Sensory information to motor cortices:

Effects of motor execution in the upper-limb contralateral to sensory input.

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Performance of efficient and precise motor output requires proper planning of movement parameters as well as integration of sensory feedback. Peripheral sensory information is projected not only to parietal somatosensory areas but also to cortical motor areas, particularly the supplementary motor area (SMA). These afferent sensory pathways to the frontal cortices are likely involved in the integration of sensory information for assistance in motor program planning and execution. It is not well understood how and where sensory information from the limb contralateral to motor output is modulated, but the SMA is a potential cortical source as it is active both before and during motor output and is particularly involved in movements that require coordination and bilateral upper-limb selection and use. A promising physiological index of sensory inflow to the SMA is the frontal N30 component of the median nerve (MN) somatosensory-evoked potential (SEP), which is generated in the SMA. The SMA has strong connections with ipsilateral areas 2, 5 and secondary somatosensory cortex (S2) as well as ipsilateral primary motor cortex (M1). As such, the SMA proves a fruitful candidate to assess how sensory information is modulated across the upper-limbs during the various stages of motor output. This thesis inquires into how somatosensory information is modulated in both the SMA and primary somatosensory cortical areas (S1) during the planning and execution of a motor output contralateral to sensory input across the upper-limbs, and further, how and what effect ipsilateral primary motor cortex (iM1) has upon modulation of sensory inputs to the SMA.

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List of Abbreviations

AMT	Active motor threshold
APB	Abductor pollicis brevis
BP	Bereitschaftspotential
DBS	Deep brain stimulation
EMG	Electromyography
EP	Evoked potential
EPSP	Excitatory post-synaptic potential
FDI	First dorsal interosseous
IPSP	Inhibitory post-synaptic potential
M1	Primary motor cortex
MEP	Motor evoked potential
MN	Median nerve
PAS	Paired associative stimulation
PD	Parkinson's disease
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SEP	Somatosensory evoked potential
SICF	Short intra-cortical facilitation
SICI	Short intra-cortical inhibition
SMA	Supplementary motor area
TBS	Theta burst stimulation
TES	Transcranial electrical stimulation
TMS	Trans-cranial magnetic stimulation
VA	Ventral anterior nucleus
VL	Ventral lateral nucleus
VPL	Ventral posterior lateral nucleus

CHAPTER 1 - Introduction

1.1 Overview of thesis

Chapter 1 begins by stating the general objective of the thesis. Relevant literature will then be reviewed in A) functional anatomy of relevant sensory and motor cortices, B) somatosensory processing, and C) sensory-motor interactions. Chapter 1 concludes with the specific research objectives and hypotheses that guided the research throughout this thesis. Chapters 2 through 5 consist of the rationale, hypotheses, methods, results and discussion of original research contributing to this thesis. Chapter 6 includes a general discussion of the findings of the thesis, its limitations, future directions for study and conclusion.

1.2 General objective of thesis

The general objective of this thesis is to understand how somatosensory afference from the upper limbs is differently modulated in the SMA and S1 as a result of movement of the hand contralateral to sensory input. Further, this thesis investigates the functional significance of sensory input to motor areas, the influence of cortical lateralization and handedness and finally, the influence of ipsilateral M1 during hand movement. Interest is focused upon how SEPs are modulated, in particular the frontal N30, which is thought to be generated in the SMA and reflects afferent input to this area.

The SMA has been implicated and is responsive to multiple and various aspects of motor planning, preparation and execution (Tanji, 1994), particularly voluntary, self-

initiated complex bilateral or coordinated upper-limb movements. In addition to its purported motor roles, the SMA is particularly responsive to somatosensory inputs (Matsuzaka & Tanji, 1996; Romo et al., 1993). The nature of these sensory inputs is somewhat curious as the SMA does not receive direct sensory afferent input via the ventro-posterior-lateral (VPL) thalamus (Barba et al., 2003; M. Wiesendanger et al., 1985) (as do S1 and S2) and is not typically active during passive or irrelevant tactile stimulation (Romo et al., 1997; Salinas & Romo, 1998; Staines et al., 2002), yet it responds to tactile input monophasically as does primary somatosensory cortex (Romo & Salinas 2001) . It is therefore suspected that SMA activity from somatosensory stimulation is a result of cortical connections with area 1, 2, 5 and S2 (Cavada & Goldman-Rakic, 1989; Geyer et al., 2000; Jurgens, 1984; Luppino et al., 1993), areas all highly responsive to passive tactile stimulation. In addition to these strong somatosensory connections, SMA has very dense direct reciprocal connections with ipsilateral M1 (Jurgens 1984; Luppino et al. 1993). As such, the SMA is a strong candidate area to study how upper-limb somatosensory information contralateral to movement is modulated during motor preparation and execution. This is an important consideration as somatosensory input is required for accurate motor performance (Pearson, 2000), learning new motor skills (Pavlides et al., 1993) and is thought to be dysfunctional in traditionally defined motor disorders such as Parkinson's disease (Abbruzzese & Berardelli, 2003).

1.3 Background Research

1.3.1 The Supplementary Motor Area (SMA)

1.3.1.1 Functional connectivity

The SMA is traditionally defined as the mesial agranular cortex (primate) that roughly corresponds in humans to the medial part of Brodmann's area 6 (BA 6) (see Luppino 1993). The majority of efferent connections from the SMA target both cortical (Brodmann area 4 and 6) and sub-cortical (putamen, caudate, ventral-anterior (VA) and ventral-lateral (VL) nuclei of the motor thalamus) motor structures as well as cortical parietal areas 2, 5 and 7 (Jurgens 1984). In addition, the SMA contributes to the cortico-spinal tract (Teitti et al., 2008). The majority of input to SMA originates from parts of the VL and VA nuclei of the thalamus (Akkal et al., 2007; DeLong, 1983; Schell & Strick, 1984; R. Wiesendanger & Wiesendanger, 1985). The VA nucleus of the thalamus primarily receives its driving afferents from the globus pallidum (internal segment) and the substantia nigra pars reticulata; output structures of the basal ganglia (Middleton & Strick, 2000). The efferents of VA target most of the frontal motor cortex as does the VL, but are densest to the SMA (Akkal et al. 2007). The SMA receives its cortical afferents mainly from the contralateral SMA, from other parts of area 6, from somatosensory areas 3, 1, 2, and 5, and from M1 (Cavada & Goldman-Rakic, 1989; Geyer et al., 2000; Jurgens, 1984; Luppino et al., 1993).

1.3.1.2 Motor Function

Ablation of SMA in primates produces no gross changes in general motor behaviour (Brinkman, 1984; Canavan et al., 1989), however subtle and specific deficits

are found in bimanual coordination, and more 'complex' sequential motor tasks (Brinkman 1984). Canavan et al. (1989) found that monkeys with the SMA ablated were poor at self-initiated movements and at a motor reversal task. These authors concluded that an SMA lesion causes difficulties in knowing which movement to make without an external guiding cue, a contention supported by further ablation studies that found internally guided rather than instructed movements were compromised (Y. C. Chen et al., 1995; Kazennikov et al., 1998; Kermadi et al., 1997; Thaler et al., 1995) as compared to animals with a pre-motor cortex (lateral BA 6) lesion that are generally impaired on cued tasks (Halsband & Passingham, 1982; Halsband & Passingham, 1985). Chemical inactivation has shown failure of sequential execution of multiple movements (Shima & Tanji, 1998) and cooling results in erroneous movements and increased reaction times (Tanji, 1985).

