move* condition. RT was calculated for high targets, low targets and responses to standard non-targets as the time between the presentation of a VibT stimulus and first response (i.e. peak) made on the response device. MT was calculated as the total duration of consecutive responses made in sequence before the presentation of the next VibT stimulus. Sequence response times (RespT) were calculated by summing RT and MT (see Table 3.2).

A one-way ANOVA was performed for dependent measures RT and MT with the factor VibT target amplitude (High, Low, Standard) to determine if there were differences in the speed to detect VibT stimuli then respond to high or low targets compared to responses to standard non-targets.

3.4. Results

3.4.1. SEPs

No significant differences in peak latency were observed for any SEP (N30 (32.5 +/- 3 ms), P20 (20.4 +/- 1.6 ms), N20 (20.3 +/- 1.1 ms), P27 (30.1 +/- 3.2 ms), P50 (46.8 +/- 3.6 ms) or P100 (96.4 +/- 7.8 ms)) ($p>0.05$).

Frontal SEPs - P20, N30 and N60

A significant main effect of MN timing ($F(3,27)=6.0$, $p=0.003$) and significant interaction between condition and MN timing ($F(3,27)=4.4$, $p=0.01$) was found for peak amplitude of frontal N30 at FCz. Tukey's post hoc analysis revealed that N30 peak amplitude was significantly

enhanced (i.e. more negative) in *Attend Index and Move* compared to *No Task* condition when MN stimulation followed VibT stimulation by 750 ms. In addition, the N30 peak amplitude was significantly enhanced in the *Attend Index and Move* (but not in the *No Task)* condition when MN stimulation followed VibT stimulation by 750 ms compared to 250 ms before or 250 ms after (see Figures 3.1 and 3.2).

There was a significant main effect of condition for N60 peak amplitude at FCz ($F(1,9)=9.7$, $p=0.01$), which demonstrated that N60 peak amplitude was enhanced (i.e. more negative) in the *Attend Index and Move* compared to *No Task* condition. In addition, there was also a significant main effect of MN timing for N60 peak amplitude ($F(3,27)= 9.9$, $p=0.0002$). Tukey's post hoc analysis revealed N60 peak amplitude was enhanced (i.e. more negative) 250 ms after VibT stimulation compared to either 250 ms before or 750 ms after VibT stimulation regardless of condition. In addition, N60 peak amplitude was suppressed when MN stimulation occurred 250 ms before VibT stimulation compared to 1250 ms after VibT stimulation regardless of condition (see Figures 3.1 and 3.2).

There was also a significant main effect of MN timing on P20 peak amplitude at FCz ($F(3,27)=5.0$, $p=0.007$). Tukey's post hoc revealed that P20 peak amplitude was larger when MN stimulation followed by 250 ms compared to 750 ms after VibT stimulation.

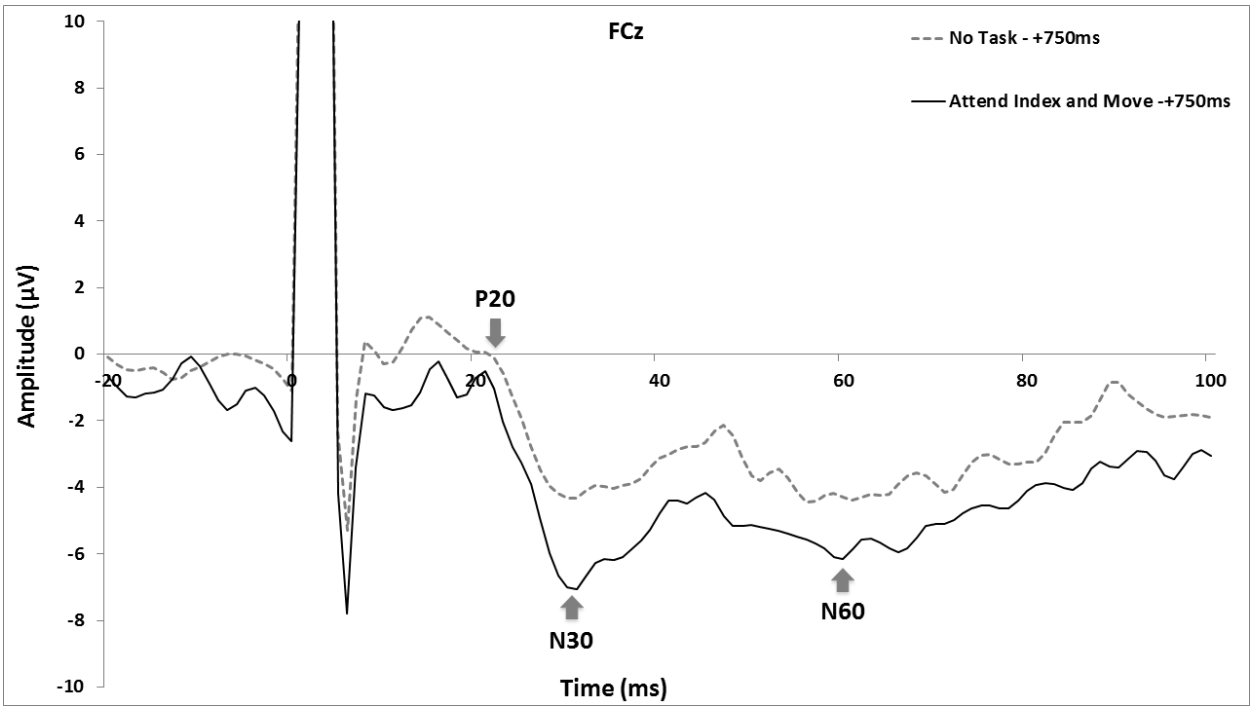

Figure 3.1 – Grand-averaged (n=10) waveforms in microvolts (μV) at FCz electrode comparing the effects frontal SEPs measured from left median nerve (MN) stimulation ~750 ms after (750A) vibrotactile (VibT) stimulations to the left index finger between conditions *Attend Index and Move and No Task* conditions.

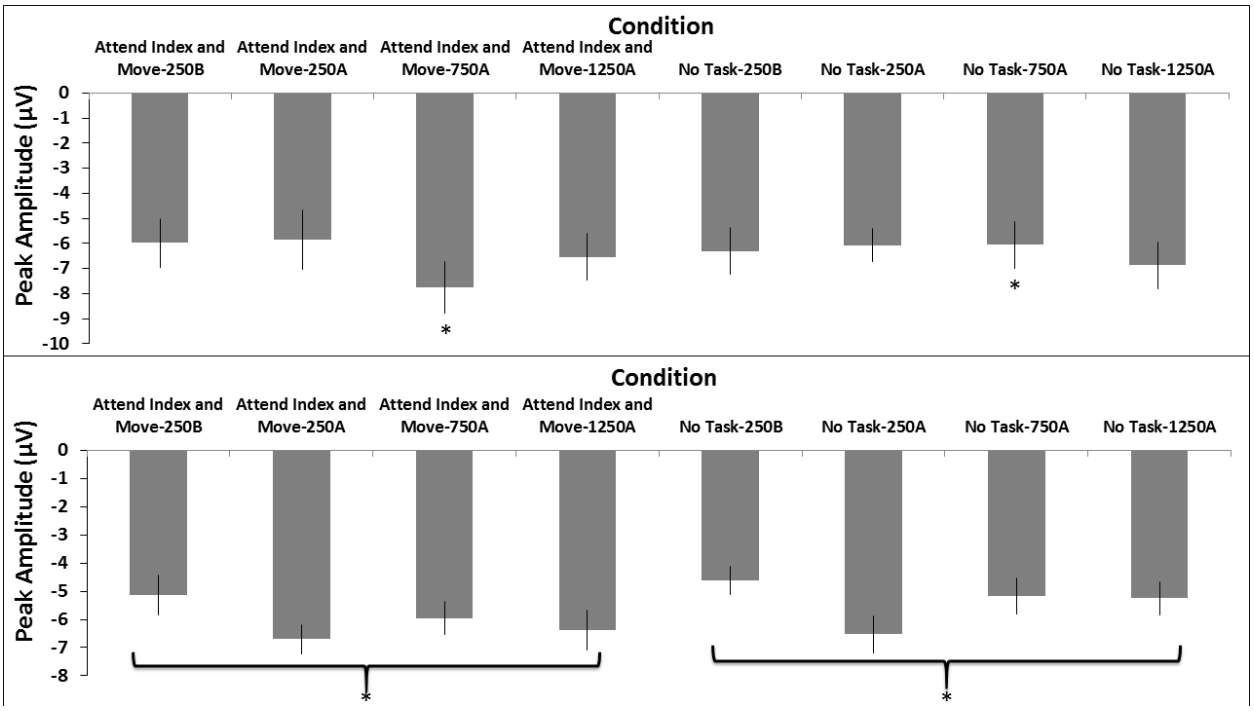

Figure 3.2 – Averaged (n=10) *(top)* N30 and *(bottom)* N60 peak amplitudes (μV) at FCz electrode comparing the effects between *Attend Index and Move* and *No Task* conditions with left median nerve (MN) stimulation occurring 250 ms before (250B), 250 ms after (250A), 750 ms after (750A) or 1250 ms after (1250A) vibrotactile (VibT) stimulation to the left index finger. Error bars represent standard error and asterisk (*) denotes statistically significant differences.

Parietal SEPs - N20, P27, P50 and P100

There was a significant main effect of MN timing on P50 peak amplitude at CP4 ($F(3,27)=7.1$, $p=0.001$). Tukey's post hoc analysis confirmed that the P50 peak amplitudes were significantly larger when MN stimulation occurred 250 ms before or 250 ms after VibT stimulation compared to 750 ms after regardless of condition. In addition, P50 peak amplitude was significantly larger when MN stimulation occurred 250 ms after VibT stimulation compared to 1250 ms after regardless of condition.

There was no significant main effects or interaction for N20, P27 or P100 peak amplitudes at CP4 (see Figure 3.3).

SEPs elicited by MN stimulation after or before pinky (D5) VibT stimulation

No significant main effect of condition was revealed for any frontal (P20 or N30) or parietal (N20, P27, P50, P100) SEPs for either peak amplitude or latency ($p>0.05$).

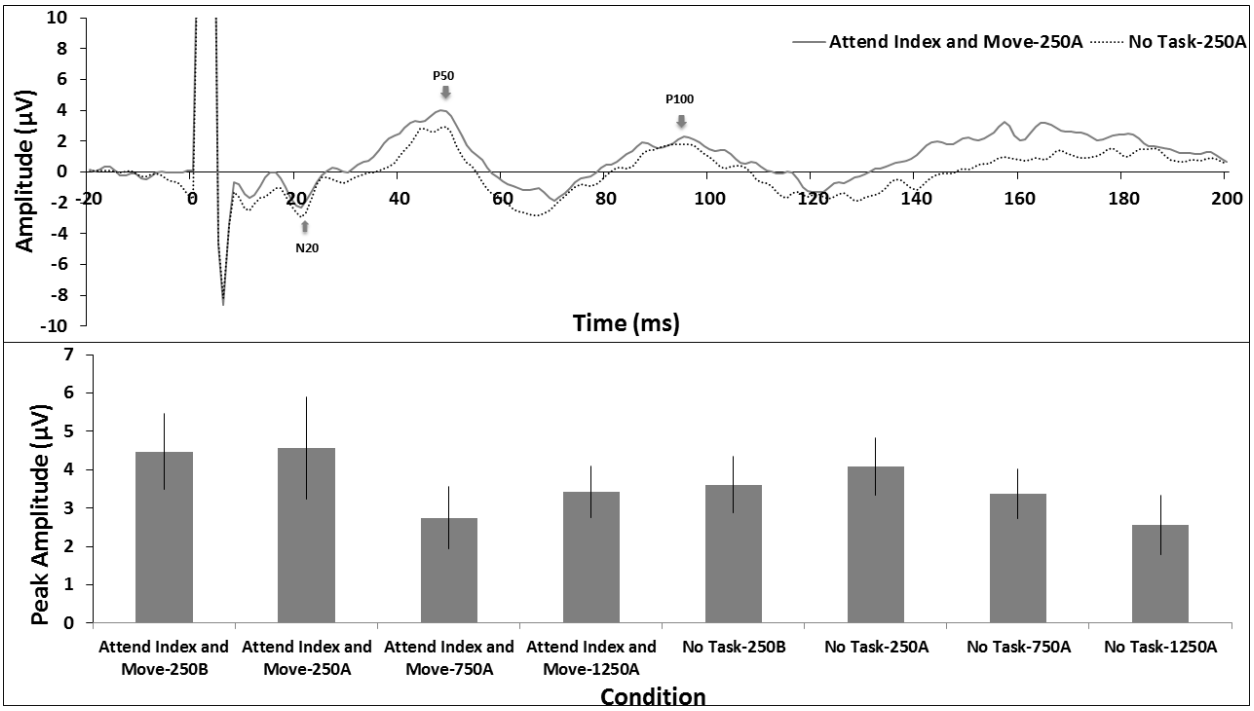

Figure 3.3 – (*top)* Grand-averaged (n=10) waveforms at CP4 electrode comparing the effects of parietal SEPs measured from left median nerve (MN) stimulation ~250 ms after (250A) vibrotactile (VibT) stimulations to the left index finger between conditions *Attend Index and Move and No Task* conditions. (*bottom)* Averaged (n=10) P50 peak amplitudes (μV) at CP4 electrode comparing the effects between *Attend Index and Move* and *No Task* conditions with left median nerve (MN) stimulation occurring 250 ms before (250B), 250 ms after (250A), 750 ms after (750A) or 1250 ms after (1250A) vibrotactile (VibT) stimulation to the left index finger. Error bars represent standard error and asterisk (*) denotes statistically significant differences.

3.4.2. Behavioural Data

The average error rate was 19.6% (see Table 3.1). A significant main effect of VibT target amplitude was revealed for RT ($F(2,18)=6.7$, $p=0.007$). Tukey's post hoc analysis showed slower RT when participants responded to standard VibT stimuli compared to high or low VibT

stimuli (see Table 3.2). In addition, MT was not significantly different when participants responded to high, low, or standard VibT stimuli ($p>0.05$).

Table 3.1 – The amount of total errors and error rate averaged across all participants (n=10) in the *Attend Index and Move* condition determined through target misses to target VibT stimuli and false positives to non-target VibT stimuli (*n.b.* error rates are calculated as the total errors divided by each participants total # of VibT stimuli which varies by participant).

	Target Misses	False Positives	Total Errors	Error Rate (%)
	41.1 (+/- 29.5)	59 (+- 40.0)	100.1 (+/- 55.0)	19.69 (+/- 7.8)
TOTAL	411	590	1001	

Table 3.2 – Reaction time (RT), movement time (MT) and response time (Rest) (ms) measured for participants (n=10) responses to high target, low target and standard non-target VibT stimuli in the *Attend Index and Move* condition.

	Reaction Time (RT) (ms)	Movement Time (MT) (ms)	Response Time (RespT) (ms)
High Targets	1078 (+/- 97)	1571 (+/- 104)	2649 (+/- 310)
Low Targets	1071 (+/- 358)	1617 (+/- 79)	2669 (+/- 374)
Standard Non-Targets with Response	1319 (+/- 93)	1545(+/- 111)	2864 (+/- 375)

3.5. Discussion

The novel finding of the current study was that frontal N30 peak amplitudes were enhanced during the late stages of preparing movement sequences with the contralateral dominant hand, ~750 ms after attended somatosensory stimuli cued movement. Furthermore, significant enhancements in the frontal N60 peak amplitude were also revealed when individuals attended to somatosensory input that was used to plan and execute movements (compared to the *No Task* condition) regardless of when MN stimulation occurred. In addition, small non-significant decreases in N30 amplitudes were observed both prior to and right after vibrotactile cues to prepare movement sequences but this gating was much smaller compared to the significant enhancement of frontal N30 peaks in the late stages of movement preparation.

3.5.1. Enhancements of Frontal SEPs

It has been well-documented that centrifugal mechanisms that originate from active neurons in motor areas, play a key role in modulating somatosensory input from MN stimulation (Kida, Wasaka, Nakata, Akatsuka, et al., 2006b; Kida, Wasaka, Nakata, & Kakigi, 2006; Kida, Wasaka, Inui, Akatsuka, et al., 2006). Previous research has demonstrated that frontal N30 peaks are enhanced during the execution but not during the preparation of contralatetal movements (Legon et al., 2010, 2008; Rossini et al., 1997). Specifically, Rossini *et al*. (1997) found an enhancement of frontal N30 peaks during the execution of repetitive finger-to-thumb opposition movements with the left hand while Legon *et al*. (2008) found that both frontal N30 and N60 peak amplitudes were increased during self-initiated contralateral repetitive gripping

movements. Further investigation by Legon *et al.* (2010) revealed that frontal N30 peaks were facilitated during the movement phase of contralateral non-dominant (compared to dominant) gripping movements when compared to early movement preparation phase in both right and left-hand dominant participants (Legon et al., 2010). It was argued that the enhancement of N30 peaks during non-dominant limb movement may be caused by increased activity in SMA, M1 and/or basal ganglia (Legon et al., 2010) that occurs specifically with non-dominant compared to dominant limb movements (Kawashima et al., 1993). However, these previous findings (Legon et al., 2010, 2008; Rossini et al., 1997) cannot fully explain the current results as facilitation of N30 peaks was observed with dominant rather than non-dominant limb movements as well as during the late preparatory rather than during the execution phase of movement.

One major difference between the current study and previous experiments (Legon et al., 2010, 2008; Rossini et al., 1997) was that individuals were planning, initiating and executing movement sequences that were cued by vibrotactile input to an attended spatial location. The amount of frontal N30 SEP modulation in the current study was likely dependent on the amount of activity in movement-related regions since previous research has demonstrated greater gating of frontal N30 SEPs when preparing and executing 60% compared to 10% or 30% ipsilateral MVC (Kida, Wasaka, Nakata, & Kakigi, 2006). It is possible that the complexity in preparing finger sequences (compared to gripping movements) may have contributed to the observed modulation of frontal N30 and N60 peaks. Increased regional cerebral blood flow (rCBF) has been observed during positron emission tomography (PET) in motor areas such as the rostral SMA (i.e. pre-SMA), ipsilateral M1 as well as in basal ganglia with increases in complexity of executing overlearned movement sequences (Boecker et al., 1998). Furthermore, increases in BOLD signals were correlated with increased length and complexity of finger sequences in

particular neural areas including the contralateral (left) dorsal lateral premotor cortex (BA 6) and bilaterally in the inferior frontal cortex (BA44/9) (Haslinger et al., 2002). Similarly, increases in complexity of finger sequences resulted in increased BOLD signals in several areas including the lateral premotor area, SMA as well as inferior and superior parietal lobes (Bortoletto & Cunnington, 2010). Based on these neuroimaging studies, increased activity in several neural areas including the pre-SMA, SMA, ipsilateral M1, basal ganglia, premotor cortex and inferior frontal cortex could contribute to the enhancement of N30 and N60 peaks observed in the current experiment.

Based on the sensory-cued movement used in the current study, it is likely that the PMC may be particularly involved in N30 peak modulation during late stages of movement preparation. Neurons in the PMC are known to be responsive to somatosensory stimuli (Kansaku, Hanakawa, Wu, & Hallett, 2004; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981). In addition deficits in sensory-cued movements have been observed with lesions to the PMC (Chouinard & Paus, 2006; Passingham, 1985). Interestingly, increases in N30 peak amplitude (evoked by right MN stimulation) have been observed after low frequency (0.2 Hz) repetitive transcranial magnetic stimulation (rTMS) over the ipsilateral (left) PMC but not M1 or SMA (Urushihara et al., 2006). It is likely that the observed facilitative effects on the N30 peaks are the result of interhemispheric connections through the corpus callosum between premotor areas that have been revealed by diffusion magnetic resonance imaging tractography in humans (Zarei et al., 2006) and could reflect a disinhibition or increased excitation between hemispheres. In the current study, it is possible that increased activity in the left PMC, that were specific during the late stages of right hand movement preparation, had similar effects of low-frequency rTMS and may have contributed to a disinhibition or facilitation of the generators of frontal N30 peaks in

the contralateral hemisphere resulting in an enhancement of the frontal N30 peaks. It should be noted that although average reaction times (based on our behavioural data) were slower than 1000 ms, some individuals (particularly to low target stimuli) initiated their response before MN stimulation at 750 ms after vibrotactile stimulation. Thus, it remains possible that the enhancement effects of the frontal N30 may be driven in part by activity in M1 during early movement execution. It should also be noted that the lack of change in frontal N30 peak amplitude in the *No Task* condition after MN stimulation followed both an index finger vibration (by 750 ms) as well as a previous MN stimulation (250 ms before vibration) supports that these effects are not just driven by systematic effects of the dual MN stimulation design.

There is no consensus from direct intracerebral recordings in humans on the generators of the frontal N30 (Barba et al., 2003, 2001, 2005; Kaňovský et al., 2003). Direct intracerebral recordings have found evidence that the frontal N30 is generated from neuronal populations in the dorsolateral PMC and SMA (Kaňovský et al., 2003) and this has been supported by several TMS studies (Hosono et al., 2008; Legon, Dionne, & Staines, 2013b; Urushihara et al., 2006).. If this is true, this would support that the enhancement of somatosensory input (represented by frontal N30 peaks) during late stages of movement preparation and/or early movement execution occurs through inter-hemispheric connections between PMC or M1 to PMC and/or SMA. However, other studies have suggested through dipole modelling (Rossini et al., 1999; Valeriani, Le Pera, Niddam, Arendt-Nielsen, & Chen, 2000; Waberski et al., 1999) and intracerebral recordings (Balzamo et al., 2004) that the frontal N30 may be generated by summated somatosensory input into SI and M1 rather than exclusively premotor areas. If this were the case, then increased frontal N30 peaks could reflect disinhibition or increased excitation in a more widespread network that includes PMC, SMA, M1 and/or SI. Although the current

experimental design cannot fully discount this hypothesis, parietal P27/P30 SEPs (occurring at nearly the same time as frontal N30 peak) were not modulated like the frontal N30 peaks during this period of late movement preparation. Furthermore, our results also did not find a similar modulation of frontal N30 peaks during the period of sequence execution when M1 activity would likely be greatest. Collectively, the current findings support that premotor areas are likely the primary location of the frontal N30 peak modulation. However, future studies should carefully consider this hypothesis.

Although the PMC and M1 are likely candidates to contribute to the modulation of N30 peak amplitude observed in the current experiment, both basal ganglia and prefrontal cortex may also contribute. N30 peak amplitudes are significantly depressed in individuals with Parkinson's disease (Bostantjopoulou et al., 2000; Cheron et al., 1994; Cheron, 1999; Garcia et al., 1995; Rossini et al., 1995; Rossini, Babiloni, et al., 1989; Ulivelli et al., 1999) but are increased with apomorphine (dopamine-agonist) injection (Pierantozzi et al., 1999; Rossini et al., 1995; Ulivelli et al., 1999) and deep brain stimulation of internal globus pallidus or subthalamic nuclei (Pierantozzi et al., 1999). As noted above, increased rCBF has been documented in bilateral globus pallidus and putamen with increased movement sequence complexity (Boecker et al., 1998). Similarly, increases in BOLD signals in bilateral prefrontal cortex (BA 9/44) were correlated with increases in movement sequence length and complexity (Haslinger et al., 2002). Furthermore, increased cerebral blood flow has also been observed in dorsolateral prefrontal cortex (BA 9,10 and 46) in tasks that require individuals to make decisions on timing the initiation of finger extension compared to auditory-cued extensions (Jahanshahi et al., 1995). Functional imaging has also revealed that the superior frontal (BA 10-46) and medial orbito-frontal cortices (BA 11-47) have greater activation when having to focus on timing the initiation

of finger sequences (Bortoletto & Cunnington, 2010). Thus, it is possible that increased activity in basal ganglia and/or prefrontal cortex may have contributed to the enhancement frontal N30 and N60 peak amplitudes.

The prefrontal cortex is known to be involved in the top-down regulation of spatial attention for task-relevant somatosensory input (Staines et al., 2002) as well as top-down anticipatory activity for somatosensory input (Haegens et al., 2011). Previous research has shown that unilateral lesions to the prefrontal cortex localized to BA 9 and 46 results in increased frontal SEPs in the range of the frontal N30 at rest (Yamaguchi & Knight, 1990). Based on these findings, it was proposed that top-down attentional mechanisms could contribute to N30 peak amplitude modulation when MN stimulation occurred in the pre-stimulus (i.e. 250 ms before) in the current experiment. However, the current results do not support this hypothesis. Small decreases in N30 peak amplitude were observed during the pre-stimulus and first post-stimulus period but this did not reach significance. Thus, based on these findings and previous research investigating attentional effects on N30 peak amplitude (Brown & Staines, 2015a; Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004) top-down attentional effects regulated by the prefrontal cortex do not appear to modulate frontal N30 SEPs *per se*. In contrast, it is possible that a separate region of the lateral prefrontal cortex that is recruited for the executive control of movements (Dosenbach et al., 2007; Petersen & Posner, 2012) may contribute to the modulation of frontal N30 (and potentially N60) SEPs. Interestingly, if lateral prefrontal cortex was involved in the frontal N30 peak modulation, it would suggest the early modulation captured in the current study likely reflects the combined increased prefrontal attentional activity and premotor motor preparedness. However, further investigation is needed

to clarify the specific role that the prefrontal cortex may have on modulating early somatosensory input.

3.6. Conclusion

The current results demonstrated that frontal N30 peak amplitudes are enhanced during the late preparatory/early execution phase when performing contralateral finger sequences that were cued to vibrotactile input. When taken into consideration with previous findings (Brown & Staines, 2015a; Kida, Wasaka, Nakata, Akatsuka, et al., 2006b; Kida, Wasaka, Nakata, & Kakigi, 2006; Kida, Wasaka, Inui, Akatsuka, et al., 2006; Legon et al., 2010, 2008; Rossini et al., 1997), early somatosensory input into non-primary motor areas is differentially modulated (i.e. gating and enhancement) during different periods depending on the movement complexity and neural areas recruited for a given movement. The significant enhancement in frontal N30 peak amplitudes observed in the current study were likely caused through inter-hemispheric disinhibition or excitation from the PMC or M1 on the generators of the frontal N30 in the contralateral PMC and/or SMA. However, it is also possible that increased activity in the prefrontal cortex and/or basal ganglia could have also contributed to the enhancement of frontal N30 peak amplitudes. Functionally, enhanced N30 SEPs may be necessary to facilitate somatosensory processing in non-primary motor areas due to the overall increased neural activity and subsequently, physiologically 'noisy environment' in these areas during movement sequence preparation. Future research is required to clarify the roles of these different neural areas in modulating somatosensory information in non-primary motor areas and the behavioural significance of this modulation.

Chapter 4 - Differential effects of continuous theta burst stimulation (cTBS) over left premotor cortex (PMC) and right prefrontal cortex (PFC) on modulating upper limb somatosensory input

Chapter Research Objectives

This chapter attempted to answer specific research questions 3 and 6 (see section 1.5.)

4.1. Abstract

Somatosensory evoked potentials (SEPs) recorded from cortical surface electroencephalography (EEG) after median nerve (MN) stimulation measure mixed afferent somatosensory input relevant for upper limb motor control. SEPs recorded maximally over frontal electrodes, such as frontal N30 and N60 peaks, represent somatosensory processing in non-primary motor areas whereas parietal SEPs (i.e. P50) represent relay into somatosensory cortices. Several neural areas including the premotor cortex (PMC) and prefrontal cortex (PFC) have been associated with the preparation and planning of upper limb movements. However, it is currently unclear how PMC and PFC are involved in somatosensory processing for upper limb motor control. In the current study, two experiments examined SEP modulations after continuous theta burst stimulation (cTBS), a specific type of repetitive transcranial magnetic stimulation, to produce transient disruptions of left PMC (*Experiment 1)* and right PFC (*Experiment 2).* In both *Experiment 1* (n=15) and *Experiment 2* (n=16) pre-post experimental designs, participants

performed a task requiring detection of varying amplitudes of attended vibrotactile (VibT) stimuli to the left index finger (D5) and execution of a pre-matched finger sequence with the right (contralateral) hand to specific VibT targets. During the task, SEPs were measured to MN stimulations time-locked during pre-stimulus (250 ms before VibT), early response selection (250 ms after VibT), late preparatory (750 ms after VibT) and execution (1250 ms VibT) phases. The key findings of *Experiment 1* revealed significant decreases in N30 and N60 peak amplitudes after cTBS to PMC. In contrast, the results of *Experiment 2*, also found significant decreased N60 peak amplitudes as well as trends for increased N30 and P50 peak amplitudes. A direct comparison of *Experiment 1* and *Experiment 2* confirmed differential modulation of N30 peak amplitudes after PMC (gated) compared to PFC (enhanced) cTBS. Collectively, these results support that both the left PMC and right PFC have modulatory roles on early somatosensory input into non-primary motor areas such as PMC and supplementary motor area (SMA) represented by frontal N30 and N60 SEPs. These results confirm that PMC and PFC are both part of a network that regulates somatosensory input for upper limb motor control.

4.2. Introduction

Mixed afferent somatosensory input from peripheral receptors in the upper limbs is critical in providing information to the central nervous system (CNS) about static and dynamic limb position that can be used for upper limb motor control (Cordo et al., 2011; Johansson & Flanagan, 2009; Proske & Gandevia, 2012; Scott, 2004). Premotor areas such as premotor cortex (PMC) and supplementary motor area (SMA) have important roles in preparing movements to be executed through the primary motor cortex (M1) (Chouinard & Paus, 2006; Geyer et al., 2000; Hoshi & Tanji, 2004a, 2004b; Tanji, 2001). Furthermore, there is a growing body of research

that the lateral prefrontal cortex (PFC) has an important contribution and may form the highest hierarchical control center for upper limb motor control (Badre, 2008; Fuster, 2004; Goldman-Rakic, 1987; Koechlin et al., 2003; Miller & Cohen, 2001). However, it is currently unclear how the PFC and PMC interact to modulate somatosensory input for upper limb motor control.

Mixed somatosensory input can be recorded by somatosensory evoked potentials (SEPs) using cortical surface electroencephalography (EEG) time-locked to median nerve (MN) stimulation (Brown & Staines, 2015a; Cebolla et al., 2014; Cohen & Starr, 1987; Kida, Wasaka, Nakata, & Kakigi, 2006; Legon et al., 2010, 2008; Rossini et al., 1999). SEPs recorded by electrodes over the parietal cortex (i.e. CP4) between 20-100 ms after MN stimulation are representative of the earliest relay and processing of mixed afferent input in primary (SI) and secondary (SII) somatosensory cortices (Allison et al., 1989; Balzamo et al., 2004; Buchner et al., 1995; Goff et al., 1977). EEG surface recordings have also recorded frontal SEPs after MN stimulation such as the frontal N30 and N60 peaks that are maximal over premotor areas (i.e. FCz) (Brown & Staines, 2015a; Cebolla et al., 2014; Cohen & Starr, 1987; Kida, Wasaka, Nakata, & Kakigi, 2006; Legon et al., 2010, 2008; Rossini et al., 1999). Frontal N30 peaks may represent somatosensory input into the dorsolateral portion of Brodmann's area (BA) 6 (representative of dorsal premotor cortex, PMd) and medial portion of BA 6 (representative of the SMA) (Kaňovský et al., 2003). Thus, SEP modulations can be used to examine contributions of PMC and PFC to upper limb somatosensory processing in both sensory cortices and motor areas.

Preparation, execution or imagination of movements ipsilateral to MN stimulation have been shown to decrease (i.e. gate) frontal N30 SEPs (Böcker et al., 1993; Cebolla et al., 2009; Cheron & Borenstein, 1987, 1991; Cohen & Starr, 1987). In contrast, enhancements of frontal

N30 SEPs have been observed during execution of repetitive movements contralateral to MN stimulation (Legon et al., 2010, 2008; Rossini et al., 1997). These observations support that both PMC and M1 have modulatory roles on early somatosensory processing in premotor areas. Interestingly, inhibitory continuous theta burst stimulation (cTBS), a specific type of repetitive transcranial magnetic stimulation (rTMS), was shown to decrease frontal N30 peaks elicited by right MN stimulation when applied over the SMA (Legon et al., 2013). In contrast, monophasic 0.2Hz rTMS over the left PMC significantly increased N30 peak amplitudes elicited by right MN stimulation but had no effect when applied over SMA or M1 (Hosono et al., 2008; Urushihara et al., 2006). The facilitation after 0.2 Hz rTMS rather than inhibition of frontal N30 peaks was surprising considering that low frequency rTMS (between 0.1 to 1 Hz) typically decreases excitability when applied over M1 (Chen & Seitz, 2001; Fitzgerald et al., 2006). Nevertheless, these rTMS studies confirm a modulatory role of premotor areas on upper limb somtatosensory processing represented by frontal N30 SEPs.

In contrast, the role of the PFC in modulating somatosensory input, particularly frontal SEPs, for upper limb motor control is currently poorly understood. Parietal SEPs, including the P50 and P100 peaks, can be enhanced in the hemisphere contralateral to MN stimulation during selective spatial attention (Desmedt & Tomberg, 1989; Eimer & Forster, 2003; Garcia-Larrea et al., 1991; Schubert et al., 2008; Zopf et al., 2004). However, similar effects on frontal SEPs, such as frontal N30, have not been observed during selective spatial attention (Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004; Kida, Wasaka, Nakata, Akatsuka, et al., 2006b; Kida, Wasaka, Nakata, & Kakigi, 2006). Surface recordings of SEPs at rest in unilateral prefrontal lesion patients (centered around BA 9 and BA 46) have shown that frontal SEPs around 30 ms (frontal N28) are increased in amplitude compared to control participants

(Yamaguchi & Knight, 1990). Furthermore, increased rCBF changes were revealed using single photon emission computed tomography (SPECT) in both PMC and PFC with increased frontal N30 SEPs after 0.2 Hz rTMS to PMC (Urushihara et al., 2006). These results suggest that the prefrontal cortex (BA 9 and BA 46) may contribute to inhibitory modulation of early somatosensory processing in non-primary motor areas. Our lab recently identified that frontal N30 peaks (elicited by left MN stimulation) were gated during early response selection (Brown & Staines, 2015a) but facilitated during the late preparation (Brown & Staines, 2015b) of finger movement sequences with the right limb contralateral to MN stimulation that was cued by attended vibrotactile (VibT) input to the left index finger. It was argued that the gating and enhancement effects on frontal N30 SEPs may be driven by different activity that occurs in both inter- and intracortical networks involving the PMC, SMA, PFC as well as potentially M1 and basal ganglia (Brown & Staines, 2015a, 2015b). However, the contributions of the PFC or PMC to these SEP modulations has not been verified.

Thus, the current study evaluated SEP modulations, particularly frontal N30 peak amplitude changes, elicited by left MN stimulation during preparing and executing finger sequences with the right limb to attended VibT input at the left index finger (Brown & Staines, 2015a, 2015b). In separate experiments cTBS was applied to the left PMC (*Experiment 1)* or right PFC (*Experiment 2)* to evaluate the contributions of these areas to SEP modulations during different periods when individuals prepared and executed finger sequences cued to attended vibrotactile input. MN stimulation was time-locked to four different periods relative to VibT stimuli similar to our previous experiment (Brown & Staines, 2015b) to evaluate the effects of a) pre-stimulus anticipatory activity regulated primarily by PFC, b) early response selection and late movement preparatory activity occurring involving activity in PFC and premotor areas such

as PMC, and c) activity related to the finger sequence execution driven by M1 activity. It was hypothesized that enhancement effects of frontal N30 peaks during the late stages of preparing right hand finger sequence preparation (Brown & Staines, 2015b) would be significantly decreased after left PMC cTBS supporting its role in frontal N30 SEP modulation that has previously been hypothesized (Brown & Staines, 2015a, 2015b). Furthermore, it was hypothesized that an increase in N30 peak amplitudes would be observed after right PFC cTBS particularly during the pre-stimulus period supporting the PFC role in the inhibitory modulation of early somatosensory input (Yamaguchi & Knight, 1990).

4.3. Methods

4.3.1. Participants

Thirty-one healthy adults were recruited to participate in the current study. Fifteen (n=15, 10 males, 26.4 +/- 4.2 years, range 21-34 years) individuals participated in *Experiment 1* and sixteen (n=16, 23.3 +/- 2.75 years, range 20-31 years) participated in *Experiment 2*. All participants completed a TMS screening form (Keel, Smith, & Wassermann, 2001) and provided written informed consent prior to participation. All procedures for these experiments were approved by the University of Waterloo Human Research Ethics board.

4.3.2. Experimental Task

Participants performed the same experimental task in both *Experiment 1* and *Experiment 2* that has been described in detail elsewhere (Brown & Staines, 2015b). Briefly, vibrotactile (VibT) stimulation occurred at either the left index (D2) or pinky (D5) fingers at three different amplitudes (low, standard and high). In one condition, *Attend Index and Move*, participants

attended to VibT input at D2 and performed different predetermined finger sequences with the right (contralateral) hand to perceived high and low amplitude VibT stimuli (i.e. targets) while ignoring D2 standard amplitude and D5 VibT stimulation (i.e. non-targets). The other condition, *No Task*, involved passive VibT stimulation with no attention or movement requirements. Overall, each trial was composed of approximately 70% targets and 30% non-targets VibT stimuli. Transcutaneous electrical stimulation of the left median nerve (MN) occurred throughout both conditions, but was not part of the behavioural task.

4.3.3. Experimental Design

In both experiments, a pre-post design was used to evaluate the effects of cTBS on SEPs time-locked to MN stimulation. cTBS was applied to either the left PMC (*Experiment 1*) or right PFC (*Experiment 2)* between pre-cTBS and post-cTBS EEG sessions. In both pre-cTBS and post-cTBS EEG sessions, participants were instructed to perform one of two experimental conditions, *Attend Index and Move* or *No Task*, in pseudo-randomized trials while receiving VibT and MN stimulation. In both conditions, participants were seated with D2 and D5 of the left hand resting on a VibT stimulation device and D2 through D5 of right hand resting on the response buttons with eyes fixated forward. In the *Attend Index and Move* condition, the pre-matched finger sequences involved seven sequential finger button presses with digits D2 through D5 of the right (contralateral) hand as follows: D2-D2-D3-D4-D4-D4-D5 and D5-D5-D4-D3-D2-D2-D2. Finger sequences to low or high amplitude VibT targets were counter-balanced across participants. Each EEG testing session consisted of at least four trials of the two different experimental conditions (*No Task, Attend Index and Move*), although additional trials were recorded when necessary to ensure adequate amount of SEPs for analysis. Each trial lasted

approximately 500 seconds and consisted of approximately 150 VibT and 300 MN stimulations. Each EEG session lasted approximately 60 minutes.

4.3.4. Stimulation and Recording

VibT stimulation and finger sequence response device

In both experiments, VibT stimulation was delivered to the fingertips of either D2 or D5 using a smooth plastic dowel (1 cm diameter) attached to ceramic piezo actuators (Noliac North America Inc., Alpharetta, Georgia, USA). A custom-made program (LabVIEW 8.5, National Instruments Corporation, Austin, Texas, USA) generated waveforms for VibT stimulation at low, high or standard amplitudes that were converted to an analog signal (DAQCard 6024E, National Instruments Corporation, Austin, Texas, USA) then amplified (Bryston 2B-LP, Peterborough, Ontario, Canada). Changes in the driving voltage resulted in different forces on the fingertips at a constant stimulation frequency (25 Hz) with the passing fluctuating sine wave current. Thresholds for high, standard and low VibT stimulation were set at 1.8, 1 and 0.3 (% of standard) for all participants similar to our previous experiments (Brown & Staines, 2015a, 2015b). All participants listened to whitenoise through earphones that was generated from a commercially available software application for mobile devices (Whitenoise, TM Soft) to eliminate auditory perception of VibT stimuli. In addition, right hand finger sequences were recorded from four separate push buttons mounted in a piece of plexiglass under digits D2 through D5 of the right hand. Each participant was familiarized with the three different amplitudes of VibT stimulation and both finger sequences before beginning experiments.

SEPs

SEPs were measured to time-locked left MN stimulation in both experiments. MN stimulation was delivered using 0.2 ms square wave pulses through a surface electrode (anode distal) produced by a stimulation unit (GRASS SD9, West Warwick, Rhode Island, USA). The voltage of left MN stimulation was set before experiments as the lowest voltage to elicit a visible left thumb twitch (i.e. motor threshold). Waveforms for MN stimulation were generated in Labview (Labview 8.5) and time-locked to VibT as follows: (a) 250 ms (range 230-270 ms) before VibT stimulation, (b) 250 ms (range 230-270 ms) after VibT stimulation, (c) 750 ms (range 730-770 ms) after VibT stimulation and (d) 1250 ms (range 1230-1270 ms) after VibT stimulation. Two MN stimulations with (a)-(c) or (b)-(d) combinations were delivered for each VibT stimulation and randomized during each experimental condition. Time-locking of MN stimulation to VibT stimulation was used to capture the different modulatory effects that may be present and influenced by cTBS during pre-stimulus anticipatory period (250ms before VibT), early response selection (250ms after VibT), late movement preparation (750ms after VibT) and movement execution (1250ms after VibT) as described in our previous experiment (Brown & Staines, 2015b).