In human subjects, ablation of the medial frontal cortex has been shown to be much more dramatic. For instance, Laplane et al. (1977) noticed that immediately after operation, patients do not move or speak on their own but upon recovery from this acute state perform simple limb movements that are indistinguishable from those observed preoperatively. The only long-lasting deficit reported in this study was a disturbance of alternating movements of the hands. Additional clinical cases have reported varying motor and speech disturbances including a reduction in spontaneous movements (Krainik et al., 2001), an inability to generate a fixed sequence of three movements (Halsband & Passingham, 1982), difficulty performing multi-phased movements (Dick et al., 1986), bimanually coordinated movements (Halsband et al.,

1993), and retrieval of a correct movement or motor sequence from memory (Gaymard et al., 1990; Halsband et al., 1993).

Trans-cranial magnetic stimulation (TMS) studies of the SMA are limited but high frequency repetitive stimulation over a fronto-central scalp site has been shown to disrupt certain aspects of bimanual motor performance (Gerloff et al., 1997; Obhi et al., 2002; Serrien et al., 2002; Steyvers et al., 2003) and to increase motor-evoked potential (MEP) amplitudes but leave short intra-cortical inhibition (SICI), short intra-cortical facilitation (SICF), cortical silent period or H-reflexes unaffected. Low frequency 1Hz repetitive TMS (rTMS) has been demonstrated to disrupt a sequence task (Verwey et al., 2002) and motor output during a pre-cued reaction time task (Terao et al., 2007). Conditioning of the SMA with a threshold or supra-threshold single pulse has been reported to reduce the excitability of ipsilateral M1 (Civardi et al., 2001), but increase it after visual stimuli with emotional valence (Oliveri et al., 2003).

TMS of the SMA has also been tested as an intervention in the Parkinson's (PD) population with mixed results. Cunnington et al. (1996) reported that single-pulses delivered at maximal stimulator output at various times during a sequential button pressing task disrupted movement timing in a Parkinson's group but had no effect on controls. Koch et al. (2005) found that low frequency rTMS (1Hz for 15min) reduced dyskinesia but trains of 5Hz stimulation did not, and a recent study by Hamada et al. (2008) on a very large PD sample reported that 5Hz rTMS at 110% motor-threshold improved motor functioning in a PD population as compared to sham.

Functional studies with an intact SMA reveal it to be particularly active both before (Brinkman & Porter, 1979; Smith, 1979; Tanji & Shima, 1994) and during volitional or internally generated movements (Alexander et al., 1990; Hoshi & Tanji, 2004; Matsuzaka et al., 1992; Rizzolatti et al., 1990) rather than movements based upon visual cues (Deiber et al., 1991; Halsband et al., 1993; Halsband et al., 1994; Mushiake et al., 1991). Of the motor areas, the SMA is particularly active for movements requiring bimanual use or upper-limb selection (Donchin et al., 2002; Tanji et al., 1987; Tanji et al., 1988) including the linking of different movements (Shima & Tanji, 2000; Tanji, 2001), movements that involve multiple or sequential steps (Halsband et al., 1994; Mushiake et al., 1991; Roland et al., 1980), the ordering of particular movements (Tanji & Shima, 1994), and movement sequences based upon memory (Mushiake et al., 1991; Tanji & Shima, 1994).

1.3.1.3 Sensory Function

Single-cell studies in the primate have demonstrated that cells in the SMA respond to auditory, visual and somatosensory cues that trigger or instruct a voluntary movement (Kurata & Tanji 1985; Tanji & Kurata 1985; Romo & Schultz 1987, 1992), although Romo et al. (1993) reported strong responses of SMA neurons to somatosensory input rather than visual during a discrimination task. Further work by the Romo lab has demonstrated that SMA neurons code vibrotactile stimulus frequency in their firing rate, similar to neurons in both primary somatosensory cortex and secondary somatosensory cortex, but with the caveat that they appear later and not during passive stimulation (Romo et al. 1993; Hernandez et al. 2000; Salinas et al.

2000). It is suggested that the initial coding of vibrotactile frequency is performed in S1 and S2 and passed to SMA for integration with motor demands. This interpretation coincides well with the serial processing model of the somatosensory cortices and the timing of activation of each area relative to stimulus onset (Hernandez et al., 2002) (see Romo for review (Romo & Salinas, 2003), such that the SMA responds after both S1 and S2. A role for the SMA in somatosensory processing is strengthened by the findings of Lacruz et al. (1991) who report a reduction in tactile discrimination as a result of bilateral SMA lesion – a finding similar to patients who have an S1 lesion.

Interestingly, the majority of cells in SMA respond ipsilaterally to vibration of the finger (Romo et al. 1993). Typically, at least for motor function, SMA activity, like M1, represents contralateral limb use. However, when a motor task requires selection of ipsilateral, contralateral or bilateral digits or arm, the SMA representation is no longer solely contralateral (Brinkman & Porter, 1979; Donchin et al., 2002; Tanji et al., 1987; Tanji et al., 1988).

1.3.2 Somatosensory Processing

It is generally assumed that cortical somatosensory processing is serial in nature from S1 to S2 due to the timing of activation and strong connections between the two (Burton et al., 1995; Cusick et al., 1989; Friedman & Murray, 1986; Jones et al., 1978). S1 activation typically precedes S2 (Allison et al., 1989; Allison et al., 1989; Hari et al., 1983; Luders et al., 1985; Mauguiere et al., 1997; Mima et al., 1997) and ablation of S1 renders S2 unresponsive (Garraghty et al., 1990; Pons et al., 1987; Pons et al., 1992).

However, additional connections also suggest that cortical processing of somatosensory information has the potential to be done in parallel as the VPL sends direct reciprocal projections to both the S1 and S2 (Jones & Powell, 1969c), though sparse to S2 (Manzoni et al., 1984) and dense to all four sub-regions of S1 (Pons & Kaas, 1986), suggesting a heavy weighting of thalamo-cortical projections to S1 for initial processing.

It is currently unclear how SMA fits into this processing stream. As stated, SMA does not receive direct thalamo-cortical inputs from VPL (Barba et al., 2003) yet is responsive to somatosensory inputs (Lemon et al., 1976; Matsuzaka et al., 1992; Romo et al., 1993). Despite the lack of direct VPL projections, the SMA does receive very dense projections from the motor nuclei of the thalamus,VA and VL (Morel et al., 2005), which have been recently shown to have inter-thalamic connections with VPL (Morel, 2005) – a potential transfer site of sensory information. The SMA receives modest input from area 3b of S1 (Jones et al. 1978; Vogt et al. 1978; Weisendanger 1984; Jurgens 1984), but progressively stronger inputs from area 1, 2, and 5 with the majority of post-rolandic input from posterior parietal cortex and S2 (Jurgens, 1984; Luppino et al., 1993). Therefore, somatosensory input to SMA may arrive as the result of direct SMA-parietal connections with one or more of these areas, or via recurrent connections between thalamus, S1, and SMA. It is interesting to speculate that there may be a direct SMA-S2 influence as the SMA is known to be active bilaterally and so too is S2, and further, that S2 is responsive to sensory stimulation used or combined with motor output (Huttunen et al., 1996). The strongest SMA connections however

are to ipsilateral M1, a finding that agrees with the motor role of SMA but may also mediate the role of the SMA in a somatosensory network, as M1 has been shown to have influence upon and to be influenced by ipsilateral S1 (Nelson, 1996b).

Where the SMA fits into the hierarchical processing stream for somatosensory information is indeterminate; however, it is currently accepted that areas 3a and 3b perform the initial processing of proprioceptive and cutaneous sensory information respectively, and then distributes this information posteriorly through S1 to the association cortices and S2.

1.3.3 The frontal N30 Somatosensory Evoked Potential

An induced change in brain electrical activity is called an evoked potential (EP). Evoked potentials differ from the so-called spontaneous electrical changes in the brain in that they bear a definite temporal relationship to the onset of the stimulus. EPs have a definite latent period determined by the conduction distance between the point of stimulation and the point of recording. Structured around these premises, somatosensory evoked potentials (SEPs) can be induced via median nerve (MN) stimulation and recorded by surface electrodes on the scalp. The SEP waveform to MN stimulation is well-mapped and understood (Allison, McCarthy, Wood, & Jones, 1991b; Desmedt & Cheron, 1980). The various inflections or peaks mostly represent the summation of excitatory (EPSP) and inhibitory post-synaptic potentials (IPSP) over populations of neurons.

The N30 is a large negative potential recorded maximally over frontal central electrode sites roughly 30 ms after stimulation of the MN at the wrist (Allison et al., 1989; Cheron & Borenstein, 1991; Desmedt et al., 1987; Kakigi, 1994; Rossini et al., 1990). An exact generator(s) is not as yet resolved as a result of difficulties in recording polarity-reversal in the frontal lobe due to cortical convolution (Barba & Valeriani, 2004; Barba et al., 2005). As such, in addition to an SMA generator site (Desmedt et al., 1987; Kakigi, 1994; Mauguiere et al., 1983; Rossini et al., 1989; Rossini et al., 1991), both the motor cortex (Waberski et al., 1999) and premotor cortex (Kanovsky et al., 2003) have been proposed as contributing to N30 generation.

Unlike the early parietal potentials, the type of somatosensory information coded by the cells that contribute to N30 amplitude is not well understood. Work by Restuccia et al. (1999, 2002) suggests that the population of cells contributing to N30 amplitude primarily represents proprioceptive afferent information as evidenced by a simple subtraction of a waveform produced by both cutaneous and proprioceptive input minus a cutaneous one left the N30 intact. Despite the conjecture suggesting the N30 is merely a volume conducted mirror of early parietal potentials (Allison, McCarthy, Wood, & Jones, 1991a), research shows that the N30 is attenuated independently of early parietal SEP potentials under a variety of conditions such as aging (Desmedt & Cheron, 1981) and during ideation of a motor task (Cheron & Borenstein, 1992; Rossini et al.,1996b), but facilitated during non-cued voluntary movement (Legon et al., 2008; Rossini et al., 1999a), and is affected by specific lesions of either the SMA or S1 (Mauguiere et al., 1983; Slimp et al., 1986).

The N30 is abnormally large in patients with cortical myoclonus (Ebner & Deuschl, 1988), increased in dystonic patients (Reilly et al., 1992), depressed in patients with Parkinson's disease (Cheron et al., 1994; Rossini et al., 1989; Rossini et al., 1991) but subsequently increased during deep brain stimulation (DBS) of the internal globus pallidus or the sub-thalamic nucleus (Pierantozzi et al., 1999) as well as after pallidotomy (Gironell et al., 2002), apomorphine injection (Cheron et al., 1994; Rossini et al., 1995), or L-dopa medication (Rossini et al., 1991). As such, it has been suggested that the frontal N30 component reflects the modulatory action of cortico-subcortico-cortical circuitry involving the SMA and basal ganglia (Cheron, 1999; Rossini et al., 1991).

1.3.4 Sensory-Motor Integration

Sensory-motor integration is the process whereby sensory input is processed by the central nervous system to assist motor planning, preparation and execution. The disruption of this process from abnormalities in afferent input, or in the response to these inputs can lead to deficits in motor execution. Somatosensory input has been demonstrated to be necessary for fine motor control (Rabin & Gordon, 2004), the learning of new motor skills (Pavlides et al., 1993), as well as accurate and precise performance of previously learned skills (Pearson, 2000). In the clinical population, patients with decreased somatosensory input due to peripheral deafferentation display abnormal motor behaviour (Rothwell et al., 1982) and those with a stroke involving the somatosensory cortex report a slower recovery of motor function (Pavlides et al., 1993).

The motor and sensory cortices are densely interconnected ipsilaterally (Ghosh et al., 1987; Huerta & Pons, 1990; Jones et al., 1978; Porter, 1991; Porter, 1992; Schwark et al., 1992) and display overlap of sensory receptive fields and motor fields (Lemon & Porter, 1976; Rosen & Asanuma, 1972). The majority of these connections originate in M1 with much sparser return connections from S1 to M1 (Schwark et al. 1992). M1 is trans-callosally connected with contralateral M1 (Cracco et al., 1989; Rouiller et al., 1994) and S1 (Jones & Powell, 1969b) providing for influence upon one another (Ferbert et al., 1992). In contrast, S1 has relatively weak trans-callosal connections with contralateral S1 (Jones & Powell, 1969b).

Both the motor cortex and somatosensory cortex have been demonstrated to be highly plastic (Calford, 2002; Nudo, 1999) and been shown to influence each other. The sections below outline some of these effects, limiting discussion to research investigating the effect of upper-limb motor activity upon SEPs.

1.3.5 Motor influence upon sensory transmission: Ipsilateral and Contralateral effects

1.3.5.1 Ipsilateral

In general, movement inhibits afferent sensory transmission at all levels of the ascending sensory system in the cat (Ghez & Lenzi, 1971), monkey (Chapman et al. 1988) and human (Rushton et al., 1981). This inhibition is often referred to as movement-related gating and is identified by a reduction in amplitude of specific parietal and frontal SEP components specific to sensory afference originating from or distal to the site of movement (Cohen & Starr, 1987; Tapia et al., 1987). Movement-

related gating of SEP components is apparent before electromyographic (EMG) activity (Cohen & Starr 1987) and during both active, passive (Chapman 1988) and imagined (Cheron & Borenstein 1992; Rossini et al. 1996) movement. Because movement-related gating has been demonstrated prior to EMG activity and during its ideation, cortical activity related to movement preparation is thought to contribute to it (Cohen & Starr, 1987; Starr & Cohen, 1985).

In contrast to the strict inhibition effects of voluntary movement, direct stimulation of the motor cortex via TMS has been demonstrated to both inhibit and facilitate both parietal and frontal SEP components depending upon the stimulation parameters used. For example, Kujirai et al. (1993) reported that a single magnetic pulse at resting motor threshold delivered to the hotspot for abductor pollicis brevis (APB) given 10-20 ms prior to a contralateral median nerve pulse increases the parietal P25 and frontal N30, reduces later parietal potentials and leaves sub-cortical and the parietal N20 unaffected. Seyal et al. (1993), using a similar technique, reported a similar increase in the N1-P1 somatosensory cortex (homologue to the N20-P27) to a single magnetic pulse at motor threshold intensity delivered 30-70ms prior to MN stimulation and also reported no effect on sub-cortical components. It is suggested from these results that SEPs conditioned by stimulation to the motor cortex are a result of cortico-cortical and not thalamo-cortical connections.