In both experiments, SEPs were recorded from the cortical surface using two 10mm Ag-AgCl cup electrodes (Technomed, King Medical, London, Ontario, Canada). These electrodes were placed on the scalp over FCz and CP4 electrode sites in accordance with the international 10-20 system and referenced to linked mastoids. Impedances were maintained below 5 kOhms during continuous EEG data recording that was amplified (40000x), filtered (DC/1Hz-200Hz) and digitized (1000 Hz) (Neuroscan 4.3, Compumedics Neurscan, Charlotte, NC, USA) before being stored on a computer for offline analysis.

Electromyography (EMG)

Surface electromyography (EMG) was recorded from the left thenar eminence and right first dorsal interosseous (FDI) in both experiments during EEG sessions using 9 mm diameter Ag-AgCl electrodes with a bipolar montage. Active electrodes were placed over the muscle belly of the FDI and thenar musculature and the reference electrode placed over the metacarpophalangeal joint of the index or thumb, respectively. The ground electrode was placed over the left clavicle. EMG recordings of the left thenar eminence were used to record M-waves representing direct motoneuronal axon activation after MN stimulation. EMG recordings from the right FDI were used to confirm responses recorded from button presses during *Attend Index and Move* conditions for classification of SEPs (see *SEP data analysis below*). EMG from the left thenar eminence and right FDI were amplified (40000x), filtered (DC/1Hz-200Hz) and digitized (1000 Hz, Neuroscan 4.3) before being stored on a computer for offline analysis.

EMG was also recorded from the right *(Experiment 1)* or left (*Experiment 2)* FDI using bipolar montages during TMS to measure motor-evoked potentials (MEPs) during cTBS sessions in both experiments. EMG recordings were amplified (2000x), band-pass filtered (20-200 Hz), and digitized (1000 Hz) using Labview (Labview 8.5).

cTBS

Continuous theta burst stimulation (cTBS) was applied over the left PMC (*Experiment 1)* or right PFC (*Experiment 2)* using a MagPro x100 stimulator (Medtronic, Minneapolis, MN, USA) and 70 mm figure-of-eight transcranial magnetic stimulation (TMS) coil (MCF-B65). cTBS applied a continuous 40 s train of bursts consisting of sets of three biphasic pulses at 50 Hz

repeated every 200 ms (5 Hz) for a total of 600 pulses (Huang et al., 2005). FDI motor hot spots in left M1 (*Experiment 1)* or right M1 (*Experiment 2)* were determined as the ideal locations to elicit maximal and consistent MEPs in the right (*Experiment 1)* or left FDI (*Experiment 2)*. The position of the TMS coil was guided to cortical targets using BrainSight Neuronavigation (Rogue Research, Canada) with a template MRI for all participants. The intensity of stimulation was set at 80% of active motor threshold (AMT) (Huang et al., 2005). AMT was determined by the minimum intensity required to produce MEPs greater than 200 uV in 5 out of 10 trials while maintaining a 20% maximum voluntary contraction (MVC) in FDIs after single pulse TMS to the FDI motor hot spots (Huang et al., 2005).

In *Experiment 1,* cTBS was applied to the left PMC, presumably PMd, 2.5 cm anterior to left FDI motor hot spot in left M1. This location was used based on previous rTMS experiments targeting PMd (Bestmann et al., 2005; Cincotta et al., 2004; Conte et al., 2007; Huang et al., 2009). In *Experiment* 2, cTBS was applied to the right PFC, seemingly dorsolateral prefrontal cortex (DLPFC), by placing the TMS coil over the F4 electrode location of the international 10-20 system similar to previous experiments (Bolton et al., 2012; Bolton & Staines, 2011; Grossheinrich et al., 2009; Xu et al., 2013).

4.3.5. Data Analysis

SEPs

SEPs were extracted from continuous EEG by averaging epochs (-100 to 200 ms) time-locked to left MN stimulation using Neuroscan (Neuroscan 4.3) in both experiments. Individual traces were baseline corrected to pre-stimulus period (-50 to 0 ms) and visually inspected for artifacts before averaging all non-contaminated epochs. Epochs were averaged based on

experimental condition (*Attend Index and Move* or *No Task*), target amplitude (high, low and standard), site of finger stimulation (D2 or D5), time period of MN stimulation (-250, +250, +750, +1250 ms relative to VibT stimulation) and EEG session (*pre-cTBS, post-cTBS).* In the *Attend Index and* Move condition, only epochs where responses were verified after low, high or standard D2 VibT stimulation were included in analyses similar to our previous experiment (Brown & Staines, 2015b). Epochs where no responses were made to D2 VibT stimulation (standard, high or low) as well as epochs to D5 VibT stimulation were excluded from analyses due to insufficient SEPs (below 50) for reliable comparisons for most participants. Peak latencies and amplitudes were measured for frontal (P20, N30 and N60) and parietal (N20, P27, P50 and P100) SEPs from FCz and CP4 electrodes, respectively. Peak latencies were measured from onset of MN stimulation to the peak amplitude. Peak amplitudes were measured relative to the post-stimulus baseline voltage (between 12-20 ms).

In both experiments, three-way analyses of variance (ANOVAs) were performed separately for each frontal and parietal SEP peak amplitude and latency with factors: experimental condition (*Attend Index and Move* or *No Task*), time period of MN stimulation (-250, +250, +750, +1250 ms relative to VibT stimulation) and EEG session (*pre-cTBS, post-cTBS).* In addition, a separate mixed-model ANOVA was performed to directly compare the effects of PMC and PFC cTBS on SEP peak amplitude differences between pre compared to post cTBS with factors: groups (*PMC cTBS, PFC cTBS*), experimental condition (*Attend Index and Move* or *No Task*), and time period of MN stimulation (-250, +250, +750, +1250 ms relative to VibT stimulation). Tukey's post hoc comparisons were used to evaluate any significant interactions. An alpha level of 0.05 was used to define statistical significance for any effects.

Behavioural Data

In both experiments, button presses for finger sequences were measured by detecting voltage peaks when each individual button was pressed (above 1 V) using Labview (Labview 8.5). Identification of peaks was necessary to appropriately classify SEPs when responses were made and for determining the onset and offset of movements for reaction time (RT) and movement time (MT) (see below). For the *Attend Index and Move* condition, VibT detection accuracy was determined by the total number of errors calculated by summing target misses (for both high and low VibT targets) and false positives (for both D2 standard and D5 finger VibT non-targets). The error rate for each participant was calculated by subtracting the amount of errors by the total # of VibT and multiplying by a hundred. Furthermore, RT and MT were both calculated for the *Attend Index and Move* condition. RT was calculated as the time between the presentation of a VibT stimulus and first button response for high targets, low targets and responses to standard non-targets. MT was calculated as the total duration of consecutive button presses made in sequence before the presentation of the next VibT stimulus. Sequence response times (RespT) were calculated by summing RT and MT.

Two-way ANOVAs were performed for each experiment to determine the effects of PMC and PFC cTBS on RT, MT and RespT with the factors: VibT amplitude (High, Low, Standard) and EEG session (*pre-cTBS, post-cTBS).* The differences between PMC (*Experiment 1*) and PFC (*Experiment 2)* cTBS on RT, MT and RespT were directly compared using mixed-model ANOVAs with factors: group (*PMC cTBS, PFC cTBS),* VibT amplitude (High, Low, Standard) and EEG session (*pre-cTBS, post-cTBS).* In addition, the effects of cTBS on VibT detection accuracy were measured using one-way ANOVAs on total errors with factor EEG

session (*pre-cTBS, post-cTBS)*. The differences between PMC (*Experiment 1*) and PFC (*Experiment 2)* cTBS on VibT detection accuracy were directly compared total errors using mixed-model ANOVAs with factors: group (*PMC cTBS, PFC cTBS),* and EEG session (*pre-cTBS, post-cTBS).* Tukey's post hoc comparisons were used to evaluate any significant interactions. An alpha level of 0.05 was used to define statistical significance for any effects.

4.4. Results

4.4.1. Experiment 1 – SEP modulation after left PMC cTBS

Frontal SEPs

N30

A significant three-way interaction was revealed for N30 peak amplitudes between experimental condition, time period of MN stimulation and EEG session ($F(3,42)=4.03$, $p=0.01$). Tukey's post hoc analysis determined that N30 peak amplitudes were significantly decreased *post-cTBS* to PMC in the *Attend Index and Move* condition at 750 ms compared to several time periods of MN stimulation in both conditions *pre-cTBS*. Furthermore, N30 peak amplitudes were also significantly decreased *post*-compared to *pre-cTBS* to PMC in *No Task* condition when MN stimulation was 250 ms before VibT stimulation (see Figure 4.1). A significant main effect of time period of MN stimulation was found for N30 peak latency ($F(3,42)=3.67$, $p=0.02$). Tukey's post hoc analysis confirmed that N30 peak latencies were earlier at 750 ms after VibT stimulation (32.4 ms) compared to either 250 ms after (33.2 ms) or 750 ms after (33.2 ms) VibT stimulation regardless of condition or EEG session.

N60

A significant main effect of EEG session was found for N60 peak amplitude ($F(1,14)=11.71$, $p=0.004$), revealing that N60 peak amplitudes were decreased in *post-cTBS* compared to *pre-cTBS* of PMC. In addition, significant main effects for N60 peak amplitudes for condition ($F(1,14)= 10.6$, $p=0.006$) and time period of MN stimulation ($F(3,42)=19.8$, $p<0.00001$) were superseded by a significant interaction between condition and time period of MN stimulation ($F(3,42)=2.87$, $p=0.047$). Tukey's post hoc analysis found that N60 peak amplitudes were decreased in *Attend Index and Move* compared to *No Task* condition when MN occurred 750 ms after VibT stimulation. In addition, N60 peak amplitudes were largest in *Attend Index and Move* condition 250 ms after VibT and smallest 750 ms after VibT stimulation while in *No Task* condition N60 peak amplitudes were also largest when VibT was 250 ms after MN stimulation but smallest 250 ms before VibT stimulation (see Figure 4.1). There were no significant difference in N60 peak latencies.

P20

A significant main effect of condition was found for P20 peak amplitude ($F(1,14)=5.64$, $p=0.03$), demonstrating that P20 peak amplitudes were larger in *Attend Index and Move* compared *No Task* condition. In addition, there was a significant main effect of time period of MN stimulation ($F(3,42)=3.36$, $p=0.03$). Tukey's post hoc analysis found that P20 peak amplitudes were larger when MN stimulation occurred 750 ms after compared to 250 ms after VibT stimuli (see Figure 4.1). A significant main effect of condition was found for P20 peak latency ($F(1,14)=4.91$, $p=0.04$), which showed that P20 peak latencies were later (21.1 ms) in *Attend Index and Move* compared *No Task* (20.9 ms) condition.

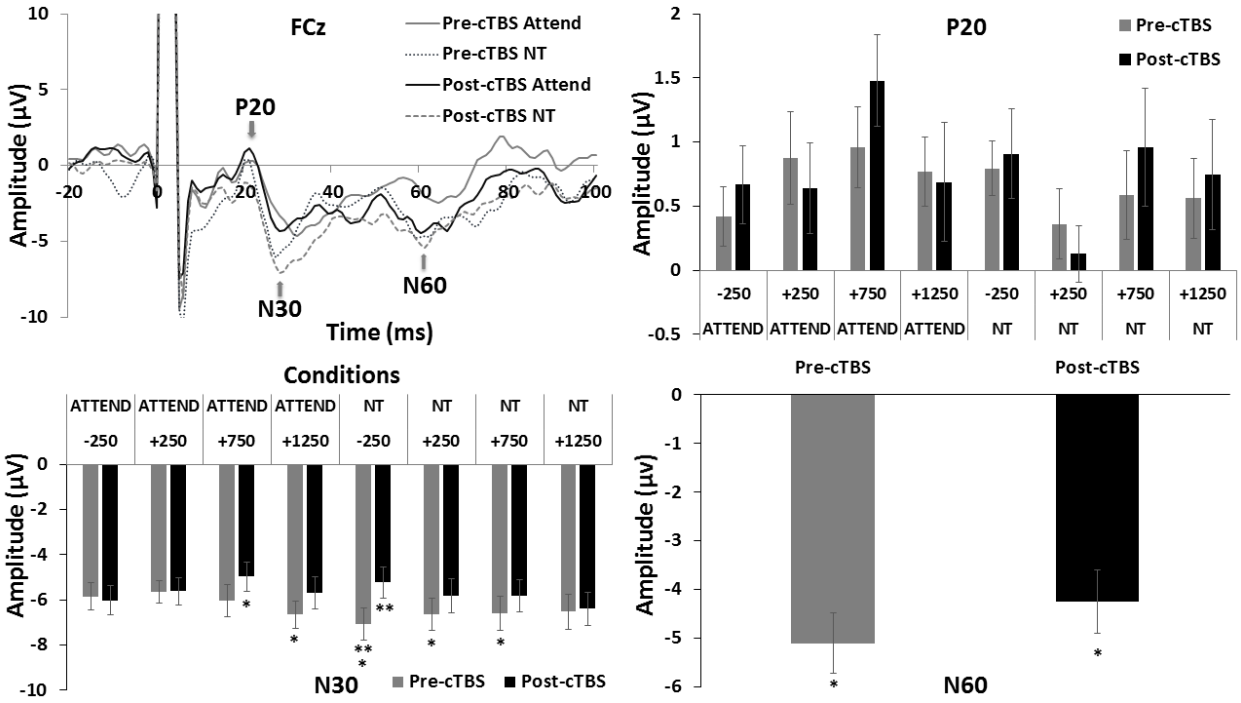

Figure 4.1 – Frontal SEPs (in microvolts, μV) elicited by left median nerve (MN) stimulation including *(top left)* representative participant sample waveforms evoked by MN stimulation occurring 750 ms after vibrtotactile (VibT) stimulation as well as mean (n=15) and standard error of (*top right)* P20, (*bottom left)* N30 and *(bottom right)* N60 SEPs in both *Attend Index and Move (Attend)* and *No Task* (NT) conditions at each time period of MN stimulation relative to VibT stimuli (-250, +250, +750, +1250) compared before (*pre-cTBS*) and after (*post-cTBS*) continuous theta burst (cTBS) stimulation over left premotor cortex (PMC). * Asterisks denote statistically significant differences.

Parietal SEPs

N20

No significant main effects or interaction were revealed for N20 peak amplitude or latencies.

P27

A significant interaction effect was found between condition and time period of MN stimulation for P27 peak amplitudes ($F(3,42)=4.15$, $p=0.01$) and P27 peak latency ($F(3,42)=3.06$, $p=0.04$). However, Tukey's post hoc analysis did not confirm any significant differences (see Figure 4.2).

P50

A significant main effect of condition for P50 peak amplitude ($F(1,14)=6.42$, $p=0.02$) showed that P50 peak amplitudes were larger in *Attend Index and Move* compared *No Task* condition. In addition, there was a significant main effect of time period of MN stimulation ($F(3,42)=5.97$, $p=0.002$). Tukey's post hoc analysis revealed that P50 peak amplitudes were larger 250 ms before and 250 ms after compared to 1250 ms after VibT stimulation (see Figure 4.2). A significant main effect on P50 peak latency between EEG session ($F(1,14)=5.23$, $p=0.04$) showed that P50 peak latencies were later in *post-cTBS* compared to *pre-cTBS* of PMC.

P100

A significant main effect of time period of MN stimulation ($F(3,42)=16.95$, $p<0.0001$) was revealed for P100 amplitudes. Tukey's post hoc analysis revealed that P100 peak amplitudes were smaller 250 ms after VibT stimulation compared to the three of time periods of MN stimulation (-250ms, +750ms and +1250ms relative to VibT stimulation). The main effect of condition narrowly missed significance ($F(1,14)=4.03$, $p=0.06$) suggesting that P100 peak

amplitudes were larger in *Attend Index and Move* compared *No Task* condition (see Figure 4.2). No significant effects were observed for P100 peak latency.

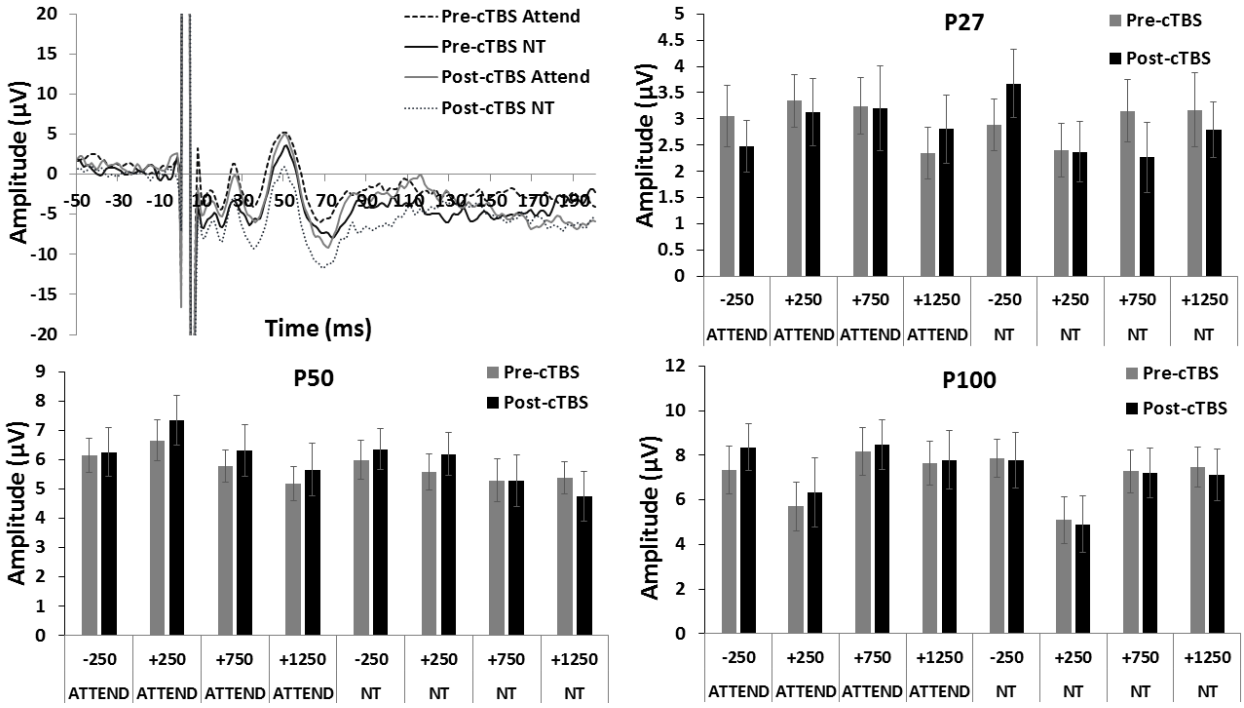

Figure 4.2 – Parietal SEPs (in microvolts, μV) elicited by left median nerve (MN) stimulation recorded from CP$ electrode including *(top left)* representative participant sample waveforms evoked by MN stimulation occurring 250 ms after vibrtotactile (VibT) stimulation as well as mean (n=15) and standard error of (*top right)* P27, (*bottom left)* P50 and *(bottom right)* P100 SEPs in both *Attend Index and Move (Attend)* and *No Task* (NT) conditions at each time period of MN stimulation relative to VibT stimuli (-250, +250, +750, +1250) compared before (*pre-cTBS*) and after (*post-cTBS*) continuous theta burst (cTBS) stimulation over left premotor cortex (PMC).

Behavioural Data

There were significant main effects of VibT amplitude on RT ($F(2,28)=7.41$, $p=0.003$) and MT ($F(2,28)=4.43$, $p=0.02$). Tukey's post hoc analyses confirmed that RT was slower to standard compared to either low or high VibT stimuli whereas MT was faster to standard

compared to low VibT stimuli (see Figure 4.3). No differences in RespT or VibT accuracy (see Table 4.1) were found.

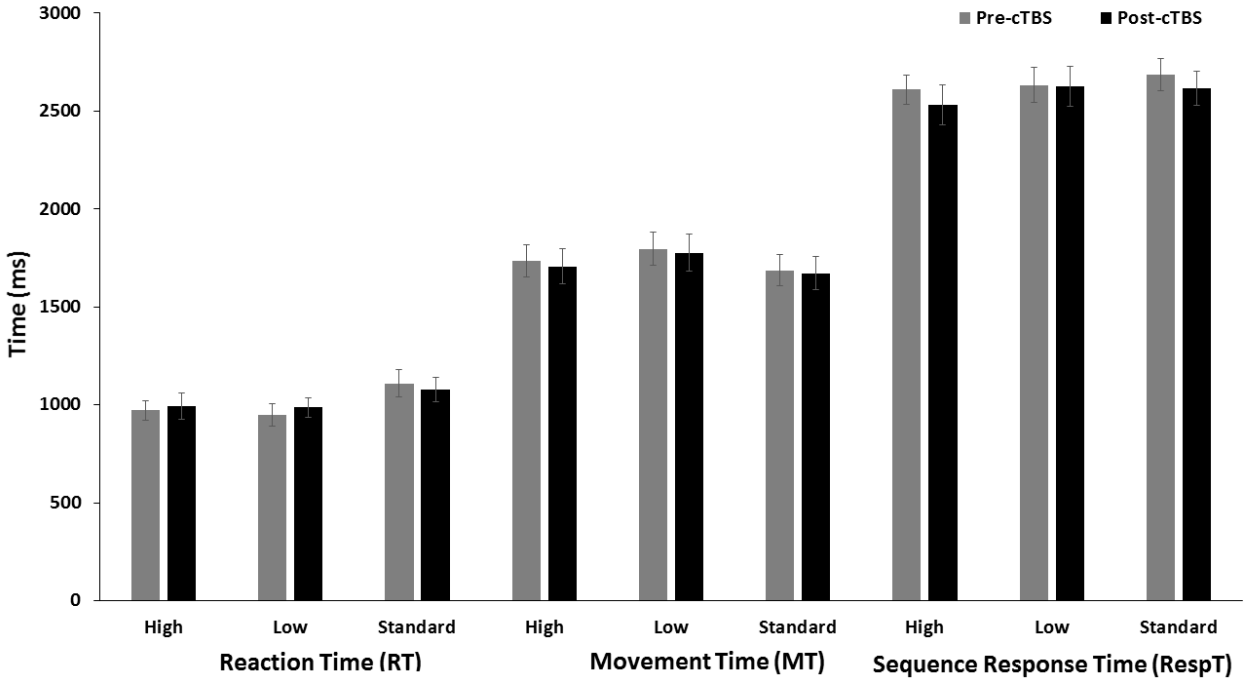

Figure 4.3 – Mean and standard error of participants (n=15) finger sequence reaction time (RT), movement time (MT) and sequence response time (RespT) to high, low and standard vibrtotactile (VibT) stimuli both pre-cTBS and post-cTBS to left premotor cortex (PMC).

Table 4.1 – Mean and standard deviation of vibrotactile (VibT) errors across all participants (n=15) including target misses, false positives, total errors and error rates during EEG sessions pre-cTBS and post-cTBS to left premotor cortex.

Pre-cTBS				Post-cTBS			
Target Misses	False Positives	Total Errors	Error Rate	Target Misses	False Positives	Total Errors	Error Rate
58.1 (+/- 29.4)	45.7 (+/- 21.9)	103.7 (+/- 32.7)	21.8 (+/- 6.7)	71.1 (+/- 31.0)	39.9 (+/- 15.3)	110.9 (+/- 35.8)	23.4 (+/- 7.4)

4.4.2. Experiment 2 – SEP modulation after right PFC cTBS

Frontal SEPs

N30

A significant main effect of time period of MN stimulation was found for N30 peak amplitudes ($F(3,45)=17.17$, $p<0.0001$) that was superseded by a significant interaction between EEG session and of time period of MN stimulation ($F(3,45)=3.07$, $p=0.04$). Tukey's post hoc analysis revealed that N30 peak amplitudes were smallest in *pre-cTBS* and *post-cTBS* of PFC at 250 ms after VibT compared to any other time period of VibT stimulation (largest at 750 ms after VibT stimulation). In addition, a trend towards increased N30 peak amplitude at 250ms before VibT stimulation were observed in *post-cTBS* compared *to pre-cTBS* of PFC ($p=0.08$). Trends toward significance were also observed in the main effect of EEG session ($p=0.09$) and interaction between condition and time period of MN stimulation ($p=0.09$) suggesting that N30 peak amplitudes were increased *post-cTBS* compared *to pre-cTBS* of PFC as well as increased in

Attend Index and Move compared *No Task* condition at 750ms after VibT stimulation (see Figure 4.4). No significant differences in N30 peak latencies were observed.

N60

A significant main effect of EEG session was observed for N60 peak amplitude ($F(1,15)=9.11$, $p=0.009$), revealing that N60 peak amplitudes were gated in *post-cTBS* compared *to pre-cTBS* of PFC. In addition, there was a significant main effect of time period of MN stimulation ($F(3,45)=12.45$, $p<0.0001$). Tukey's post hoc analysis confirmed that N60 peak amplitudes were larger at 250 ms after VibT compared to any other time period of MN stimulation relative to VibT stimuli (see Figure 4.4). No significant effects were observed for N60 peak latency.

P20

No significant main effects or interactions were observed for P20 peak amplitudes (see Figure 4.4) or latencies.

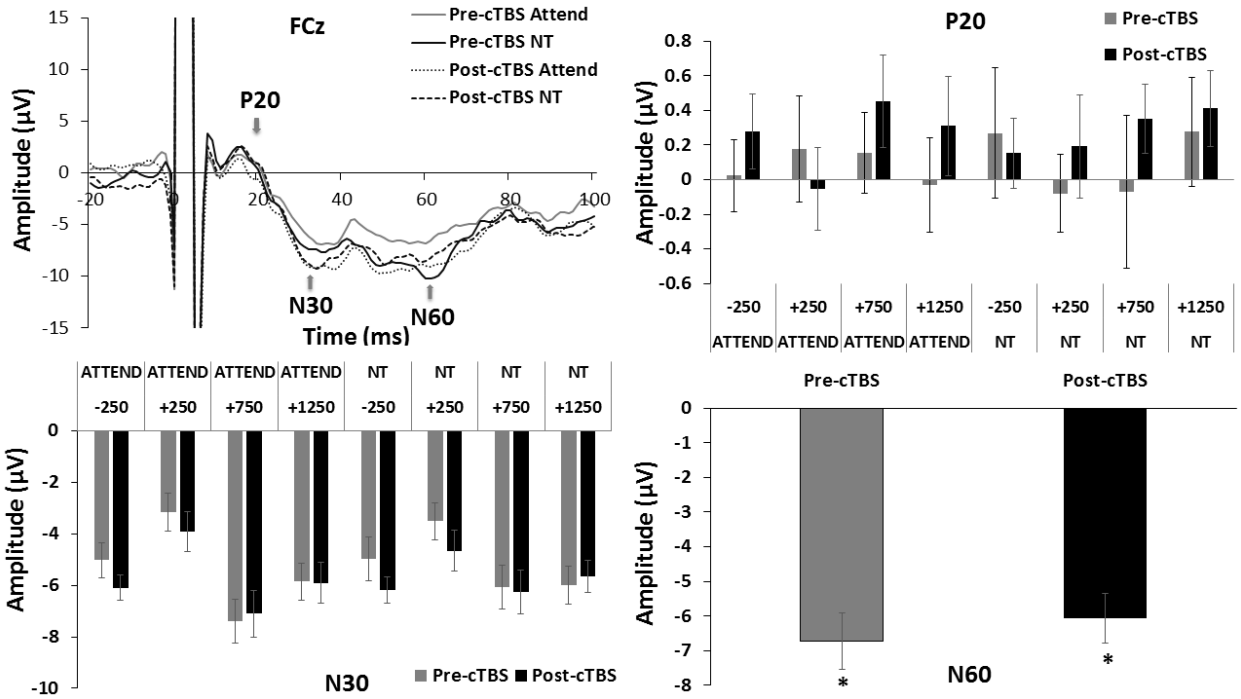

Figure 4.4 – Frontal SEPs (in microvolts, μV) elicited by left median nerve (MN) stimulation including *(top left)* representative participant sample waveforms evoked by MN stimulation occurring 250 ms after vibrtotactile (VibT) stimulation as well as mean (n=16) and standard error of (*top right)* P20, (*bottom left)* N30 and *(bottom right)* N60 SEPs in both *Attend Index and Move (Attend)* and *No Task* (NT) conditions at each time period of MN stimulation relative to VibT stimuli (-250, +250, +750, +1250) compared before (*pre-cTBS*) and after (*post-cTBS*) continuous theta burst (cTBS) stimulation over right prefrontal cortex (PFC). * Asterisks denote statistically significant differences

Parietal SEPs

N20

There was a significant interaction between EEG session and condition ($F(1,15)=4.92$, $p=0.04$) but this effect was not confirmed by Tukey's post hoc analysis (see Figures 4.5 and 4.6). No significant differences in N20 peak latency was observed.

P27

A significant main effect of condition ($F(1,15)=9.8$, $p=0.007$) was superseded by a significant three-way interaction between EEG session, condition and time period of MN stimulation ($F(3,45)=3.23$, $p=0.03$). Tukey's post hoc analysis found that P27 peak amplitudes were larger *post-cTBS* and *pre-cTBS* in *Attend Index and Move* at 750 ms after VibT stimulation compared to *pre-cTBS* in *No Task* at 750 ms after VibT stimulation. In addition, P27 peak amplitudes were also larger in *Attend Index and Move* at 250 ms before and after VibT stimulation compared to in *No* Task 750 ms after VibT stimulation in *pre-cTBS* of PFC (see Figures 4.5 and 4.6). No significant differences in P27 peak latencies were found.

P50

A significant main effect of P50 peak amplitude was revealed between conditions ($F(1,15)=5.76$, $p=0.03$), demonstrating that P50 peak amplitudes were enhanced in *Attend Index and Move* compared to *No* Task. Furthermore, there was a main effect of time period of MN stimulation ($F(3,45)=8.97$, $p=0.0001$). Tukey's post hoc analysis confirmed that P50 peak amplitudes were larger 250 ms after VibT compared to any other time period of MN stimulation. The main effect of EEG session narrowly missed significance ($p=0.06$) suggesting that P50 peak amplitudes were enhanced *post-cTBS* compared to *pre-cTBS* of PFC (see Figures 4.5 and 4.6). A significant interaction was observed between condition and time period of MN stimulation for P50 peak latency ($F(3,45)=3.39$, $p=0.03$). Tukey's post hoc analysis confirmed that P50 peak

latencies were earlier in *Attend Index and Move* at 1250 ms (45.88 ms) compared to 250 ms (48.66 ms) after VibT stimulation.

P100

There was a significant main effect of condition for P100 peak amplitude ($F(1,15)=31.48$, $p<0.0001$) as well as significant interaction between condition and time period of MN stimulation ($F(3,45)=4.77$, $p=0.006$). Tukey's post hoc revealed that P100 peak amplitudes were enhanced in *Attend Index and Move* compared to *No Task*, particularly at 250 ms after VibT stimulation. In addition, P100 peak amplitudes were larger in *Attend Index and Move* at 250 ms before, 250 ms after and 1250 ms after VibT stimulation compared to *No Task* at 250 ms after VibT stimulation (see Figures 4.5 and 4.6). No significant differences in P100 peak latencies were found.

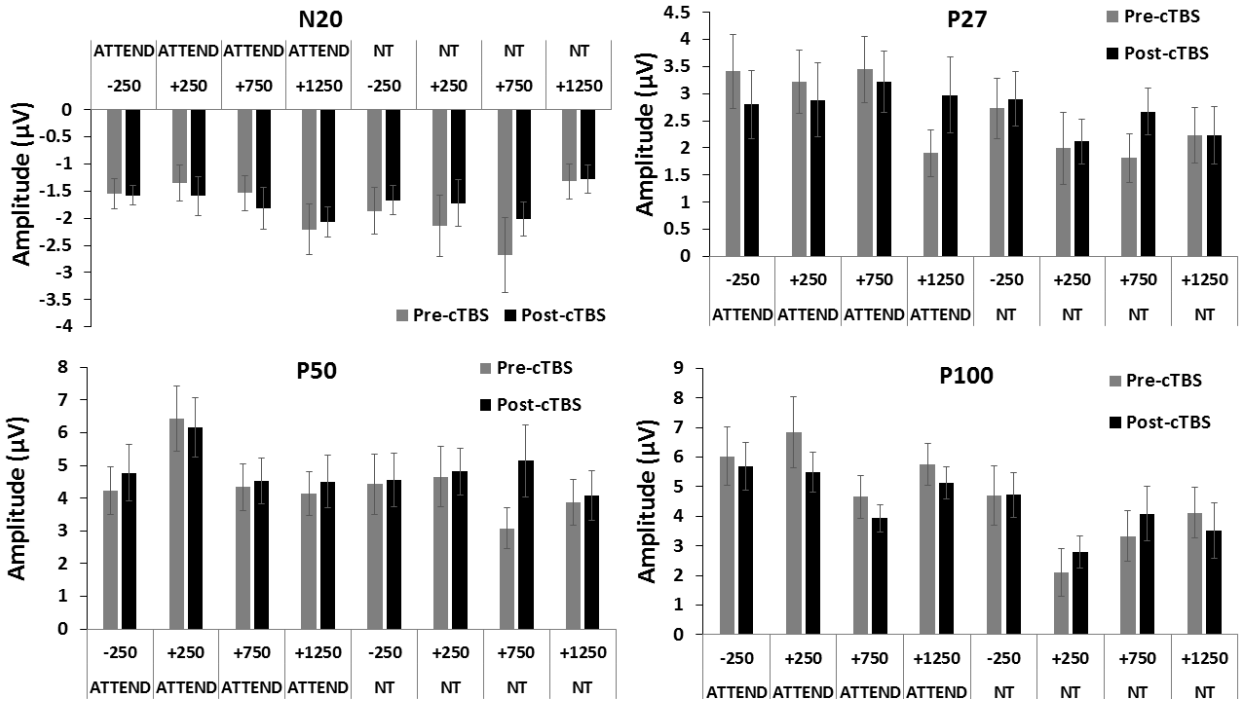

Figure 4.5 – Mean (n=16) and standard error of parietal SEPs (in microvolts, μV) elicited by left median nerve (MN) stimulation at CP4 electrode including *(top left)* N20, (*top right)* P27, (*bottom left)* P50 and *(bottom right)* P100 SEPs in both *Attend Index and Move (Attend)* and *No Task* (NT) conditions at each time period of MN stimulation relative to VibT stimuli (-250, +250, +750, +1250) compared before (*pre-cTBS*) and after (*post-cTBS*) continuous theta burst (cTBS) stimulation over right prefrontal cortex (PFC).

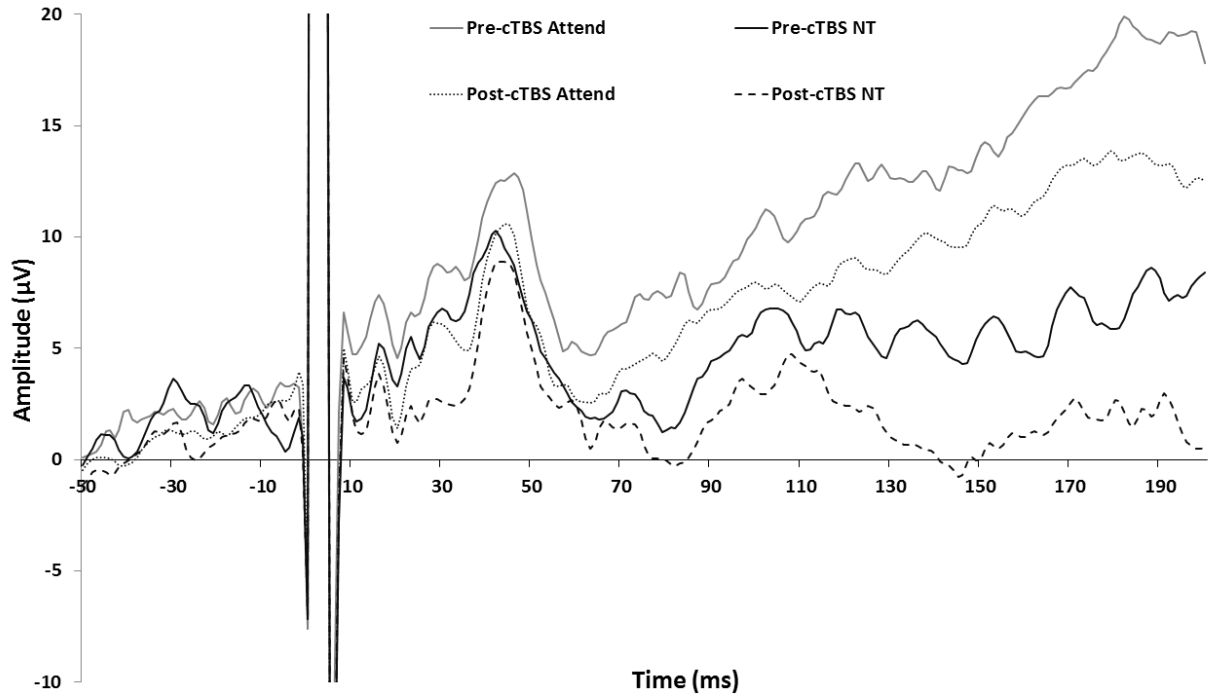

Figure 4.6 – Representative participant sample waveforms (in microvolts, µV) elicited by left median nerve (MN) stimulation at CP4 electrode in both *Attend Index and Move (Attend)* and *No Task* (NT) conditions at when MN stimulation occurred 250 ms after VibT stimuli compared before (*pre-cTBS*) and after (*post-cTBS*) continuous theta burst (cTBS) stimulation over right prefrontal cortex (PFC).

Behavioural Data

There were significant main effects of VibT amplitude on both RT ($F(2,30)=16.1$, $p<0.0001$) and RespT ($F(2,30)=17.01$, $p<0.0001$). Tukey's post hoc analysis confirmed that RT and RespT were slower to standard compared to either high or low VibT stimuli (see Figure 4.7). No significant effect was observed for VibT errors between *pre-cTBS* and *post-cTBS* of PFC (see Table 4.2).

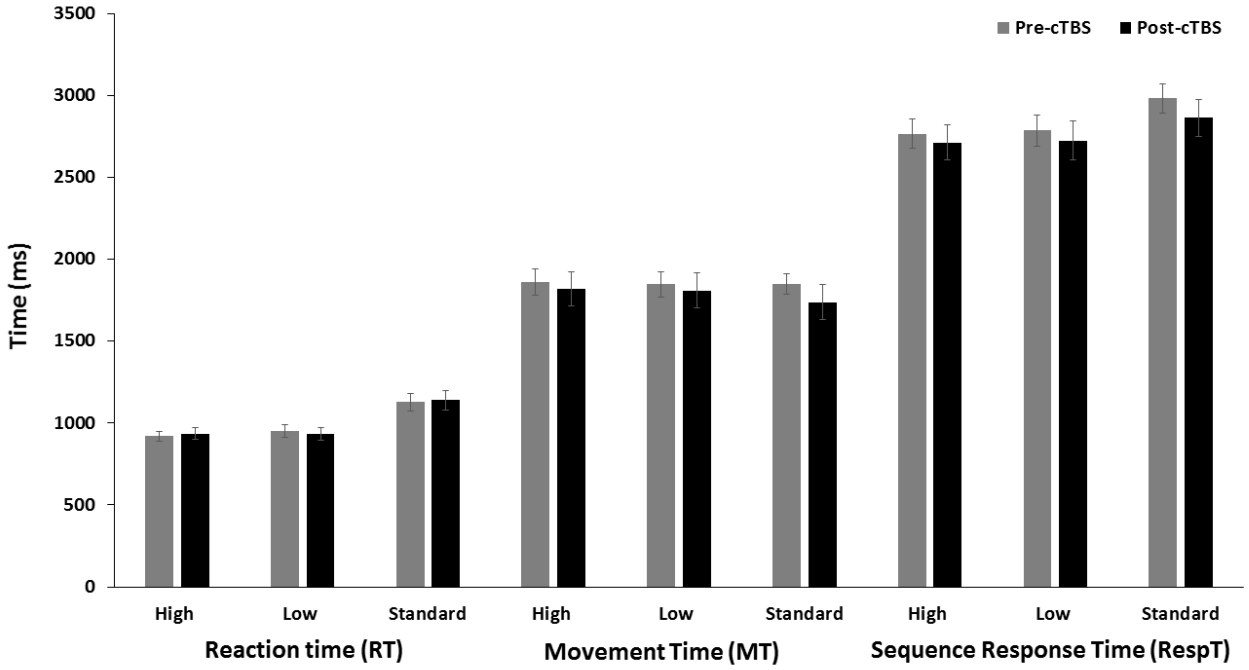

Figure 4.7 – Mean and standard error of participants (n=15) finger sequence reaction time (RT), movement time (MT) and sequence response time (RespT) to high, low and standard vibrtotactile (VibT) stimuli both pre-cTBS and post-cTBS to right prefrontal cortex (PFC).

Table 4.2 – Mean and standard deviation of vibrotactile (VibT) errors across all participant (n=15) including target misses, false positives, total errors and error rates during EEG sessions pre-cTBS and post-cTBS to left premotor cortex (PMC).