In contrast to single-pulse effects, low frequency 1Hz rTMS over the motor cortex has been reported to reduce the amplitude of the parietal N20, P25 and N33 for up to 60 min after stimulation. Interestingly, the same protocol delivered over S1 does

not result in any attenuation (Enomoto et al., 2001). It is unclear why this is so, though it is paralleled by the finding that intractable pain is better alleviated by motor rather than sensory stimulation (Nguyen et al., 1999).

Other protocols including very low frequency (0.1 Hz) rTMS combined with motor-point stimulation (Tsuji & Rothwell, 2002) and anodal transcranial direct current stimulation (Matsunaga et al., 2004), two techniques demonstrated to facilitate corticospinal activity, also facilitate both the frontal P22/N30 and early parietal SEP components.

Continuous theta-burst stimulation (TBS) of the left motor cortex (a protocol that decreases MEP amplitude through intra-cortical inhibition (Di Lazzaro et al., 2005)) increases the P25/N33 and N33/P40 SEP. The same protocol delivered over the somatosensory cortex results in an attenuation of the P25/N33 (Ishikawa et al., 2007). Interestingly, intermittent TBS (a protocol that increases MEP amplitude (Di Lazzaro et al., 2008)) has no effect upon SEP amplitudes (Katayama & Rothwell, 2007).

There are a few studies that have explored the effect of motor stimulation upon sensory perception reporting a reduction in perception as a result of a prior single-pulse (Cohen et al., 1991; McKay et al. 2003a), 1 Hz repetitive stimulation (Satow et al., 2003) and 10 Hz repetitive stimulation (Yoo et al., 2008). It is interesting to note that the behavioural results do not necessarily line-up with the SEP results, most notably the single-pulse technique which increases SEP components while reducing perceptual thresholds. This is not necessarily surprising as no relationship between evoked

potentials and perception has previously been found (Johnson et al., 1975) and is somewhat controversial (Paul & Sutton, 1973).

1.3.5.2 Contralateral

Movement of the upper-limb contralateral to sensory input does not result in movement-related gating (Cohen & Starr, 1987; Kida et al., 2006; Schmidt et al., 1990), however at least two studies have reported contralateral movement effects upon SEP components. Rossini et al. (1999b) reported an enhancement of the frontal N30 with no effect upon parietal potentials and Hoshiyama & Kakigi (1999) reported a decrease in both frontal and parietal components. The difference of effect between these two studies is likely due to experimental parameters such as the timing of stimulation relative to movement, as well as the tasks employed. Rossini et al. employed a continuous repetitive finger/thumb opposition, whereas Hoshiyama & Kakigi had subjects do a tracing task. It is unclear what exact components of these different tasks may have led to the disparate results, but it is possible that the relative musculature recruited between a simple opposition movement versus hand-writing contributes and more likely, the requirement of subjects in the Hoshiyama & Kakigi study to use visual feedback. This task would employ additional motor cortical areas such as the lateral pre-motor cortex which may differentially influence afferent sensory information from the moving limb. Of note however, both these studies reported frontal SEP effects rather than parietal.

There is limited work assessing the effects of motor cortical stimulation upon contralateral somatosensory cortex. Seyal et al. (2005) delivered low frequency (0.3 Hz) repetitive stimulation to the right motor cortex while recording both perceptual thresholds and SEP amplitudes from the ipsilateral right thumb. They reported an attenuation of both perceptual threshold and early parietal SEP amplitudes. This study did not allow for a direct explanation of the result but may stem from two possibilities. One, direct inter-hemispheric motor-to-sensory connections (Jones & Powell, 1969b) or two, an inter-hemispheric motor to motor connection that then subsequently influences sensory cortex. Mochizuki et al. (2004) provide some evidence for the latter. They delivered a conditioning stimulus to the right motor cortex 50-150 ms prior to either a TMS or trans-cranial electric stimulation (TES) test pulse or 100-200 ms prior to median nerve stimulation and found that MEPs from TES were unaffected, MEPs from TMS were reduced and SEPs were enhanced as a result of the conditioning stimulus. It can be construed from these results that the right motor cortex can indeed affect contralateral somatosensory activity and it does so via trans-callosal connections with contralateral M1 which in turn asserts an ipsilateral effect upon sensory cortex activity. However, these results are at odds with the 1 Hz rTMS results of Enomoto et al. (2001) mentioned above that reported an inhibition of MEP and SEP.

1.3.5.3 Consensus

Judging from the studies discussed above, an induced change in M1 activity is not always accompanied by a similar effect in ipsilateral SEP modulation. Of the

studies mentioned, SEP amplitudes follow MEP amplitudes in ipsilateral single pulse, 1 Hz rTMS, paired associative stimulation (PAS) and direct current stimulation protocols but differ during ipsilateral TBS and contralateral conditioning protocols. The exact mechanisms of TMS are not fully understood, however it has been demonstrated that single pulse and rTMS target different inter-neuronal pools (Di Lazzaro et al., 2005, 2007; 2008a, b). In addition to this, differences of effect may be due to the conditioning intensities employed and whether or not they directly activate trans-callosal M1-M1 connections or ipsilateral M1-S1 connections such that a relatively high intensity of magnetic stimulation (110% active motor threshold (AMT)) (Enomoto et al. 2001) effects the SEP similarly to the MEP, whereas a lower intensity (80% AMT), as typically used in the TBS protocol, may be below threshold for activating the same fibers.

1.3.6 Motor Lateralization and Inter-hemispheric Interaction

It is well understood that there is a behavioural difference for manual dexterity between the hands, with 90% of individuals showing right hand preference for multiple tasks (Goble & Brown, 2008). Differences in motor cortical physiology may underlie these behavioural differences. Imaging studies have identified an asymmetry of motor cortical activity based upon handedness (Dassonville et al., 1997; Solodkin et al., 2001) and a difference in motor cortical activity between dominant and non-dominant hand use (Cramer et al., 1999; Kawashima et al., 1993; Kim et al., 1993). For example, Kim et al. (1993) measured activation of the left and right motor cortices in response to

finger/thumb opposition movements made by each hand in both right and left handed individuals and found that the right motor cortex was primarily active for movements of only the contralateral left hand, whereas left motor cortex was active for ipsilateral hand movements regardless of handedness. These results are similar to those found for stroke patients where the motor function of the ipsilateral hand is differentially affected by lesions of the left or the right hemisphere. Specifically, left hemispheric lesions often result in motor dysfunction of the ipsilateral (left) hand, whereas lesions on the right side leave the motor function of the ipsilateral (right) hand relatively unaffected (Haaland & Harrington, 1989a, b).