Pre-cTBS				Post-cTBS			
Target Misses	False Positives	Total Errors	Error Rate	Target Misses	False Positives	Total Errors	Error Rate
53.4 (+/- 35.6)	31.8 (+/- 15.6)	85.2 (+/- 37.6)	17.7 (+/- 8.0)	59.1 (+/- 29.8)	32.4 (+/- 13.6)	91.5 (+/- 31.0)	19.2 (+/- 6.5)

4.4.3. Direct comparison of differences after left PMC compared to right PFC cTBS

Frontal SEPs

A main effect of group was found for N30 peak amplitudes difference ($F(1,29)=5.94$, $p=0.02$) revealing that N30 peak amplitudes were gated after PMC cTBS but enhanced after PFC cTBS (see Figure 4.8). No significant differences were found for N60 or P20 peak amplitudes after PMC and PFC cTBS.

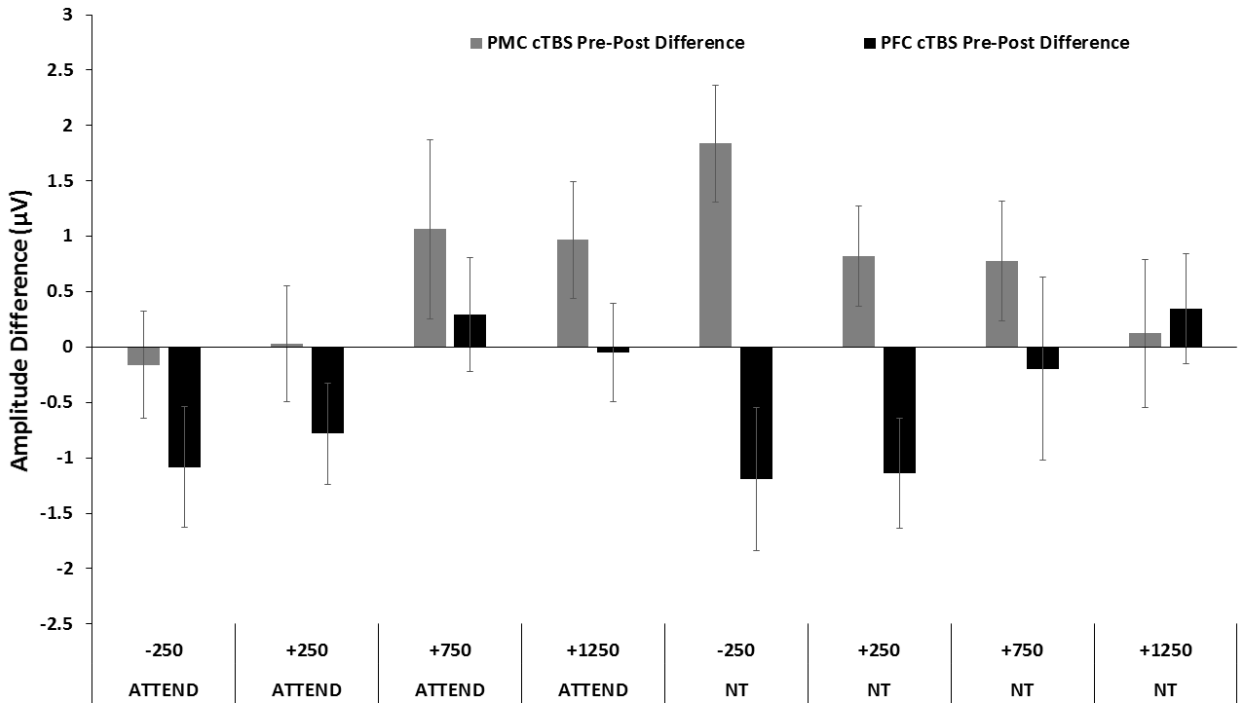

Figure 4.8 – Mean and standard error of frontal N30 peak amplitude differences (post-cTBS relative to pre-cTBS) in both *Attend Index and Move (Attend)* and *No Task (NT)* conditions and at each time period of MN stimulation .relative to vibrotactile stimuli (-250, +250, +750, +1250) after continuous theta burst stimulation (cTBS) applied over right prefrontal cortex (PFC) (n=16) and left premotor cortex (PMC) (n=15).

Parietal SEPs

There was a significant interaction for P27 peak amplitude differences between condition and time period of MN stimulation ($F(3,87)=4.1$, $p=0.009$). Tukey's post hoc analysis confirmed that P27 amplitudes decreased after both PMC and PFC cTBS in *Attend Index and Move* at 250 ms compared to increased at 1250 ms after VibT stimulation. A significant interaction between groups and condition was found for P100 peak amplitudes ($F(1,29)=4.48$, $p=0.04$). However, Tukey's post hoc analysis did not confirm a decrease in P100 peak amplitudes in *Attend Index and Move* after PFC compared to PMC cTBS. No other significant main effects or interactions were revealed for any parietal SEPs.

Behavioural Data

There were significant main effects of VibT amplitude on both RT ($F(2,58)=22.72$, $p<0.0001$) and MT ($F(2,58)=3.77$, $p=0.03$). Tukey's post hoc analysis confirmed RTs were slower after standard compared to high or low VibT stimulation as well as MT was faster to standard compared to low VibT stimulation. No differences between PMC and PFC cTBS were observed. In addition, there was a significant main effect $F(2,58)=10.57$, $p=0.0001$) as well as significant interaction between groups and VibT amplitude ($F(2,58)=3.3$, $p=0.04$) on RespT. Tukey's post hoc analysis confirmed that response times were slower to standard compared to high or low VibT stimuli only in PFC group. A trend towards increased errors was observed in *post-cTBS* compared to *pre-cTBS* ($p=0.09$), but significant differences were not observed between PMC and PFC cTBS on VibT error rates.

4.5. Discussion

The main purpose of the current study was to evaluate the roles of PMC and PFC on upper limb somatosensory processing, particularly somatosensory input into premotor areas represented by frontal N30 SEPs. The main finding of the current study was that N30 peak amplitudes were decreased after PMC cTBS but increased after PFC cTBS supporting different roles of the PMC and PFC in upper limb somatosensory processing. Specifically, cTBS to PMC was found to significantly decrease both N30 and N60 peak amplitudes in *Experiment 1* while no effects on parietal SEPs were revealed. In *Experiment 2,* cTBS to PFC was found to increase N30 peak amplitudes but decrease N60 peak amplitudes. Furthermore, increases in parietal P27 and P50 peak amplitudes were also revealed in *Experiment 2* after PFC cTBS.

4.5.1. Contribution of the left PMC to SEP modulations

In *Experiment 1,* cTBS applied over the PMC was found to decrease both N30 and N60 peak amplitudes without any significant effects on parietal SEPs. It was hypothesized that PMC cTBS would specifically decrease N30 peak amplitudes during movement preparation (i.e. only in the *Attend Index and Move* condition when compared to *No Task* condition at 750ms) based on our previous findings (Brown & Staines, 2015b). Although N30 peak amplitude were decreased in *Attend Index and Move* condition when MN stimulation occurred 750 ms after VibT stimulation to the index finger, this effect was not solely relative to *No Task* at 750 ms after VibT stimuli. In addition, N30 peak amplitudes were also decreased in *No Task* when MN stimulation occurred 250 ms before VibT stimuli. Previous research demonstrated that frontal N30 amplitudes elicited by dominant limb MN stimulation, measured at rest, were decreased 30 minutes after SMA cTBS (Legon et al., 2013). In contrast, increased N30 peak amplitudes were

revealed after monophasic 0.2 Hz rTMS over left PMC elicited by right MN stimulation but no effects were observed after M1 or SMA rTMS (Hosono et al., 2008; Urushihara et al., 2006). The current results support that transient inhibition of left PMC with cTBS was able to disrupt somatosensory processing elicited by left MN stimulation during late stages of preparing finger sequences with the right hand as well as during passive stimulation in the pre-stimulus period. Furthermore, robust decreases in frontal N60 peak amplitudes were revealed across all conditions and time periods of MN stimulation. Interestingly, the same studies that found N30 peak amplitude modulations after applying cTBS over SMA (Legon et al., 2013) and rTMS over PMC, SMA or M1 (Hosono et al., 2008; Urushihara et al., 2006) did not find significant modulations of N60 peak amplitudes.

Intracranial electrode recordings have found evidence that the frontal N30 may be generated in SMA (medial aspect of BA 6), PMd (dorsolateral of BA6) and lateral portions of BA 8 (Kaňovský et al., 2003). However, other intracranial electrode recording studies have not found evidence for involvement of SMA-proper or pre-SMA (Barba et al., 2003, 2001, 2005) and suggested even M1 involvement (Balzamo et al., 2004) in frontal N30 peak generation. Oscillatory models of N30 peak generation have suggested the N30 SEPs are generated by event-related synchronization (ERS) and phase locking (ITC) mainly involving M1 and PMC as well as PFC (BA9) (Cebolla et al., 2011). In contrast, there is evidence from intracranial recordings that the frontal N60 SEPs are generated within the pre-SMA (Barba et al., 2001, 2005). Therefore, the current results support that left PMC cTBS was able to disrupt somatosensory processing in the contralateral PMC, M1, SMA and/or PFC (as revealed by N30 peak amplitude decreases) as well as contralateral pre-SMA (as revealed by N60 peak amplitude decreases).

4.5.2. Contribution of the right PFC to SEP modulations

There were several results to support that the PFC had a role in SEP modulations including significant decreased N60 peak amplitudes as well as trends for P50 peak amplitudes ($p=0.06$) and increased N30 peak amplitudes ($p=0.08$) after PFC cTBS. Previous research showed that individuals with unilateral prefrontal lesions, primarily in the left hemisphere around BA 9 and 46, had increased parietal P26, N67 as well as increased frontal N28 (N30 equivalent) and P45 peak amplitudes at rest (Yamaguchi & Knight, 1990). In the same study, no effects were observed on parietal P40 (P50 equivalent) peaks and frontal N60 SEPs were not measured (Yamaguchi & Knight, 1990). These results provide support that the PFC is involved in tonic inhibition of several cortical generators of SEPs.

Interestingly, none of the PFC cTBS effects on frontal or parietal SEPs in the current study were unique to when individuals were attending to VibT input at the index finger for finger sequence preparation as hypothesized. Selective spatial attention to tactile stimuli has been shown to increase P50 (Schubert et al., 2008; Zopf et al., 2004) and P100 peak amplitudes (Eimer & Forster, 2003; Kida, Wasaka, Nakata, Akatsuka, et al., 2006a). These findings are in line with the current results for *Experiment 1* and *Experiment 2* and our previous research (Brown & Staines, 2015a) that found that P50 and P100 peak amplitudes were increased to MN stimulation when individuals attended to ipsilateral vibrotactile input that cued a finger sequence. Previous research has found increased BOLD in contralateral SI to task-relevant tactile stimuli that was associated with increased BOLD in the right PFC (BA 9) and decreased BOLD in ipsilateral to task-relevant tactile stimuli (Staines et al., 2002). In addition, increased P50 peak amplitudes during selective attention were associated with increased BOLD in contralateral SI and SII (Schubert et al., 2008). However, individuals with unilateral prefrontal lesions have been

shown to have reduced P100 attentional enhancements during selective spatial attention to tactile stimuli but no effects on P50 peak amplitudes (Bolton & Staines, 2014). Furthermore, cTBS to the right PFC did not reduce P100 attentional effects to attended tactile stimuli but rather increased P100 to unattended tactile stimuli (Bolton & Staines, 2011). Thus, the increase in P50 peak amplitudes after PFC cTBS in *Experiment 2* support that the PFC is involved in tonic inhibition of somatosensory inputs into SI (Knight et al., 1999) rather than excitatory modulation of task-relevant modulation.

The significant decreases in N60 peak amplitude after PFC cTBS in *Experiment 2* also suggest a role of the right PFC on regulating the cortical generators of N60 SEPs. Evidence from intracranial electrode recordings support that frontal N60 peaks are generated within the pre-SMA (Barba et al., 2003, 2001, 2005). Anatomically, the PFC is connected with the pre-SMA whereas limited connections exist with SMA-proper (Bates & Goldman-Rakic, 1993; Geyer et al., 2000; Luppino et al., 1993). Therefore, the currents results would support that right PFC may be involved in tonic excitation of pre-SMA and this is reduced after PFC cTBS. It should be noted that significant decreases in N60 peak amplitudes were also found in *Experiment 1* after PMC cTBS. Pre-SMA neuronal activity occurs almost exclusively before the onset of movement when needed to develop a motor plan (Geyer et al., 2000). Thus, the N60 SEP could represent a marker of somatosensory input used in developing motor plans, which both the left PMC and PFC contributes its modulation. However, several studies using functional imaging after 3 Hz rTMS to left PMd (Bestmann et al., 2005), 0.2 Hz rTMS to left PMC (Hosono et al., 2008; Urushihara et al., 2006) and 1 Hz rTMS over left PFC (Speer et al., 2003) have found remote physiological changes that occur under the area of stimulation but also in connected networks. Thus, it is possible that the N60 changes could have been a result of physiological changes on

pre-SMA N60 generators with cTBS itself rather than through connections with left PMC and right PFC. This result needs to be clarified by future rTMS studies by including a pre-SMA stimulation site.

4.5.3. Differences between PMC and PFC cTBS on frontal N30 SEP modulations

Direct comparison of N30 peak amplitude differences (post relative to pre cTBS peak amplitudes) revealed gated N30 peak amplitude after left PMC cTBS and enhanced N30 peak amplitudes after right PFC cTBS. It is possible that this effect was driven by the significant decrease in N30 peak amplitudes observed after left PMC cTBS in *Experiment 1*. However, a trend ($p=0.08$) was also revealed for increased N30 peak amplitudes after right PFC cTBS in *Experiment 2* suggesting that both left PMC and right PFC have a role in modulating the cortical generators of the frontal N30. As previously mentioned, N30 peak amplitudes are likely generated within PMC, SMA and/or M1 (Balzamo et al., 2004; Cebolla et al., 2011; Kaňovský et al., 2003). The decreased N30 peak amplitudes after left PMC cTBS in *Experiment* 1 are likely the result of disrupting the neurons in the generation of the frontal N30 peak through inter-hemispheric callosal connections between PMC (Zarei et al., 2006) or through the remote physiological effects of cTBS itself (Bestmann et al., 2005). Interestingly, ITC sources indicated that PFC (BA 9) contributes to frontal N30 peak generation (Cebolla et al., 2011). If this were true, than increases after cTBS to right PFC may have directly increased the pure phase-locking (ITC) of beta/gamma 30-45 Hz frequency resulting in increased N30 peak amplitudes. Alternatively, cTBS to PFC could have influenced the generators within PMC, SMA or M1 through intra-cortical connections. Anatomically, only rostral aspects of PMd and SMA are densely connected with PFC but not dorsal aspects of PMd, SMA or M1 (Barbas & Pandya,

1987; Bates & Goldman-Rakic, 1993; Geyer et al., 2000; Luppino et al., 1993). Thus, PFC could only influence N30 generators through connections that synapse first in rostral premotor areas than influence the assumed frontal N30 cortical generators in SMA-proper, PMd-proper and/or M1 through a second relay of the intracortical connections. Future research in the frequency domain could help to clarify the roles of PMC and PFC in N30 peak modulations.

4.5.4. Behavioural effects of cTBS applied over PMC and PFC

In *Experiment* 1, no significant influence on VibT detection errors or movement (RT, MT or RespT) were observed after cTBS to left PMC. Previous research has shown that rTMS over left PMC disrupted various aspects of upper limb motor behavior including increasing choice but not simple RT (Mochizuki, Franca, Huang, & Rothwell, 2005) and motor timing (Bijsterbosch, Lee, Dyson-Sutton, Barker, & Woodruff, 2011; Pollok, Rothkegel, Schnitzler, Paulus, & Lang, 2008). However, the tasks used in these experiments did not include vibrotactile cues or movements sequences. rTMS over SMA, compared to several control sites, was shown to increase errors in a complex finger sequences cued by an auditory metronome (Gerloff, Corwell, Chen, Hallett, & Cohen, 1997). Vibrotactile detection thresholds were also shown to increase 30 minutes after cTBS to SMA (Legon et al., 2013). Therefore, it is likely that the lack of behavioural effects after cTBS to left PMC were due to the involvement of the SMA in the performance of the current task and SMA was able to compensate for any disruptions to PMC.

A previous rTMS study investigating PFC and PMC effects on visual RT task and corticospinal excitability of M1 found marked effects on MEPs elicited by M1 TMS but no effects on errors or RT after either PMC or PFC rTMS (Duque, Labruna, Verset, Olivier, & Ivry, 2012). In *Experiment 2,* similar to *Experiment* 1, cTBS applied over right PFC also did not

influence VibT accuracy or finger sequence movement (RT, MT or RespT). Several studies have shown that rTMS applied over right PFC disrupts a variety of executive functions including impulsivity but not choice RT (Cho et al., 2010), working memory during Wisconsin card sorting task (Ko, Monchi, Ptito, Petrides, & Strafella, 2008), increase RT during an auditory-to-visual task switching task (Vanderhasselt, De Raedt, Baeken, Leyman, & D'haenen, 2006), and decreased response times on a visual Stroop Task (Vanderhasselt et al., 2007). However, none of these rTMS studies support a role of the right PFC in vibrotactile detection or finger sequence movements. A previous study revealed cTBS over right PFC increased accuracy to attended tactile stimuli compared to a control group, but the increased accuracy of cTBS group was no different than a sham cTBS stimulation group (Bolton & Staines, 2011). Thus, transient disruption of right PFC does not affect detection of attended vibrotactile stimuli nor right hand finger sequences.

4.6. Conclusions

In the current study, both left PMC (*Experiment 1)* and right PFC (*Experiment 2)* were found to modulate mixed somatosensory input evoked by left wrist MN stimulation. Specifically, transient disruption of the left PMC decreased frontal N30 and N60 SEPs. In contrast, transient disruption of right PFC decreased frontal N60 as well as increased frontal N30 and parietal P50 SEPs. Collectively, these results support that both left PMC and right PFC are involved in a modulatory network that influences somatosensory input from the upper limbs in non-primary motor areas such as PMC, SMA-proper and pre-SMA (represented by N30 and N60 SEPs). Although no effects on vibrotactile detection or finger sequence movement (i.e. RT) were observed after cTBS to PMC or PFC, these SEP modulations likely represent typical neural

networks and temporal patterns of mixed somatosensory input modulations for upper limb motor control. It has previously been shown that selective loss of frontal P22-N30 SEPs are associated with a variety of motor deficits including hemiplegia and motor neglect (Mauguière et al., 1983). Furthermore, it is plausible that these frontal N30 and N60 SEP modulations observed after PMC and PFC cTBS could be associated to upper limb sensorimotor deficits in prefrontal lesion patients (Knight et al., 1999; Krämer, Solbakk, Funderud, Løvstad, & Knight, 2014) and middle cerebral artery stroke patients (Jang, 2012; Seitz et al., 1998). Future research should investigate association between SEP modulations and upper limb sensoriomotor deficits in patients with affected PMC and/or PFC.

Chapter 5 - The effects of right premotor cortex (PMC) continuous theta burst stimulation (cTBS) on somatosensory input to non-primary motor areas

Chapter Research Objectives

This chapter attempted to answer specific research questions 7 and 8 (see section 1.5)

5.1. Abstract

Frontal N30 somatosensory-evoked potential (SEPs), recorded maximally by mid-frontal surface electrodes approximately 30 ms after median nerve (MN) stimulation, are thought to represent somatosensory input into premotor cortex (PMC) and supplementary motor area (SMA). Although intracranial electrode recordings have found conflicting evidence for SMA involvement, application of continuous theta burst stimulation (cTBS), a specific form of repetitive transcranial magnetic stimulation (rTMS), over SMA was shown to reduce frontal N30 SEPs. In contrast, 0.2 Hz rTMS over PMC but not SMA increased frontal N30 SEPs. These inconsistent findings in frontal N30 SEP changes after rTMS over PMC and SMA could be related to variability in response to rTMS. Recently, single-pulse TMS over primary motor cortex (M1) found that motor-evoked potential (MEP) onset latency differences with different coil orientations were associated with expected (i.e. inhibition) compared to unexpected (i.e. excitation) responses to M1 cTBS. The current study applied cTBS over the right PMC in a pre-post experimental design of sixteen (n=16) healthy adults to examine the effects on SEPs,

specifically frontal N30, elicited by both right and left MN stimulation. In addition, single-pulse TMS was applied over M1 with four different coil orientations (anterior-posterior (A-P), posterior-anterior (P-A), lateral-medial (L-M) and medial-lateral (M-L)) to measure MEP onset latency differences and their association to frontal N30 SEP changes. Results found that no significant changes in any SEP peak amplitude were observed after PMC cTBS. However, MEP onset latency differences between A-P and L-M were significantly correlated with N30 peak amplitude changes elicited by left MN stimulation up to 30 minutes after right PMC cTBS. These results revealed that individuals who have a longer MEP latency difference between A-P and L-M coil orientations were associated with an increased N30 peak amplitudes after right PMC cTBS. Therefore, individual responses to cTBS over PMC may be able to be partially predicted by MEP onset latency differences using TMS to M1 with different coil orientations. However, it remains unclear whether the PMC has a role in generating and/or modulating frontal N30 SEPs.