TMS studies have also reported left hemisphere dominance for increasing the magnitude of MEPs in ipsilateral hand muscles during the performance of a motor task with the opposite hand. In particular, it has been shown for right-handed individuals that single pulse TMS to the left compared to right motor cortex more often induces facilitation of MEPs in hand muscles in both the left and right arms. In contrast, right hemisphere stimulation elicits a response in only the contralateral left arm (Ghacibeh et al., 2007; Ziemann & Hallett, 2001). As such, it has been hypothesized that the left hemisphere might have some influence over the right hemisphere via the corpus callosum. In this case, it is thought that both hemispheres are active prior to movement initiation, at which point one hemisphere is inhibited by the other in order to execute a unilateral movement of the contralateral arm (Britton et al., 1991; Rossini et al., 1988). Based on this line of reasoning, it would seem that involvement of the left hemisphere during ipsilateral arm movements reflects a relative inability of the right hemisphere to

inhibit the left as suggested by (Chen et al., 1997). This notion is supported by several paired-pulse TMS studies where sequential stimulation of the hemispheres has shown greater inhibition of the motor cortex in the right versus left hemisphere (Kobayashi et al., 2003; Netz et al., 1995). The differences in inter-hemispheric inhibition (IHI) for movements made with either the dominant or non-dominant hand were well demonstrated in a recent study by Duque et al. (2007), who had right handed individuals make simple finger abduction movements with either the right or left hand in a paired-pulse TMS design whereby the conditioning and test stimuli were alternated between dominant and non-dominant hemispheres at various times preceding movement. Their results suggest that during right handed movement inhibition of the left motor cortex is released which is not the case in the right motor cortex during is left hand movement.

1.4 Summary & Conclusions

The SMA is active both before and during movement execution and is especially active for various movements that involve both of the upper-limbs. The SMA, like S1, is specifically responsive to vibrotactile inputs, but with two slight differences: 1) it is responsive ipsilaterally and 2) only to input that is paired with or cues a motor response. These differences may be crucial to how sensory afference is differentially modulated in SMA versus S1 during the preparation and execution of a movement contralateral to sensory input.

Movement of the limb ipsilateral to sensory input results in attenuation of SEPs in S1. Movement of the limb contralateral to sensory input does not. The effect of contralateral movement on sensory afference to the SMA has not been reported. The following section outlines, in more detail, the research objectives that guide this thesis.

1.5 Research Objectives

1.5.1 Research Objective 1

To determine how sensory information is modulated in frontal and parietal cortices during the preparation and execution of a contralateral upper-limb movement.

The SMA has been implicated in the preparation, planning and execution of voluntary motor function (for review see Tanji, 1994) and this activity arising in frontal premotor structures can be recorded in the Bereitschaftspotential (BP), a slow negative-recording cortical potential time-locked to the onset of a self-paced movement (Shibasaki & Hallett, 2006). Both the BP and the N30 may have similar cortical generator sites in the SMA; however, it is currently unclear whether the N30 can be used as an index of sensory input for the planning and preparation of motor activity or whether it bears any relationship to the different component parts of the BP.

This study tests the hypothesis that the frontal components of the median nerve SEP are differentially modulated depending upon the stage of motor preparation and execution. It is hypothesized that the N30 will be increased during the late stage of the BP as the SMA has been proposed to largely contribute this portion.

1.5.2 Research Objective 2

To determine if N30 modulation during hand movement is exclusive to non-dominant hand movement and further, to determine if hand dominance impacts this.

The frontal N30 SEP, as a result of right median nerve stimulation, is facilitated during the execution, but not the preparation, of a simple left-handed movement. The purpose of this facilitation is currently indeterminate; however, studies employing TMS have shown that movements of the left hand in right handed individuals activate ipsilateral motor cortex which may have or be the result of SMA activity due to the dense connectivity between the two and as such, lead to N30 amplitude differences. It is not clear if this is a generalized phenomenon across both left and right handed individuals and very well may not be as it is established that there are fundamental differences of motor circuitry between these groups (Solodkin et al. 2001).

This study examines the relationship between sensory input and motor output across upper limbs in both right-handed and left-handed individuals on frontal N30 amplitude. It is hypothesized that facilitation of the N30 during movement execution will not be evident in right handed participants when movement is performed with the dominant hand as ipsilateral M1 activity is generally not seen (if the M1 is mediating N30 amplitude). It is further speculated that a left/right sensory-motor input/output relation may not be the same as in right-handed participants as left handed participants generally display less cortical lateralization

1.5.3 Research Objective 3

To determine if ipsilateral left motor cortex activity impacts N30 amplitude during ipsilateral hand movement.

Study #1 had right handed participants perform a simple voluntary isotonic contraction of the left hand during repetitive MN stimulation of the right wrist. This resulted in facilitation of the frontal N30 during, but not before movement. This effect is at odds with the well understood site specific sensory-motor interactions that result in inhibition or gating of SEP components (Tapia et al., 1987; Starr et al., 1989). Be this as it may, this is not an unprecedented effect as both Hoshiyama et al. (1999) and Rossini et al. (1999) also showed modulation of SEP components derived from right MN stimulation during left-handed movement in right-handed individuals. Curiously, this effect is not present for a reversal of sensory and motor output across the upper-limbs despite different motor tasks. As such, the unique modulation of the frontal N30 SEP during left handed movement may be a result of specific motor activity unique to non-dominant hand movement, specifically ipsilateral left motor cortex activation (Kim et al. 1993; Kawashima et al. 1993).

It is the purpose of this experiment to determine if M1 activity ipsilateral to the moving limb has a direct influence upon frontal N30 amplitude by inhibiting it via TMS and facilitating it via a sequencing task that has previously been demonstrated to increase ipsilateral M1 activity (Verstynen et al., 2005). It is hypothesized that disruption or facilitation of this activity should affect N30 amplitude accordingly.

1.5.4 Research Objective 4

To determine if inhibition of the SMA attenuates the N30 and if this has any functional consequence.

The N30 SEP is a promising physiological index of sensory information to the SMA and this information likely reaches the SMA after initial processing in S1 as there are no direct connections from the VPL nucleus of the thalamus to SMA (Barba et al. 2004). Despite the known anatomy, the population(s) of cells that contribute to N30 amplitude are not precisely known and as such it is unclear what form of somatosensory information is coded in SMA and represented in N30 amplitude. There are denser proprioceptive afferent projections from muscle and joint receptors to pre-central areas than cutaneous ones (Hummelsheim et al., 1988) and work by Restuccia et al. (1999, 2002) and Rossini et al. (1996) suggest that these proprioceptive afferents contribute to N30 amplitude, whereas single-cell studies suggest that SMA neuronal firing is a monotonic function of vibrotactile stimulus frequency similar to the rapidly adapting system in S1 suggesting a cutaneous contribution (Hernandez et al., 2002; Romo & Salinas, 2001). This is further supported by the finding that lesion of the SMA can affect tactile perception (Lacruz et al., 1991).

It is the purpose of this study to probe how the SMA fits into the somatosensory processing stream by disrupting its activity via TMS and testing tactile perception thresholds. It is the further purpose of this study to assess how TMS of the SMA affects the frontal N30 as an indirect confirmation of contribution of the SMA to N30 generation.

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CHAPTER 2 - STUDY 1: The relationship between frontal somatosensory-evoked potentials and motor planning.

Adapted From: Legon, W., Meehan, S.K. & Staines, W.R. The relationship between frontal somatosensory-evoked potentials and motor planning. Neuroreport, 2008, 19, 87-91.