5.2. Introduction

The premotor cortex (PMC) is involved in movement preparation to sensory information, particularly visual cues (Chouinard & Paus, 2006; Hoshi & Tanji, 2007; Ohbayashi, Ohki, & Miyashita, 2003; Picard & Strick, 2001; Wise, Weinrich, & Mauritz, 1983). Somatosensory input also reaches PMC as evidenced through intracranial recordings in monkeys (Raos et al., 2003; Wiesendanger et al., 1985) and functional imaging in humans (Burton, Sinclair, & McLaren, 2008; Pleger et al., 2006). Intracranial electrode recordings involving the PMC in humans have identified somatosensory-evoked potentials (SEPs) after median nerve (MN) stimulation that are likely representative of scalp recorded frontal N30 SEP (Kaňovský et al., 2003). Thus,

recordings of frontal N30 SEPs over the cortical surface with electroencephalography (EEG) after MN stimulation may provide an index of somatosensory input into PMC.

Recently, application of continuous theta burst stimulation (cTBS), a specific type of repetitive transcranial magnetic stimulation (rTMS), over the supplementary motor area (SMA) was shown to reduce frontal N30 peak amplitudes 30 minutes post-cTBS stimulation (Legon et al., 2013). Although this finding supports a role of the SMA in generating frontal N30 SEPs, it is in conflict from intracerebral electrode recording studies that have not recorded frontal N30 SEPs from the SMA-proper or even pre-SMA (Barba et al., 2003, 2001, 2005). Furthermore, low-frequency 0.2 Hz rTMS was found to increase peak amplitudes of the frontal N30 when applied over the PMC but no effects were revealed after SMA or primary motor cortex (M1) rTMS (Urushihara et al., 2006). This result was replicated with monophasic 0.2 Hz but not biphasic 0.2 or 1 Hz rTMS over PMC (Hosono et al., 2008). Interestingly, low-frequency rTMS (0.1-1 Hz) (Fitzgerald et al., 2006) and cTBS (Huang et al., 2005) are both thought to have inhibitory effects on cortical excitability when applied over the cortex. Thus, it is unclear why rTMS protocols have had inhibitory and excitatory effects on frontal N30 SEPs when applied over the SMA and PMC, respectively.

Functional imaging after left dorsal premotor cortex (PMd) 3 Hz rTMS revealed local increases in left PMd as well as increased BOLD in several connected brain regions including SMA and contralateral PMd (Bestmann et al., 2005). In addition, three blocks of cTBS applied over the right pre-SMA resulted in a significant increase in several connected brain regions including the PMC as revealed through regional cerebral blood flow (rCBF) changes (Obeso et al., 2013). Therefore, modulations of frontal N30 SEPs after PMC or SMA rTMS could be the result of the spread of TMS induced excitability changes through its cortico-cortical connections

to the SMA or PMC, respectively. Furthermore, variability in individual's response to cTBS, and rTMS in general, have been well-documented (Cárdenas-Morales, Nowak, Kammer, Wolf, & Schönfeldt-Lecuona, 2010; Di Lazzaro et al., 2010; Fitzgerald et al., 2006; Hamada et al., 2013; Hoogendam, Ramakers, & Di Lazzaro, 2010; Ridding & Ziemann, 2010; Vernet et al., 2014; Ziemann et al., 2008). Recently, it was revealed that only 42% of 56 participants had reduced MEPs after cTBS to primary motor cortex (M1) (58% increased MEPs) (Hamada et al., 2013). Thus, differences in frontal N30 SEP modulations with PMC and SMA rTMS could be explained by individual variability.

Interestingly, it was found that individuals that had MEP onset latency differences greater than 4 ms between MEPs evoked with anterior-posterior (A-P) compared to lateral-medial (L-M) directed currents with single pulse M1 TMS were significantly associated with the expected inhibition after M1 cTBS (Hamada et al., 2013). A-P directed currents activate late indirect (I) waves that excite descending corticospinal fibers in M1 through complex trans-synaptic interneuronal connections (Di Lazzaro et al., 2012; Di Lazzaro, Ziemann, & Lemon, 2008). In contrast, L-M directed currents activate direct (D) wave that likely directly excite corticospinal neurons at their axons (Di Lazzaro et al., 2012; Di Lazzaro, Ziemann, et al., 2008). Thus, the expected inhibition after cTBS may be a result of individuals who late I-waves are more easily recruited and modulation of non-fast spiking inhibitory interneurons on distal dendrites of corticospinal neurons (Hamada et al., 2013). It is possible that cTBS effects on other cortical areas, such as PMC, occur through similar neurophysiological mechanisms and direction of response to cTBS (inhibition or excitation) over PMC could be associated with MEP onset latency differences between A-P and L-M directed currents after single pulse M1 TMS.

In the present study, the effects of cTBS on right PMC, presumably PMd, were evaluated using SEPs recorded by cortical surface EEG evoked by left and right MN stimulation. In addition, single pulse TMS was applied to M1 with different coil orientations to determine if MEP onset latency differences, particularly between A-P and L-M, would be associated with the direction of modulation (increases or decreases) in frontal N30 SEPs after PMC cTBS. It was hypothesized that right PMC cTBS would decrease N30 peak amplitudes elicited by left but not right MN stimulation. Furthermore, it was hypothesized that larger decreases in N30 peak amplitude would be significantly associated with longer MEP onset latency differences between A-P and L-M after M1 TMS.

5.3. Methods

5.3.1. Participants

Sixteen (n=16) individuals (11 males, age=26.3 +/- 4.15, range 21-34 years) were recruited to participate in the current experiment. All experimental procedures for this project were approved by the University of Waterloo Human Research Ethics board. All participants provided written informed consent and completed a TMS screening form prior to participation (Keel et al., 2001).

5.3.2. Experimental Design

All individuals participated in both TMS and EEG. The first part of the experiment measured active motor thresholds (AMT) and MEPs from the left first dorsal interosseous (FDI) after single-pulse TMS to the right primary motor cortex (M1) with four different coil orientations (see section 5.3.3. - Stimulation and Recording). After single-pulse M1 TMS, the

second part of the experiment involved an EEG session (pre-cTBS) recording somatosensory-evoked potentials (SEPs) elicited by both right and left median nerve (MN) stimulation followed by cTBS applied over the right PMd. The third part of the experiment involved four EEG sessions (Post 1, Post 2, Post 3 and Post 4) recording SEPs elicited by both left and right MN stimulation after right PMd cTBS; Post 1 was immediately following cTBS ($Post1_{immed}$), Post 2 was 15 minutes following cTBS ($Post2_{15min}$), Post 3 was 30 minutes following cTBS ($Post3_{30min}$) and Post 4 was 60 minutes after cTBS ($Post4_{60min}$). Each EEG session involved approximately 300 MN stimulations at a rate of 2 Hz that were randomly and equally separated to the left and right wrists while participants were at rest with eyes fixated forward.

5.3.3. Stimulation and Recording

Somatosensory-evoked potentials (SEPs)

SEPs were measured to MN stimulation elicited by 0.2 ms duration square wave pulses delivered through surface electrodes (anode distal) over left and right wrists using two separate stimulation units (GRASS SD9, West Warwick, Rhode Island, USA). The voltage of stimulation to both left and right MN was set to the smallest voltage sufficient to elicit a visible thumb twitch (i.e. motor threshold).

SEPs were recorded using two 10mm Ag-AgCl cup electrodes (Technomed, King Medical, London, Ontario, Canada) that were placed on the scalp over FCz and CP4 electrode sites in accordance with the international 10-20 system referenced to linked mastoids. Impedances were kept below 5 kOhms during continuous EEG data recording that was amplified (40000x), filtered (1-200Hz) and digitized at 1000 Hz (Neuroscan 4.3, Compumedics Neurscan, Charlotte, NC, USA) before being stored on a computer for offline analysis.

Electromyographic (EMG)

Surface EMG was recorded from left FDI muscle during TMS using 9 mm diameter Ag-AgCl electrodes with a bipolar montage. Active electrodes were placed over the muscle belly of the FDI and the reference electrode placed over the metacarpophalangeal joint of the index. The ground electrode was placed over the left clavicle. EMG recordings during TMS were amplified (1000x), band-pass filtered (2Hz-2.5kHz; Intronix, Technologies Corporation, Model 2024F, Canada), digitized (5kHz, Micro1401, Cambridge Electronics Design, Cambridge, UK) then recorded by a computer using software (Signal 4.3, Cambridge Electronics Devices, Cambridge, UK) before being stored for offline analysis.

In addition, surface EMG was recorded during EEG from the left and right thenar musculatures using bipolar montages and grounded to the left clavicle; these EMGs were used to record M-waves that represented the direct stimulation of the motoneuronal axons after MN stimulation. EMG from the left and right thenar musculature were amplified (40000x), filtered (1-200Hz) and digitized (1000 Hz, Neuroscan 4.3) before being stored on a computer for offline analysis.

Transcranial magnetic stimulation (TMS)

Single-pulse monophasic focal TMS was applied over the right M1 using a MagStim 200^2 stimulator (Magstim, Whitland, UK) and a custom-built figure-8 50mm stimulation coil. The position of the TMS coil to cortical targets was guided using BrainSight Neuronavigation (Rogue Research, Canada) using a template MRI for all participants. FDI motor hotspot in the right hemisphere M1 was determined as the optimal location for large and consistent left FDI

MEPs evoked using TMS with posterior-anterior (P-A) directed currents. This position was marked with a red pencil on the scalp for repositioning of the coil with different coil orientations (see below). AMTs were measured using a criterion of the lowest stimulus intensity that would elicit five out ten MEPs with peak-to-peak amplitudes greater than or equal to 200 μV while participants maintained a mild (10-20%) maximum voluntary contraction (MVC) in the left FDI using visual feedback (Huang et al., 2005).

Single-pulse monophasic TMS was applied in one of four coil orientations to measure differences in the descending corticospinal volley induced by the different directed currents similar to previous research (Hamada et al., 2013). Posterior-anterior (P-A) directed currents were produced by holding the figure-8 coil at a 45º angle to the mid-sagittal plane, which preferentially elicits early indirect (I) waves. A-P directed currents were elicited by holding the figure-8 coil at a 45º angle (opposite of P-A) to the mid-sagittal plane, which preferentially elicits late I-waves. L-M directed currents were produced by holding the figure-8 coil held at a 90º angle to the mid-sagittal plane, which preferentially recruits direct (D) waves at high stimulus intensities (Di Lazzaro, Pilato, et al., 2008; Hamada et al., 2013). The current experiment also included medial-lateral (M-L) directed currents that were elicited by holding the figure-8 coil at a 90º angle (opposite L-M) to the mid-sagittal plane as a control. AMTs were measured in blocks with A-P (AMT_{AP}), P-A (AMT_{PA}), L-M (AMT_{LM}) and M-L (AMT_{ML}) directed currents. In addition, 20 MEPs were collected within each block with the A-P and P-A currents over the FDI motor hot spot at 110% AMT_{AP} and AMT_{PA}, respectively. In contrast, 10 MEPs were collected in each block with L-M and M-L currents over FDI motor spot at 150% AMT_{LM} and AMT_{ML}, respectively. MEPs were always collected while individuals maintained 10% MVC in the target FDI muscle to ensure adequate corticospinal drive, particularly to elicit

D waves when combined with high stimulus intensities for L-M directed currents (Hamada et al., 2013; Werhahn et al., 1994).

Continuous theta burst stimulation (cTBS)

The current experiment used cTBS to modulate the cortical excitability of the right PMd using a MagPro x 100 stimulator (Medtronic, Minneapolis, MN, USA) and figure-8 (MCF-B65) 70mm stimulation coil. The cTBS protocol continuously applied 3 biphasic pulses at 50 Hz repeated every 200ms for a total of 600 pulses over 40 s at 80% AMT (Hamada et al., 2013; Huang et al., 2005). AMT_{bi} was measured over the same FDI motor hot spot as single pulse TMS using biphasic pulses guided by BrainSight. The handle of the coil was directed posteriorly and at a 45º angle relative to the midline for cTBS. The right PMd location was determined as 2.5cm anterior to the FDI motor hot spot in right M1 similar to previous experiments (Huang et al., 2009; Neva, Vesia, Singh, & Staines, 2014; Stinear et al., 2009).

5.3.4. Data Analysis

SEPs

SEPs were extracted from continuous EEG data by averaging epochs time-locked to either left or right MN stimulation (-100 to 200 ms) using NeuroScan (NeuroScan 4.3). Individual traces were baseline-corrected from the pre-stimulus period (-50 to 0 ms) and then visually inspected for rejection of epochs contaminated by artifacts before averaging. Latencies and amplitudes were measured for frontal (P20, N30 and N60) and parietal (N20, P27, P50 and P100) SEPs from FCz and CP4 electrodes, respectively. Peak amplitudes were measured relative

to the post-stimulus baseline voltage (between 12-20 ms) whereas peak latencies were measured from MN stimulus onset to peak amplitude.

Two-way analyses of variance (ANOVAs) were performed separately for each frontal SEP peak amplitude and latency with factors: EEG session (*pre cTBS, Post 1, Post 2, Post 3, Post 4*) and MN stimulation side (*left, right).* In addition, two-way ANOVAs were performed on frontal SEPs peak amplitude differences in pre compared to post sessions with factors: EEG session (*Pre-Post 1, Pre-Post 2, Pre-Post 3, Pre-Post 4*) and MN stimulation side (*left, right).* Separate one way ANOVAs for parietal SEPs peak amplitude and latency after left (contralateral to CP4) MN stimulation with the factor EEG session (*pre cTBS, Post 1, Post 2, Post 3, Post 4*). Similar to frontal SEPs, additional one-way ANOVAs were performed on parietal SEPs peak amplitude differences in pre compared to post sessions with the factor EEG session (*Pre-Post 1, Pre-Post 2, Pre-Post 3, Pre-Post 4*). Tukey's post hoc comparisons were used to confirm any significant interactions. An alpha level of 0.05 was used to define statistical significance for any main or interaction effects.

MEPs and MEP onset latency differences

MEP onset latencies and peak-to-peak amplitudes were measured by an automated detection program (Labview 8.5, National Instruments Corporation, Austin, Texas, USA). The MEP detection program measured onset latencies using a double-threshold method (Hodges & Bui, 1996). First, it was determined when the rectified EMG activity exceeded the average pre-stimulus background activity (-100 to 0 ms) by two standard deviations and second, stayed above the background activity for a minimum of 5 ms. Peak-to-peak amplitudes were calculated for each detected MEP after onset latencies were determined. The earliest MEP onset latencies were

calculated as the shortest MEP onset latency calculated for each coil orientation A-P, P-A, L-M, and M-L. MEP onset latency differences were measured between each directed current (A-P/P-A, A-P/L-M, A-P/M-L, P-A/L-M, P-A/M-L and L-M/M-L) from the earliest MEP onset latency similar to previous methods (Hamada et al., 2013). In addition, the mean MEP onset latencies and MEP peak-to-peak amplitudes were determined by averaging all detected MEPs for each coil orientation. Automated detection was used over visual-inspection to reduce experimenter bias.

One-way ANOVAs were performed for mean MEP onset latencies, earliest MEP onset latencies and MEP peak-to-peak amplitude with coil orientation (*A-P, P-A, L-M, M-L*) as the factor to confirm previous relationships between the different currents (i.e. L-M inducing the earliest MEP onsets). Tukey's post hoc comparisons were used to confirm any significant interactions. An alpha level of 0.05 was used to define statistical significance for any main or interaction effects.

Correlational and additional SEP Analyses

Pearson's product-moment correlational analyses were used to determine the association between MEP onset latency differences with the various directed currents and direction (increased excitability or inhibition) of response to cTBS over the PMd. Normal distribution of the data was confirmed using the Kolmogorov-Smirnov goodness-of-fit test. N30 peak amplitude differences at each post cTBS session compared to pre cTBS sessions after left MN stimulation were used to evaluate the response of cTBS over right PMd similar to changes in MEP amplitudes that have been used to measure cTBS responses over M1 (Hamada et al., 2013). In addition, ad hoc analyses were planned, based on the outcome of the correlational analyses, by

separating participants into groups based on significant correlations for MEP onset latency differences; these ad hoc analyses used mixed-model ANOVA to compare frontal N30 peak amplitude differences in post sessions with within-subject factor EEG session (*Pre-Post 1, Pre-Post 2, Pre-Post 3, Pre-Post 4*) and between-subject factor group (group 1, group 2). Tukey's post hoc comparisons were used to confirm any significant interactions. An alpha level of 0.05 was used to define statistical significance for any main or interaction effects.

5.4. Results

All sixteen participants were included in SEP analyses. However, one participant was removed from MEP analyses due to inability to elicit reliable MEPs in the A-P direction even with very high stimulation intensities.

5.4.1. SEPs

Frontal SEPs

A significant main effect of EEG session was observed for N30 peak amplitude ($F(4,60)=2.66$, $p=0.04$). However, Tukey's post hoc analysis did not confirm that N30 peak amplitudes were significantly decreased post-cTBS, particularly at *Post 4* compared to *Pre-cTBS* (see Figure 5.1). Therefore, no significant differences in P20, N30 or N60 peak amplitude or peak amplitude change were found for any EEG session regardless of whether SEPs were elicited by either left or right MN stimulation (see Figure 5.1).

A significant main effect of MN stimulation side on N60 peak latency was observed ($F,15)=4.87$, $p=0.04$) revealing that N60 peak latencies were significantly shorter after left (57 ms) compared to right (54.6 ms) MN stimulation. No significant peak latency differences were observed for P20 or N30 SEPs.

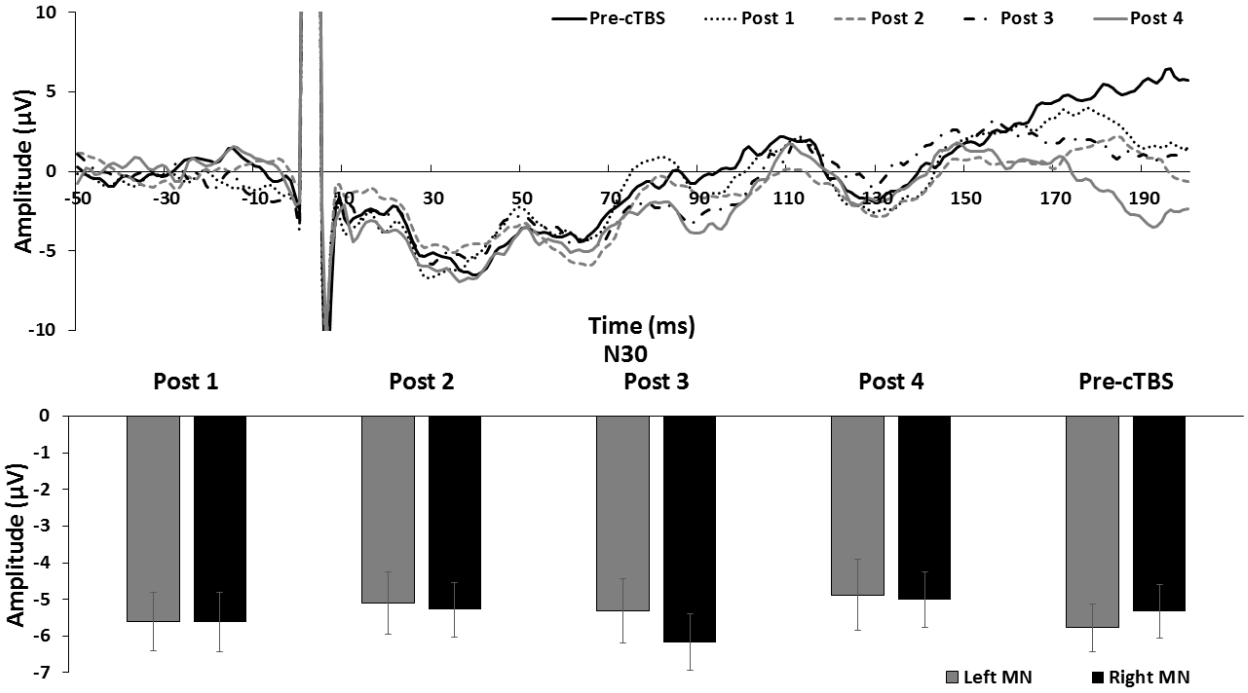

Figure 5.1 – Frontal SEPs displayed by (*top)* representative participant sample waveforms in microvolts (μV) after left median nerve (MN) stimulation at each EEG session and (*bottom*) mean and standard error across all participants (n=16) of frontal N30 SEPs elicited after left and right MN stimulation in pre-cTBS, $Post1_{immed}$, $Post2_{15mins}$, $Post3_{30mins}$, and $Post4_{60mins}$.