2.1 Overview

Performance of efficient and precise movement requires the proper planning of motor parameters as well as the integration of sensory feedback. This study tests the hypothesis that the frontal components of the median nerve somatosensory-evoked potentials are differentially modulated, depending on (1) the stage of motor preparation and (2) the moving limb. Participants were instructed to make intermittent voluntary contractions with either their right or left hands while receiving median nerve stimulation to the right wrist only. The results indicate that the frontal N30 demonstrated a significant increase in amplitude during the execution, but not the preparation, of a movement contralateral to median nerve stimulation. These data have implications for inter-hemispheric control of sensory information within the primary and premotor cortices.

2.2 Introduction

The performance of efficient and precise voluntary movement requires the proper planning of movement parameters, as well as the integration of peripheral sensory feedback. Peripheral sensory information is projected not only to primary somatosensory cortical areas but also to cortical motor areas (Hummelsheim et al. 1988). These afferent sensory pathways to the frontal cortices are likely involved in the integration of sensory information for assistance in motor program planning and execution. A promising physiological index of sensory inflow to cortical motor areas is the frontal N30 component of the median nerve SEP, which is currently thought to be generated in frontal midline cortical structures including the SMA (Desmedt et al., 1987; Mauguiere et al., 1983). The SMA has been implicated in the preparation, planning and coordination of voluntary upper-limb function (Roland et al., 1980; Tanji, 1994), and this activity arising in frontal premotor structures can be recorded in the Bereitschaftspotential (BP), a slow negative-recording cortical potential time-locked to the onset of a self-paced movement (Shibasaki & Hallett, 2006). Both the BP and the N30 might have similar cortico-frontal generator(s) sites; however, it is currently unclear whether the N30 can be used as an index of sensory input for the planning and preparation of motor activity or whether it bears any relationship to the different component parts of the BP. The N30 has been well investigated under various gating paradigms: it has been shown to be inhibited contralaterally both during and before active flexion movements of the hand and during interfering cutaneous and proprioceptive stimulation (Cheron & Borenstein, 1991; Cohen & Starr, 1987). The

N30 might play a specific role in sensory-motor control, as it has been shown to be specifically attenuated during motor imagery (Cheron & Borenstein 1992; Rossini et al. 1996) and is specifically affected, independent of early parietal SEP components, in various motor pathologies including Parkinson's disease (Cheron 1999).

Previous research has investigated the relationship between the different components of the BP and median nerve SEPs, but for the parietal components only (Wasaka et al., 2005), as well as for both contralateral and ipsilateral upper-limb movements (Rossini et al. 1999). Rossini et al. (1999) had participants perform repetitive sequential movements with either their right or left hands, and found an increase in the frontal N30 amplitude for the motor task contralateral to the median nerve stimulation. Their paradigm, however, did not allow for the investigation of N30 activity that is time-locked to the onset of movement. Therefore, this study probed the relationship between the stage of motor planning, as evidenced by epochs corresponding to the early, late and movement potentials of the BP and the amplitude of the frontal N30 during the purposeful voluntary movement of the upper limb, both contralateral and ipsilateral to median nerve stimulation.

2.3 Methods

2.3.1 Subjects

Eight participants (four women, four men, age 21–31 years) provided written informed consent to participate in the study. None reported any history of neurological or musculoskeletal impairments, and all were paid a nominal fee for their participation. The University of Waterloo Office of Research Ethics approved all experimental procedures.

2.3.2 Behavioural task

Participants were seated comfortably in a chair, with arms being supported, in a sound-attenuating booth. They were instructed to perform a quick voluntary isotonic squeeze of a pressure-sensitive bulb held in either the right or the left hand while fixating straight ahead. Participants were instructed to perform squeezes roughly every 5 s, but were allowed to perform the movement at their own pace. For both the right and the left hands, participants performed squeezes for 1 min blocks repeated six times with a 15 s rest interval between blocks. Squeeze and rest periods were indicated by an auditory tone. Each hand repeated this series twice, alternating hands between successive trials to avoid possible fatigue.

2.3.3 Stimulation and recording

SEPs were derived from the electrical stimulation of the median nerve of the right wrist only, for both right-hand and left-hand squeeze trials. Square wave pulses of 0.2-ms duration (GRASS S88 stimulator with SIU5 stimulus isolation unit; West

Warwick, Rhode Island, USA) were delivered through surface electrodes, with the anode distal, fixed over the median nerve with a rubber band. Median nerve stimuli were delivered randomly during task performance at an average rate of 2Hz (range 0.4–0.8 s) at a voltage sufficient to elicit a noticeable thumb twitch. Surface electromyography (EMG) was recorded from the thenar musculature as well as the flexor digitorum superficialis of the hand performing the squeeze. EMG recordings were amplified (2000x), band-pass filtered (DC–200 Hz), digitized and stored for later analysis, using customized Labview software (National Instruments; Austin, Texas, USA). Thenar electrodes were used to record the M-wave, an EMG wave resulting from the direct stimulation of the motoneuronal axons serving the thenar musculature. M-wave amplitude, measured peak-to-peak, was used to confirm the consistency of stimulus intensity. The onset of the squeeze was evidenced by the onset of flexor digitorum superficialis EMG activity. SEPs were elicited continuously throughout the squeeze blocks and rest periods. Electroencephalographic data were recorded from 15 electrode sites (FC4, FC2, FZ, FC1, FC3, C4, C2, CZ, C1, C3, CP4, CP2, CPZ, CP1 and CP3), in accordance with the international 10–20 system for electrode placement referenced to the linked mastoids (impedance <5kohms). Electroencephalographic data were amplified (40 000x), filtered (DC–200 Hz) and digitized at 1000 Hz (NeuroScan 4.3; Compumedics; El Paso, Texas, USA), before being stored on a computer for subsequent analysis. SEPs were extracted by averaging epochs time-locked to the median nerve stimulation (-50 to 300 ms). Individual traces were high-pass filtered (2

Hz) and visually inspected for artifacts (i.e. from blinks, eye movements or contraction of scalp musculature). Any contaminated epochs were eliminated before averaging.

2.3.4 Data analysis

Bereitschaftspotentials were averaged on the basis of the onset of the rectified flexor digitorum superficialis EMGs from the hand performing the squeeze. Median nerve stimulations were averaged in bins time-locked to EMG onset in flexor digitorum superficialis, according to predetermined movement epochs (Fig. 1). Median nerve stimulations that did not fall within the determined epochs were averaged and used as control. Latencies and amplitudes of the frontal and parietal SEPs were measured from the individual participant averages for each movement epoch from the electrode sites that displayed the maximal amplitudes, FCZ and CP3, respectively. Latencies were measured from stimulus onset to the peak of each SEP (frontal P20, N30 and N60; parietal P18, N20, P27 and P50). A clearly defined peak was necessary for inclusion. All amplitudes were measured as peak voltage relative to a post-stimulus baseline. Separate two-way repeated-measures analyses of variance (ANOVAs) were performed for each SEP of interest (amplitude and latency) with Movement Hand (Left/Right) and Movement Epoch (Control/Early BP/Late BP/Movement/ Post-Movement) as factors. Pre-planned contrasts were conducted to assess the effects of the stages of motor planning on SEP amplitudes for each hand. A one-way repeated-measures ANOVA was performed for peak-to-peak M-wave amplitudes across movement epochs.