Parietal SEPs

No significant differences between EEG sessions was observed for any SEP (N20, P27, P50 or P100) peak amplitude or latency elicited by left MN stimulation (see Figure 5.2).

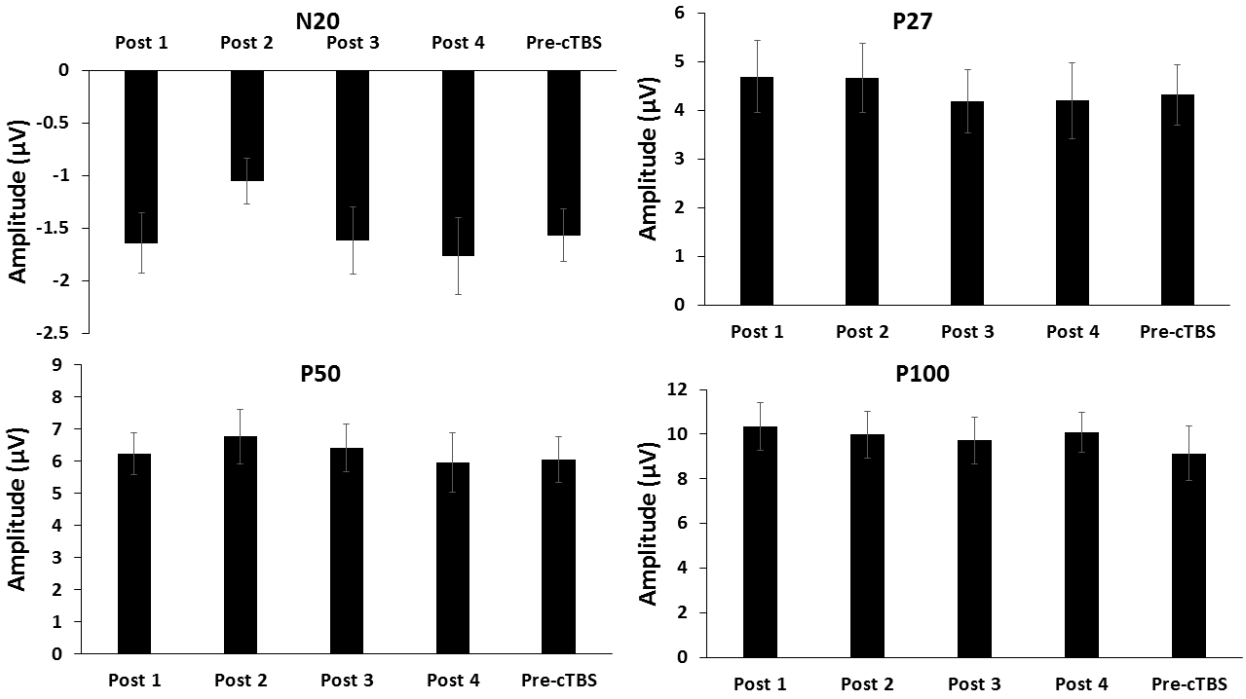

Figure 5.2 – Mean and standard error across all participants (n=16) in microvolts (µV) of (*top left)* N20, (*top right)* P27, (*bottom left*) P50, and (*bottom right*) P100 parietal SEPs elicited after left and right MN stimulation in pre-cTBS, $Post1_{immed}$, $Post2_{15mins}$, $Post3_{30mins}$, and $Post4_{60mins}$.

5.4.2. MEPs

A significant main effect of coil orientation was found for MEP peak amplitudes ($F(3,42)=6.32$, $p=0.001$). Tukey's post hoc analysis confirmed that MEP peak amplitudes were larger with both L-M and M-L compared to A-P or P-A coil orientations. In addition, a significant main effect of coil orientations was revealed for MEP mean onset latency ($F(3,42)=7.86$, $p=0.0003$), which Tukey's post hoc analysis showed that MEPs had an earlier onset with L-M and M-L compared to A-P coil orientations. Similarly, an effect of coil orientations was demonstrated for minimum MEP onset latency ($F(3,42)=21.5$, $p<0.00001$). Tukey's post hoc analysis confirmed that MEP onset latencies were significantly earlier

compared to each coil orientations in successive order (L-M earliest then M-L then P-A then A-P).

Table 5.1 – Group average (n=15) and standard error of MEP peak-to-peak amplitudes, mean MEP onset latencies and earliest MEP onset latencies.

MEP Peak-to-Peak Amplitude (μV)				Mean MEP Onset Latencies (ms)				Earliest MEP Onset Latencies (ms)			
A-P	P-A	L-M	M-L	A-P	P-A	L-M	M-L	A-P	P-A	L-M	M-L
1.65 (+/- 0.55)	1.98 (+/- 0.51)	3.87 (+/- 0.81)	3.81 (+/- 0.99)	29.73 (+/- 2.02)	26.21 (+/- 0.65)	23.18 (+/- 0.38)	25.16 (+/- 0.65)	26.35 (+/- 0.64)	24.68 (+/- 0.55)	22.27 (+/- 0.39)	23.91 (+/- 0.48)

5.4.3. Correlations between MEP onset latency differences with M1 coil orientation and frontal N30 peak amplitudes difference in each post cTBS session

Correlational analyses between MEP onset latency differences with A-P, P-A. L-M and M-L directed currents and N30 peak amplitude differences at each post session revealed significant negative correlations between A-P and M-L latency differences and N30 peak amplitude differences after left MN stimulation at Post 1 ($r(15)= -0.78$, $r^2= 0.60$, $t=-4.45$, $p=0.0007$), Post 2 ($r(15)= -0.57$, $r^2= 0.32$, $t=-2.48$, $p=0.03$)) and Post 3 ($r(15)= -0.52$, $r^2= 0.27$, $t=-2.17$, $p=0.049$) (see Figure 5.3). These results revealed an association that individuals with larger MEP onset latency differences between A-P and L-M coil orientations had enhanced (more negative) N30 peak amplitudes at Post 1, 2 and 3 sessions compared to pre cTBS session

after left MN stimulation. No other significant correlations were revealed between any MEP onset latency differences for N30 peak amplitude differences after left MN stimulation.

5.4.4. Ad hoc analysis - Effects of cTBS on N30 peak amplitudes based on different groups based on A-P and L-M MEP onset latency differences

Based on the correlational analyses, individuals were separated into two different groups: a) individuals (n=8) with A-P/L-M latency differences that were below 2 ms and associated with decreased N30 peak amplitudes in post cTBS sessions and b) individuals (n=7) with A-P/L-M latency differences that were above 2ms and associated with increased N30 peak amplitudes in cTBS post sessions. A trend towards significance was revealed between groups ($F(1,13)=3.81$, $p=0.07$), which suggested that right PMd cTBS enhanced N30 peak amplitudes in individuals with A-P/L-M latency differences above 2 ms and gated N30 peak amplitudes in individuals with A-P/L-M latency differences below 2 ms across all post sessions (see Figure 5.3 *bottom right*).

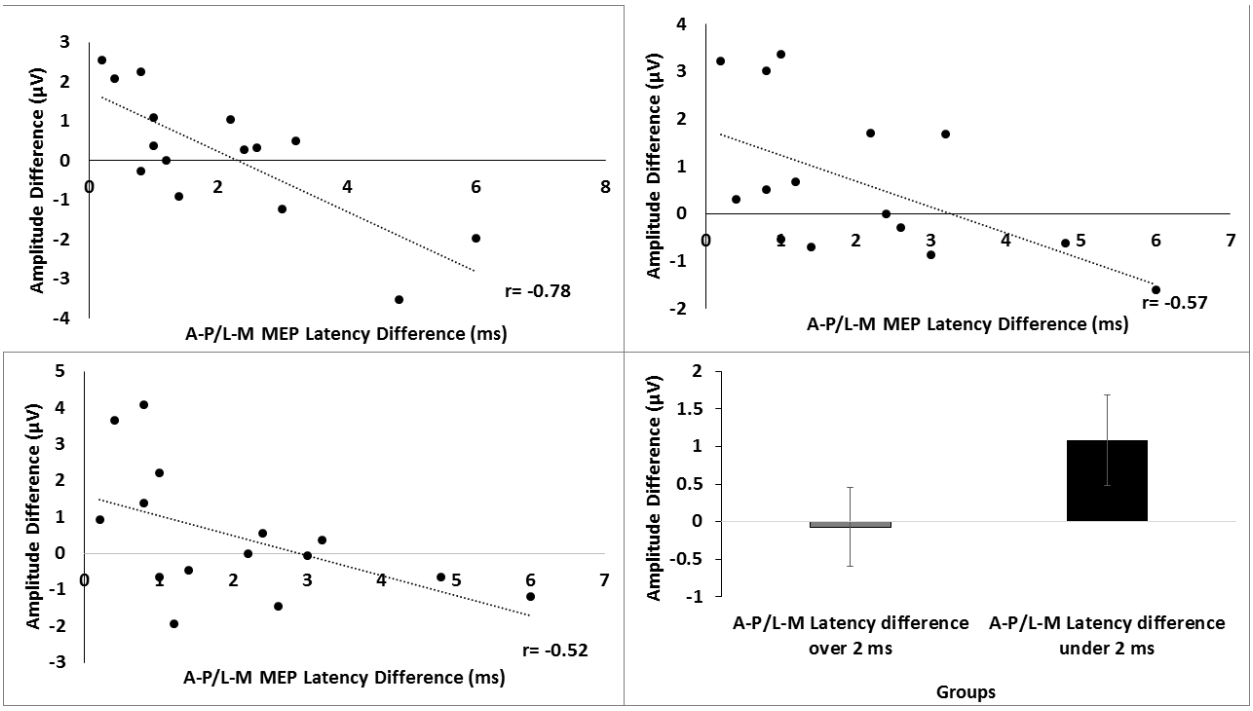

Figure 5.3 – Correlations of participants (n=15) of N30 peak amplitude differences (μV) at (*Top Left)* Post 1, *(Top Right)* Post 2, and (*Bottom Left)* Post 3 compared to pre sessions after left median nerve stimulation with MEP onset latencies elicited by right M1 TMS with anterior-posterior (A-P) and lateral-medial (L-M) coil orientations. (*Bottom Right*) N30 peak amplitude differences across all post sessions in individuals that had A-P/L-M MEP onset latency differences above 2 ms (n=7) and below 2 ms (n=8).

5.5. Discussion

The main finding of the current experiment was that MEP onset latency differences between A-P and L-M directed currents with M1 TMS were significantly negatively correlated with N30 peak amplitude changes, elicited by left MN stimulation, up to 30 minutes after right PMC cTBS. No significant differences in any SEP peak amplitudes, particularly frontal N30, were observed across all participants after right PMC cTBS. However, ad hoc analysis indicated a strong trend (p=0.07) that individuals who had a A-P/L-M onset latency difference greater than

2 ms had increased N30 peak amplitudes while individuals with A-P/L-M onset latency difference less than 2 ms had decreased N30 peak amplitudes.

5.5.1. MEP onset latencies after M1 TMS and cTBS responses

Previous research by Hamada *et al.* (2013) found that MEP onset latency differences between A-P and L-M directed currents were associated with individual responses of M1 cTBS (and iTBS) on MEPs. Specifically, MEP onset latency differences greater than 4 ms between A-P and L-M directed currents were associated with the expected inhibition (i.e. reduction of MEPs) in almost 60% of participants. It was concluded that more efficient late I wave recruitment, indicated by larger latency differences, could predict over 50% of the individual variability in response to M1 cTBS. It was argued that the association with late I wave recruitment was indicative of how cTBS influences the complex multi-synaptic inputs on distal dendrites of corticospinal neurons (Hamada et al., 2013). However, MEP recordings from electrodes implanted in cervical epidural space of four patients undergoing pain treatment found that M1 cTBS preferentially decreased early I1 waves, produced by monosynaptic input onto corticospinal neurons, but not later I waves (Di Lazzaro et al., 2005). Although the current study cannot provide a resolution to these different theories, both theories suggest that cTBS involves disruption of MEPs through at least one monosynaptic input rather than directly at the corticospinal axons.

The current study found that individuals who had larger latency differences between MEP onset latencies with A-P and L-M directed currents were associated with increased (enhanced) N30 peak amplitudes. However, understanding the neurophysiological mechanism based on current evidence that associates these M1 MEP latency differences and cTBS responses

is challenging. SEPs recorded from the cortical surface are summations of postsynaptic potentials that are volume conducted throughout the CNS and do not provide information about individual neurons but rather groups of neurons that dipoles are spatially and temporally aligned (Buzsáki, Anastassiou, & Koch, 2012). The spatial alignment of afferent input into parallel organized apical dendrites of pyramidal neurons make them ideal for spatially and temporally summated dipoles (Buzsáki et al., 2012). M1 is composed of densely packed giant pyramidal cells in layer V and absence of granular layer IV (Barbas & Pandya, 1987; Geyer et al., 2000). In contrast, caudal parts of PMd and SMA are also missing granular layer IV and composed of less densely distributed pyramidal cells in layer V but greater in layer III (Barbas & Pandya, 1987; Geyer et al., 2000). In SI, thalamocortical afferent inputs from the dorsal column-medial lemniscus pathway are prominent in layer IV (Tommerdahl, Favorov, & Whitsel, 2010). GABAergic double-bouquet inhibitory neurons from superficial layers in SI project across layers III and IV and synapse on pyramidal cells in layer V (Tommerdahl et al., 2010). Double-bouquet cells are also prominent in M1 (Yáñez et al., 2005), although their distribution in PMC were not investigated. One possible theory is that in certain individuals cTBS preferentially influences specific types of inhibitory interneurons, such as double-bouquet inhibitory interneurons, and influences somtatosensory input and motor output at pyramidal neurons in a similar manner. Research using intracranial electrode recordings combined with cTBS are required to investigate this theory.

5.5.2. PMC and frontal N30 SEPs

Most intracerebral electrode recordings in SMA-proper and pre-SMA (Barba et al., 2003, 2001, 2005) have found no evidence that the SMA is involved in the generation of the

scalp-recorded frontal N30 SEP, although there is some evidence from both intracerebral electrode recordings (Kaňovský et al., 2003) and cTBS (Legon et al., 2013). Interestingly, intracerebral electrode recordings (Kaňovský et al., 2003) and rTMS studies (Hosono et al., 2008; Urushihara et al., 2006) have found evidence for the involvement of PMC in the generation of frontal N30 SEPs. The current results cannot confirm nor dispute the role of the PMC in the generation of frontal N30 SEPs since Tukey's post-hoc analysis did not confirm the significant main effect that N30 peak amplitudes were decreased particularly at Post 4 compared to pre-cTBS. Thus, no significant differences in frontal N30 peak amplitudes, elicited by either left or right MN stimulation, were observed up to 60 minutes after right PMC cTBS across all participants. However, the lack of significant differences at the group level may be partially related to the opposite response (inhibition or excitation) to PMC cTBS. A trend towards N30 peak modulation after right PMC cTBS was observed after separating participants based on MEP onset latency differences elicited by different coil orientation with M1. Importantly, these results demonstrated that some participants increased while others decreased N30 peak amplitudes elicited by left MN stimulation across all post sessions after right PMC cTBS. Functional imaging after left PMd 3 Hz rTMS at 110% RMT revealed increased BOLD in both left and right PMd as well as other bilateral ventral premotor region, SMA and cingulate motor area amongst other connected cortical and subcortical regions (Bestmann et al., 2005). Thus, the PMC is involved, at the very least, in the modulation and possibly generation of frontal N30 SEPs.

5.6. Conclusions

Right PMC, presumably PMd, cTBS did not significantly modulate SEP peak amplitudes, specifically frontal N30 SEPs, across all participants. Individual responses to right PMC cTBS

measured by N30 peak amplitude (elicited by left MN stimulation) change were negatively associated with latency differences between A-P and L-M directed currents with M1 TMS. Specifically, individuals with larger latency differences were associated with increases (more negative) in N30 peak amplitudes up to 30 minutes post right PMC cTBS. It may be possible that A-P and L-M latency differences with M1 TMS were able to measure individual recruitment patterns elicited by TMS that are similar across both M1 and PMC. Further investigation into the association between MEP onset latency differences after M1 TMS with various directed currents and cTBS responses across multiple cortical areas is required. EEG and evoked potentials such as SEPs may be a valuable tool to help understand the underlying physiological mechanisms underlying cTBS and other forms of rTMS on cortical areas such as PMC.

Chapter 6 – General Discussion

6.1. Summary and Interpretation of Main Findings

The main objective of this thesis was to evaluate how and when mixed afferent upper limb somatosensory input is modulated in both non-primary motor areas and SI/SII by PFC and PMC activity. The main results of the studies within this thesis revealed that early somatosensory input into cortical premotor areas, represented by frontal N30 and N60 SEPs, could be differentially modulated (enhanced and gated) during preparing contralateral finger sequence movements to attended vibrotactile input as well as through transiently disrupting activity of the left (contralateral) PMC or right (ipsilateral) PFC. Furthermore, somatosensory input into SI/SII, represented by P50 and P100 SEPs, was consistently enhanced by attending to somatosensory input. These results support different modulatory roles of PMC and PFC on upper limb somatosensory input into non-primary motor areas and SI/SII.

In Chapter 1, the results of *Experiment 1* confirmed our hypothesis (specific research question #4) that sustained top-down attention to somatosensory input does not modulate somatosensory input into non-primary motor areas represented by frontal N30 SEPs. This finding was not surprising given previous results (Cheron & Borenstein, 1992; Garcia-Larrea et al., 1991; Kida, Nishihira, Wasaka, Sakajiri, et al., 2004). However, one significant oversight of these studies was that attended somatosensory input was not associated with the planning/preparation of movements. It was hypothesized (specific research question #4) associating attended somatosensory input with movement would be necessary to demonstrate SEP modulations in non-primary motor areas due to the recruitment of the top-down executive control attentional system during planning movements when there is competition and decision-

making required (Badre, 2008; Fuster, 2004; Koechlin et al., 2003; Miller & Cohen, 2001; Petersen & Posner, 2012). In *Experiment 2* of Chapter 1, this hypothesis was partially confirmed as attending to vibrotactile input that was relevant for planning a finger sequence response with the right (contralateral) hand reduced both frontal N30 and N60 peak amplitudes. Importantly, these gating effects of frontal SEPs were not solely the effect of self-initiating the finger sequence movements. However, gating compared to enhancement of these frontal SEPs was unexpected given that somatosensory input into SI/SII (i.e. P50 and P100) is usually enhanced by top-down attention (Adler et al., 2009; Bolton & Staines, 2011; Desmedt & Tomberg, 1989; Eimer & Forster, 2003; Garcia-Larrea et al., 1991; Giabbiconi et al., 2004; Michie et al., 1987; Schubert et al., 2008; Zopf et al., 2004); a finding that was confirmed in both *Experiment 1* and *Experiment 2* of Chapter 1 since both sustained attention and attending to vibrotactile input that was relevant for planning a finger sequence response with the right (contralateral) hand enhanced somtasensory input into SI/SII (i.e. P50 and P100 SEPs). Collectively, these results suggested that the gating of frontal SEPs was the result of a different network than the top-down attentional system involved in parietal SEP enhancements.

Chapter 3 aimed to clarify the results of Chapter 2 by manipulating the temporal relationship between when SEPs were being evoked: either before or after attended somatosensory (i.e. vibrotactile) input, or during preparation and execution of the cued right (contralateral) finger sequence. The results of Chapter 3 supported our hypotheses (specific research questions #1 and #2) by revealing enhanced somatosensory input into non-primary motor areas through increased frontal N30 and N60 SEPs, specifically during late stages of preparing finger sequence responses with the right (contralateral) hand to attended to vibrotactile input. Unfortunately, only minor (insignificant) gating of frontal SEPs was observed in Chapter 3

as demonstrated in *Experiment 2* of Chapter 2 when SEPs were measured right after attended somatosensory input during early response selection. It is likely that *Experiment 2* of Chapter 2 revealed very subtle frontal SEP modulations that were masked by the large frontal N30 and N60 enhancements observed in Chapter 3.