2.4 Results

All eight participants showed clear frontal and parietal SEPs. No latency differences were observed for any of the SEPs measured across Movement Hand or Epoch. No main effects of Movement Hand or Epoch were evidenced on either the frontal P20 or the parietal P18 SEP amplitudes. M-wave amplitudes did not significantly differ across epochs for either hand performing the motor output (Left/ Right: ($F(4,28) = 0.77/1.1$, p=NS).

2.4.1 Frontal components

N30

The ANOVA for the N30 amplitudes from right median nerve stimulation revealed a main effect of Movement Hand ($F(1,7)=16.53$, $p<0.05$) and an interaction between Movement and Hand Epoch ($F(1,28) = 3.51$, $p<0.02$). Contrasts revealed that the interaction could be attributed largely to the facilitation of N30 in the movement epoch relative to the control epoch for the movement of the left hand, contralateral to the median nerve stimulation. A trend for movement-related gating in the same epoch was observed for movement of the right hand ipsilateral to median nerve stimulation ($p<0.08$) (see Table 1; Figures 2a & b)

N60

Significant main effects were present on N60 amplitudes for both Movement Hand ($F(1,7) = 26.07$, $p < 0.002$) and Epoch ($F(4,28) = 2.88$, $p<0.05$), as well as a significant Movement Hand x Epoch interaction ($F(4,28) = 2.88$, $p<0.05$). During left-

handed movements, N60 amplitudes were significantly greater during the movement epoch compared with controls. In contrast, N60 amplitudes were significantly smaller during the movement and post-movement epochs, relative to controls, for right-handed movements (see Table 1; Figures 2a & b).

2.4.2 Parietal components

N20

A significant main effect was present for Movement Hand ($F(1,7) = 9.86$, $p<0.02$), but not Epoch, on N20 amplitudes such that N20 amplitude was lower for right hand movement . A weak trend was observed for attenuation of the N20 during the movement and post-movement epochs of the right hand.

P27

A main effect was observed for both Movement Hand ($F(1,7) = 5.75$, $p<0.05$) and Epoch ($F(4,28) = 3.46$, $p<0.02$) on P27 amplitudes. P27 amplitude is lower during right hand movement. During left-handed movements (movement epoch) - contralateral to median nerve stimulation - P27 amplitudes were significantly reduced compared with controls. Owing to the high variability of the control value for the right hand, contrasts to test for movement-related effects were performed relative to the Early BP epoch. This epoch showed no significant difference from control. Strong trends were present for the movement-related reduction of the P27 amplitude for Late BP and Movement ($p<0.07$), compared with Early BP (see Figures 2c & d).

P50

The ANOVA for the P50 amplitude revealed a significant main effect for Movement Hand ($F(1,7) = 6.21$, $p<0.05$) and an interaction between Movement Hand and Epoch ($F(4,28) = 3.89$, $p<0.02$). Compared with controls, P50 amplitudes for participants were significantly reduced during the movement and the post-movement epochs, during left-handed and right-handed movements, respectively (see Table 1; Figures 2c & d).

2.5 Discussion

The novel findings of this study were a differential modulation of the frontal (N30/N60 increased) and parietal (P27/P50 decreased) median nerve SEP amplitudes during the execution, but not during the preparation, of a self paced voluntary grip of the hand contralateral to median nerve stimulation. Rossini et al. (1999) also found N30 facilitation as a result of contralateral hand movement to median nerve stimulation. It was, however, unclear from their study whether the facilitation of the N30 was a result of cortical areas involved in movement planning or in movement execution. Our results suggest that the N30 and N60 facilitation during left-handed movement (contralateral to median nerve stimulation) is brought about by the cortical areas responsible for the execution of a voluntary movement, and not necessarily the planning.

Currently, it is not clear why the median nerve N30 and N60 are amplified during hand movements contralateral to median nerve stimulation. Furthermore, the amplification takes place only during the execution but not during the preparation periods. This seems somewhat counterintuitive, as the N30, and likely the N60, are thought to be generated largely in premotor areas, which have traditionally been defined as contributing to motor preparation rather than to execution. Motor cortical activity ipsilateral to the moving hand has been shown for simple movements (Verstynen et al. 2005; Kawashima et al. 1993). Kawashima et al. (1993) studied regional cerebral blood flow during either a right-handed or a left-handed movement in right-handed individuals, and found that the left primary motor cortex, but not the left premotor area or SMA, showed increased activity for left-handed movements. It is

unclear whether these effects can be directly related to the frontal median nerve SEP (N30 and N60) amplitudes or whether the mechanisms mediating both N30 and N60 amplitudes are similar. It is possible in this case, however, that the frontal median nerve SEP amplitude changes are a result of a direct interaction between the two primary motor cortices. Such inter-hemispheric interactions between motor cortical areas have been shown, using dual stimulation paired-pulse transcranial magnetic stimulation (TMS) (Ferbert et al., 1992). Kobayashi et al. (2003) showed that participants who demonstrated ipsilateral primary motor cortex activity in response to left-handed simple movements also showed strong inhibition of motor-evoked potentials in the left flexor digitorum interpositus, evoked by the test TMS of the right hemisphere after the conditioning TMS of the left hemisphere. A link between increased N30 or N60 SEP amplitudes and activity in primary motor cortex is currently lacking, but might reflect increased inhibition. This has been hypothesized by Urushihara et al. (2006), who showed; using repetitive TMS, that low-frequency stimulation of premotor cortex increased the amplitude of the N30 ipsilaterally. This is noteworthy, as low-frequency repetitive TMS has an inhibitory effect. In this case, however, it resulted in an increase in the N30 amplitude, suggesting that perhaps the increase in N30 amplitude does indeed represent a summation either of the inhibitory collaterals between ipsilateral premotor areas and primary motor cortex or of the transcallosal recurrent inhibitory collaterals between the two primary motor cortices.

Finally, it should be noted that both the parietal P27 and P50 were attenuated during the same condition as that which increased the N30 and N60. This result seems

contrary to those from previous studies, which have demonstrated the specificity of movement-related gating of the median nerve SEPs to movements of the limb segments generated by the stimulated nerve (Tapia et al. 1987). The motor task in this study, however, differs substantially in the relative musculature recruited. In the light of the novel findings of the frontal potentials, it is possible that trans-callosal inter-hemispheric inhibition might govern the transmission of somatosensory information centrifugally in S1, as it is well known that there are extensive connections between the posterior crown of the post-central gyrus and both premotor and primary motor cortices (Jones et al. 1978). Primary motor cortex, in particular, has a strong modulatory role on somatosensory information (Canedo, 1997). Further work is needed to establish these relationships.

2.6 Conclusion

The frontal N30 SEP, as a result of right median nerve stimulation, is facilitated during the execution, but not the preparation, of a simple left-handed movement.