Importantly, the differential gating and enhancements of frontal N30 SEPs during different stages of contralateral movement preparation provide valuable new evidence into sensory gating. Previous studies have exclusively found enhancements during repetitive contralateral movements (Legon et al., 2010, 2008; Rossini et al., 1997) and gating during preparation, imagination and execution of ipsilateral movements (Cebolla et al., 2009; Cheron & Borenstein, 1987, 1991, 1992; Cheron et al., 2000). Collectively, the results of Chapters 2 and 3 support two conclusions: 1) the presence of modulation during movement preparation is dependent on the task and/or complexity of movement, and 2) different mechanisms related to the networks active during preparing and executing right (contralateral) finger sequences to attended somatosensory input are able to differentially gate or enhance somatosensory input into non-primary motor areas during the time course of an upper limb movement. In the early response selection stages, gating of frontal SEPs in *Experiment 2* of Chapter 2 were likely the result of inhibition caused by a PFC/pre-PMd/pre-SMA network that are known to be active during the earliest stages when stimulus-response associations are being decided on (Fuster, 2004; Hoshi & Tanji, 2004a, 2004b; Ikeda et al., 1999; Koechlin et al., 2003). In contrast, enhancement effects on frontal SEPs during very late stages of finger sequence preparation in Chapter 3 were likely primarily driven by excitation or disinhibition related to activity in the left PMd-proper, SMA-proper and/or M1 that is known to precede the execution of cued movements (Hoshi & Tanji, 2004a, 2004b; Ikeda et al., 1999). It should be noted that no effects were

observed on frontal SEPs during the pre-stimulus period in opposition of the hypothesis (specific research question #5), which further confirms that the top-down PFC attentional system alone does not modulate frontal SEPs.

In Chapter 4, the contributions of two of the suspected cortical nodes, left PMC and right PFC, to the SEP modulations observed in Chapters 2 and 3 were examined in *Experiment 1* and *Experiment 2* of Chapter 4, respectively. Transient disruption of the left PMC with cTBS in *Experiment 1* of Chapter 4 was shown to decrease both frontal N30 and N60 SEPs. The decreased N30 SEPs after disrupting left PMC were largest during late stages of preparing finger sequences to attended somatosensory input with the right (contralateral) hand, although the decreased N60 was observed regardless of condition or time period when SEPs were evoked. These results partially support the hypothesis (specific research question #3) that the left PMC does contribute to frontal N30 SEP modulations during the late stages of preparing finger sequence. Moreover, the decreased N30 and N60 SEPs support a more generalizable role of left (contralateral) PMC on the tonic excitation of somatosensory input into non-primary motor areas. In *Experiment 2* of Chapter 4, transient disruption right (ipsilateral) PFC increased frontal N30 while decreasing frontal N60 SEPs. These results partially support the hypothesis (specific research question #6) for the role of PFC in frontal SEP modulations but these effects were not found specifically during the pre-stimulus period. Therefore, it is likely these changes reflect disruption of tonic inhibition and excitation of PFC on somatosensory input into PMd/SMA-proper/M1 (N30 generators) (Balzamo et al., 2004; Kaňovský et al., 2003) and pre-SMA (N60 generators) (Barba et al., 2005), respectively. These results support the essential role of PFC in inhibitory control (Knight et al., 1999) as well as the deficits in inhibiting somatosensory input that has been previously observed in prefrontal lesion patients (Yamaguchi & Knight, 1990).

Chapter 5 had its own unique contribution to this thesis as the role of the right PMC in the generation (rather than modulation) of frontal N30 SEPs was explored at rest without any additional somatosensory (i.e. vibrotactile) input and/or movement task like Chapters 2-4. However, the results of Chapter 5 were unable to support the hypothesis (specific research question #7) and clarify the role of PMC in the generation of frontal N30 SEPs. Increased as well as decreased N30 SEPs were observed after transient disruption of right PMC with cTBS only after separating participants into two different groups. However, these changes in frontal N30 SEPs do provide support that the right (ipsilateral) PMC is, at the very least, involved in the modulation of N30 SEP generators in SMA-proper, PMd and/or M1 (Balzamo et al., 2004; Kaňovský et al., 2003). Interestingly, the results from Chapter 5 supported the hypothesis (specific research question #8) that measuring MEP onset latency differences evoked by L-M and A-P directed currents with single pulse TMS over M1 could potentially be a marker of the underlying physiology of how neurons within PMC and M1 respond to cTBS. This hypothesis was based on findings that found associations between different directed currents induced by M1 TMS and TBS over M1 (Hamada et al., 2013). Although anatomical and functional differences exist between M1 and PMC, these results support that PMC and M1 may share a common physiological response to cTBS. The current thesis cannot provide any direct insight into this potential common physiological mechanism that may exist but it may be that cTBS affects a specific subpopulation of neurons (ex. double-bouquet inhibitory neurons) in particular individuals, which can be measured by M1 TMS with different directed currents. If this notion is true, it could provide a reliable means to separate individuals into different groups when performing cTBS.

A secondary objective of this thesis was to evaluate the effects that SEP modulations had on finger sequence movement performance and vibrotactile detection accuracy. In Chapter 4, neither accuracy of detecting somatosensory (i.e. vibrotactile) input nor finger sequence movement performance (i.e. RT, MT and RespT) were different despite frontal or parietal SEP modulations. Previous research has found no effects on RT in visual RT task despite changes on MEPs evoked by M1 TMS after PMC and PFC rTMS (Duque et al., 2012). Furthermore, sequential finger tapping was unaffected after cTBS to M1 despite measured significant increases in cerebral blood flow measured by arterial spin labeling (Orosz et al., 2012). It was suggested that acute plasticity changes induced by cTBS are observable at the metabolic level but may not always be measurable at the behavioural level (Orosz et al., 2012). The results of Chapter 4 would support a similar view since neurophysiological changes were measured after cTBS without changes in behaviour. Unfortunately, a direct link between N30 or N60 SEP modulations and dysfunctional upper limb sensorimotor control cannot be confirmed based on the results of the current thesis since no behavioural effects were observed. However, it remains possible that frontal SEP modulations may be associated with dysfunctional upper limb motor control. Individuals with basal ganglia dysfunction that are known to have impairments in upper limb sensorimotor control such as PD (Cheron et al., 1994; Cheron, 1999; Pierantozzi et al., 1999; Rossini, 1996; Rossini, Babiloni, et al., 1989; Ulivelli et al., 1999), Huntington's disease (HD) (Abbruzzese & Berardelli, 2003; Topper, Schwarz, Podoll, Domges, & Noth, 1993), dystonia (Murase et al., 2000; Reilly, Hallett, Cohen, Tarkka, & Dang, 1992), or even children with striatal lesions (Kato et al., 2007) have demonstrated significant modulations and even abolishment of frontal N30 SEPs. These results confirm that the N30 SEP may be an important physiological index of the basal ganglia motor loop (putamen-thalamus-cortical motor areas)

(Cheron, 1999). However, these frontal N30 modulations are not unique to basal ganglia dysfunction as they have been observed in patients with cerebral palsy (Tomita et al., 2006), unilateral precentral lesions (Mauguière et al., 1983; Slimp et al., 1986) and even aging (Desmedt & Cheron, 1980). To date, no direct association has been found between frontal N30 modulations and dysfunctional upper limb motor control in these populations but it seems very plausible that one exists. Collectively, the behavioural and SEP results of Chapter 4 would suggest that multiple SEP modulations can occur without significant effects on tactile detection or finger sequence movement performance. It is unclear whether this is because there is redundancy in the somatosensory input into non-primary motor areas (i.e. frontal N30 and N60) as well as SI/SII that can overcome decreased or increased somatosensory input at a different processing stage. Alternatively, SEP modulations may need to be extremely large or even multiple SEP changes are required for noticeable behavioural effects. These are important considerations to associate frontal and/or parietal SEP modulations with upper limb motor control.

6.2. Conclusions

Frontal N30 and N60 SEPs are differentially modulated, gated and enhanced, during early compared to late stages when individuals prepare right (contralateral) finger sequences to attended somatosensory input. These frontal SEP modulations were partially caused by changes in tonic excitation or inhibition by the left (contralateral) PMC and right (ipsilateral) PFC. However, these modulatory effects on somatosensory input into non-primary motor areas were not caused by the top-down PFC attentional system that was responsible for enhanced somatosensory input into SI/SII, represented by P50 and P100 SEPs.

The results of this thesis demonstrated that sensory gating and enhancement is not lateralized with movement to one side of the body but rather that the direction of frontal N30 SEP modulation is very dependent on networks, rather than a single neural area, that are active at any given point in time. Furthermore, SEP modulations were not associated with any noticeable behavioural effects, either on accuracy of detecting vibrotactile stimuli or finger sequence movement performance. Although it is possible that these SEP modulations represent typical mechanisms involved in upper limb somatosensory processing based on varying background neural activity, it is also possible that the finger sequence task and measures used were not sensitive enough to show behavioural differences (see section 6.3.3. for more detailed discussion). Future research should examine different tasks and measures to evaluate the behavioural changes associated with SEP modulations.

6.3. Limitations

The current thesis was limited by several factors including (but not limited to) spatial limitations of EEG, unknown physiological effects of cTBS, response device issues, non-individualized vibrotactile thresholds and lack of control groups. These limitations are discussed in detail below.

6.3.1. EEG

EEG has a major advantage over several other neurophysiological techniques to give temporal precision to the millisecond. However, cortical surface EEG is limited by the lack of spatial specificity to the individual neurons or even population of neurons in a single neural area that contribute to the generation or modulation due to volume conduction. Despite the large body

of literature including intracranial recordings that currently exists on the main dependent measure of this thesis, the frontal N30, there is still uncertainty about the exact location(s) where the neurons that contribute to its generation exist. However, it is clear that it is not the result of GABA-dependent hyperpolarization (Restuccia et al., 2002) and it is likely representative of depolarization after afferent relay. Therefore, the interpretation of N30 modulations cannot account for changes in single population of neurons in a given neural area but rather the generating network. Although adopting a network model to EEG SEP modulations can still be valuable, it is possible that it fails to capture unique changes that are occurring within specific nodes of the network such as those observed in PMd during active compared to SMA during mental movement that was observed with intracranial recordings (Kaňovský et al., 2003). If this were the case, then SEP amplitude differences, such as frontal N30 modulations observed in the current thesis, could reflect decreased or increased activity in one area involved in the generating network but not the others. In other situations, there could be differential decreased and increased activity in a different population of neurons involved in the network, which could washout the effects. Considering the main findings of this thesis support that the direction of frontal SEP modulations are temporally dependent on network activity at any given point in time, this could be a significant contributor to variability observed in the current thesis as well as all the previous research that has relied on SEP peak amplitude changes.

6.3.2. cTBS

cTBS, and low-frequency rTMS techniques before it, have consistently been used over the past two decades to induce transient decreases in cortical activity through NMDA-dependent LTD-like neuroplasticity changes to simulate cortical lesions. The major limitation with this

notion is that when cTBS or any rTMS is applied over M1, there has been a considerable amount of variability (inhibition or excitation) in response measured through MEP changes (Fitzgerald et al., 2006; Hamada et al., 2013; Ridding & Ziemann, 2010). This may be consequence of a variety of environment and individual factors (see Ridding & Ziemann, 2010 for review) and based on the results of Chapter 5 in the current thesis this variability does not appear unique to M1. Functional neuroimaging have found haemodynamic changes that occur throughout the connected network not solely in the stimulated area with rTMS (Bestmann et al., 2005; Mastropasqua et al., 2014; Obeso et al., 2013; Speer et al., 2003). Most importantly, there is still a fundamental lack of understanding of the specific neurophysiological changes that are caused by rTMS such as cTBS (Di Lazzaro, Ziemann, et al., 2008; Hoogendam et al., 2010). This notion is particularly true for cortical areas outside M1 and therefore limits the interpretation of the directionality of the changes induced by cTBS or even the exact loci. Similar to EEG, cTBS-induced changes likely are limited to interpreting changes in a network rather than a specific node. Adopting this notion when applying cTBS can help to limit the localization limitations of cTBS without MRI that exist for a variety of locations including PFC (Ahdab, Ayache, Brugières, Goujon, & Lefaucheur, 2010; Mylius et al., 2013) and PMC (Ahdab et al., 2014, 2010). Importantly, there is no clear and reliable method to separate differential responders to cTBS, which may lead to decreasing or even washing out of true effects at the group level (as observed in Chapter 5). Although the results of Chapter 5 as well as research by Hamada *et al*. (2013) have found evidence that may predict the direction of individual responses to cTBS, these findings are very preliminary. Therefore, these are limitations that users of cTBS must accept until the technique is improved.

6.3.3. Response and vibrotactile devices

Different response devices were used throughout this thesis (each experiment in Chapters 2-4) in an attempt to record the fast individual sequential finger presses performed by individuals. Unexpectedly, none of the response devices used in this current thesis were able to reliably record every single finger movement within the sequence, which limited the ability to evaluate accuracy of finger sequences. Ideally, individual finger muscle activity would have been recorded but this is not possible with surface EMG due to cross-talk in the small finger muscles (Barry, 1991; Stegeman, Blok, Hermens, & Roeleveld, 2000). Therefore, some behavioural effects after cTBS in Chapter 4 on finger sequence accuracy may have been missed due to the inability to measure individual finger movements with the response devices used. Subsequently, this could have limited the ability to associate behavioural effects with SEP modulations.

Individual vibrotactile (VibT) threshold for high, low and standard amplitudes were standardized across participants throughout this thesis (excluded five participants in *Experiment 1* of Chapter 2). This standardization of VibT thresholds was based on exclusive values measured by a small sample of participants in *Experiment 1* of Chapter 2 where low was 30%, and high was 180% of standard. Previous research on two-point discrimination found that perceived difference in vibrotactile amplitude changed linearly with increasing stimulus magnitude and individuals can detect differences of 9.21 μm in amplitudes of 25 Hz vibrations (Francisco, Tannan, Zhang, Holden, & Tommerdahl, 2008). Therefore, it was expected that individuals would not have issues detecting differences between the different vibrotactile amplitudes despite potential individual differences in thresholds. Based on VibT error data from Chapters 2 through 4, differences in individual perceptual thresholds may have contributed to large error rates (around 30%) in some individuals that may be related to differences in receptive

fields and/or receptor thresholds (Johansson & Flanagan, 2009). However, these VibT errors may have also been caused by MN stimulation ipsilateral to vibrotactile stimuli rather than perceptual differences to VibT stimuli. Regardless of the source of the source of VibT errors, the individual variability in tactile detection accuracy was a limitation of the current thesis.

6.3.4. Control groups

Sham stimulation techniques are often used as a control (either within- or between-subjects) when cTBS or any rTMS is used as an intervention. Recently, it has been found that sham stimulation can evoke changes in SEPs and increase phase coupling (Opitz et al., 2015). This would suggest that sham stimulation may not be a true control as it has the ability to affect cortical activity. Other studies have used non-active control site cTBS, such as over occipital lobe in a non-visual experiment, in lieu of sham stimulation. However, widespread haemodynamic changes occur throughout connected networks with rTMS (Bestmann et al., 2005; Mastropasqua et al., 2014; Speer et al., 2003). Therefore, neither sham stimulation nor non-active control site cTBS provide true, reliable control groups despite their widespread use. Therefore, a direct comparison between cTBS applied over two different active sites was used in Chapter 4 rather than sham or non-active rTMS control groups. This method may not be ideal for true experimental designs but practically speaking it allowed a pseudo-control by directly comparing SEP and behavioural effects after cTBS to PFC and PMC. It could be argued that to achieve a true experimental design in Chapter 4, a non-TMS control group was also required to evaluate differences in EEG and behaviour (i.e. practice or fatigue) that occur regardless of an intervention. Although a control group would be especially necessary if SEP were the same with both locations of cTBS, this was not by the majority of SEP results of Chapter 4. Furthermore,

there were no differences in behavioural measures pre- compared to post-cTBS in either experiment of Chapter 4 supporting that a non-TMS control group was not truly necessary. In addition, participants served as their own controls for individual factors with to the pre-post experimental design. However, the lack of TMS and non-TMS control groups could be considered a limitation of the current thesis.

6.3.5. Effect sizes and power

Several statistically significant differences were measured throughout this thesis but due to all the sources of variability discussed in detail above (see sections 6.3.1. through 6.3.4.), there is the possibility that some of the analyses contained within this thesis did not contain a large enough sample size and therefore, lacked the appropriate power to determine significant results. For example, in *Experiment 2* of Chapter 4, a trend ($p=0.09$) was revealed for the significant main effect between *EEG session* for N30 peak amplitude suggesting that N30 peak amplitudes increased in the *Attend and Move* compared to *No Task* condition. The partial eta-squared for this main effect was 0.18 or and the observed power was 0.40. The effect size (based on the partial eta-squared) was determined to be 0.47, which based on an *a priori* power analysis would require a total sample size of 17 participants for a significant main effect. Another example of a trend in the current thesis was observed for the *ad hoc* analysis in Chapter 5, which determined a trend ($p=0.07$) of a difference between the two different groups after separation based on MEP onset latency differences. The partial eta-squared for this effect was 0.18 and the observed power was 0.44. The effect size (based on the partial eta-squared) was determined to be 1.38, which based on an *a priori* power analysis would require a total sample size of 8 participants in each group to determine statistical significance. Therefore, an additional couple participants in

Experiment 2 of Chapter 4 and for the *ad hoc analysis* in Chapter 5 may have been able to determine a statistically significant difference assuming the effect size (therefore mean and standard error) remained constant for these two main effects. Overall, the current thesis, on a couple of occasions as outlined above, may have required an additional few participants to confirm a statistically significant difference. However, as a whole, the current thesis was able to find many statistically significant differences with similar effects sizes suggesting this was not a major limitation of the current thesis.

6.4. Future Directions

The results of the current thesis suggest that somatosensory input into non-primary motor areas, represented by frontal N30 and N60 SEPs, is modulated during preparation of right (contralateral) finger sequences, and these effects may be in part due to tonic influences of left PMC and right PFC. However, there are likely several other cortical nodes within networks connected with PMC and PFC that contribute, or are even primarily responsible for these frontal SEP modulations. For example, activity in M1 could contribute to enhancements in late stages of movement preparation while pre-SMA or contralateral PFC could contribute to gating in early response selection stages. The use of brain stimulation techniques such as cTBS, iTBS or transcranial direct current stimulation (tDCS), could be applied over these other cortical nodes in the network to investigate their contributions to frontal SEP modulations. Alternatively, it may be possible to use short-trains of rTMS or even online TMS over these cortical nodes to measure their effects on frontal SEP changes.

As previously suggested (see section 6.3.1 in Limitations), SEP modulations could be the result of changes in different populations of neurons in different areas that contribute to the

generation of the given SEP. A logical progression to evaluating SEP modulations found in the current thesis at a single maximal electrode would be to measure these frontal SEPs with dense 64 or 128-channel EEG recordings combined with source modelling techniques. Ideally, intracranial recordings could be used to measure these frontal SEP modulations in different cortical sites, but this type of recording is rare. Therefore, source modelling techniques such as swLORETA may help to alleviate some of the spatial constraints imposed by the experimental designs within the current thesis.

Oscillatory changes in time-frequency bands may be an important compliment to use with SEP peak amplitude changes. Event-related synchronization (ERS) in beta-gamma (25-35 Hz) frequency and phase-locking measured through inter-trials coherence (ITC) localized to M1, PMC and PFC has been shown to contribute to N30 SEPs (Cebolla et al., 2009, 2011, 2014; Cheron et al., 2007). Finger movements ipsilateral to MN stimulation have been shown to decrease N30 peak amplitudes as well as interfere with the ERS and phase-locking (Cebolla et al., 2009). Recent research has demonstrated that observation of movements has also been shown to increase N30 peak amplitudes which correlated with increased alpha, beta and gamma ERS as well as increased alpha and beta ITC (Cebolla et al., 2014). Therefore, the use of high-density EEG with source modelling such as swLORETA while measuring both SEP peak amplitude changes as well as ERS and ITC could provide more detailed mechanisms behind the changes observed in the current thesis.

Ideally, a more thorough and detailed approach to measuring and analyzing the mechanisms behind frontal SEP peak amplitude modulations could have beneficial applications for future research in the area. For example, they could be used to help clarify the mechanisms behind SEP modulations with contralateral movement or they could expand into new areas such

as effects during bilateral movements, or during cross-modal sensory integration. Arguably, the most valuable contribution of a more detailed understanding of the mechanisms behind frontal SEP modulations and their associations to movement impairments for the patient populations. As previously mentioned, a variety of disorders that have upper limb motor control issues including PD, HD, dystonia, writer's cramp, pre-central frontal lesions, cerebral palsy as well as aging have shown irregular frontal N30 SEPs modulations. In the case of basal ganglia dysfunctions, measuring of frontal N30 SEPs in both traditional and oscillatory models could help to specify the exact mechanism that contributes to the deficits and its association with upper limb movement impairments. If the underlying mechanisms and association with movement impairments are determined, then the frontal N30 SEP could be used as a reliable physiological index before and after various interventions such as neurorehabilitation or even drug therapies. This could be an extremely valuable area of future research as the research community continues to develop ideal treatment strategies for neurological disorders.

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