2.7 Figures and Tables

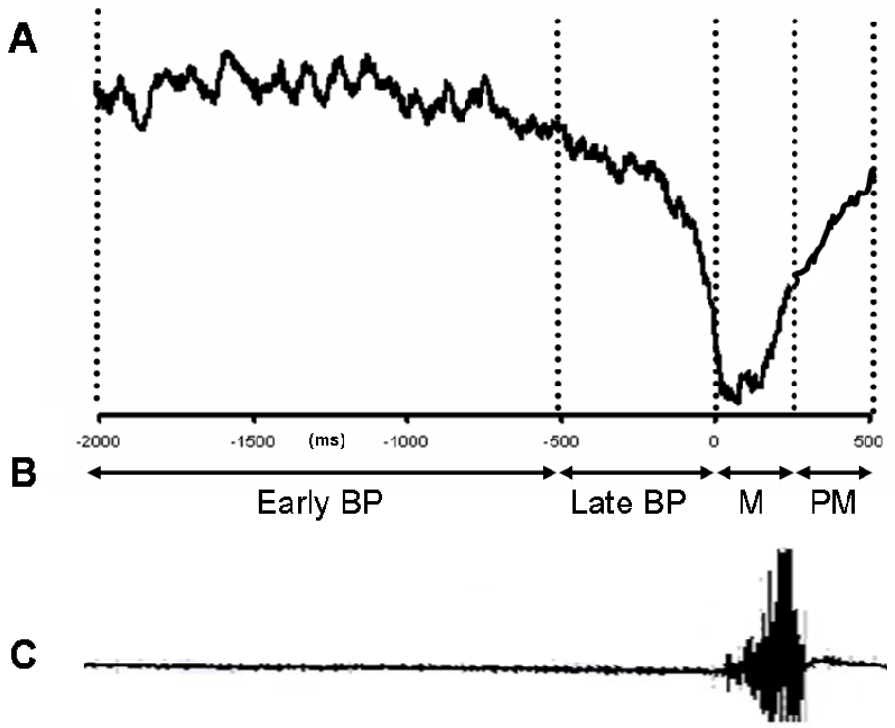

Figure 1

(A) Example of an averaged Bereitschaftspotential (BP) as recorded from electrode site FCZ. Time along x-axis in milliseconds (ms) with zero (0) representing the onset of the rectified electromyography (EMG). (B) Schema of the timing of epochs used to parse median nerve stimulations into BP epochs representing the various components of the BP. Early BP: -2000ms to -500ms before the onset of movement;
Late BP: -500ms to 0ms; M = Movement: 1ms to +250ms after movement onset; PM = Post-Movement: +251ms to +500 ms after movement. (C) Example of the raw EMG from flexor digitorum superficialis of the hand performing the voluntary squeeze.

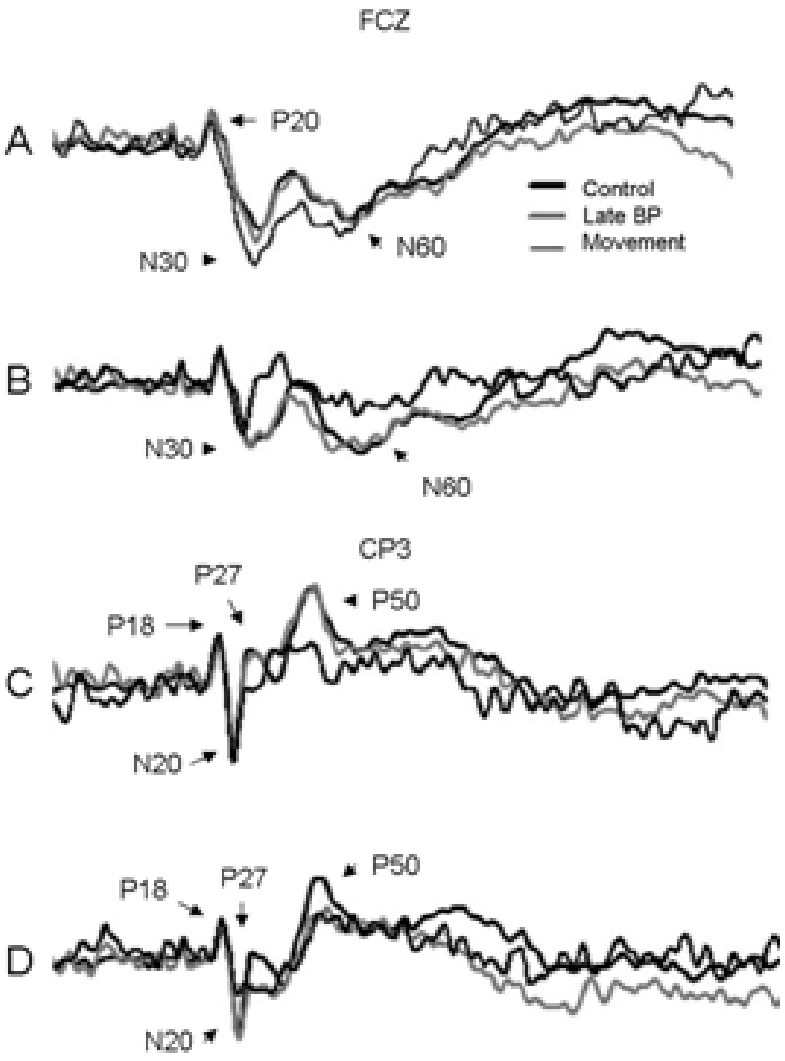

Figure 2

Grand average somatosensory-evoked potential (SEP; right median nerve) traces (n=8) for three Bereitschaftspotential (BP) epochs: Control, Late BP and Movement. Traces (A) and (B) were recorded from electrode site FCZ during (A) a left-handed movement and (B) a right handed movement. Traces (C) and (D) were recorded from electrode site CP3 during (C) a left-handed movement and (D) a right-handed movement. Potentials of interest are marked on the traces.

LH	*FCZ*				*CP3*					
	N30	***P***	***N60***	***P***	***N20***	***P***	***P27***	***P***	***P50***	***P***
C	-3.45±0.34	---	-2.93±0.48	---	-2.00±0.44	---	1.34±0.33	---	3.13±0.39	---
E BP	-3.71±0.43	*NS*	-2.86±0.49	*NS*	-1.93±0.42	*NS*	1.30±0.34	*NS*	3.04±0.38	*NS*
L BP	-3.93±0.33	*NS*	-3.33±0.84	*NS*	-2.03±0.30	*NS*	1.19±0.64	*NS*	3.14±0.57	*NS*
M	-5.11±0.91	**0.04**	-4.54±0.58	**0.01**	-2.43±0.39	*NS*	0.59±0.44	**0.04**	2.01±0.60	**0.01**
P-M	-2.66±0.62	*NS*	-2.89±0.62	*NS*	-2.45±0.43	*NS*	0.67±0.40	*NS*	3.25±0.72	NS

RH	*FCZ*				*CP3*					
	N30	***P***	***N60***	*P*	***N20***	***P***	***P27***	***P***	***P50***	P
C	-2.54±0.33	---	-2.77±0.57	---	-2.23±0.43	---	0.64±0.46	---	2.61±0.27	---
E BP	-2.92±053	*NS*	-2.72±0.69	*NS*	-1.98±0.50	*NS*	1.01±0.33	---	2.87±0.21	*NS*
L BP	-2.63±0.44	*NS*	-3.38±0.76	*NS*	-2.33±0.54	*NS*	-0.09±0.35	***0.07**	2.16±0.38	*NS*
M	-1.66±0.45	**0.08**	-1.35±0.48	**0.02**	-1.32±0.32	*NS*	0.18±0.36	***0.07**	2.42±0.80	*NS*
P-M	-1.15±0.68	*NS*	-1.25±0.35	**0.01**	-1.42±0.57	*NS*	-0.07±0.50	*NS*	1.00±0.45	**0.01**

Table 1.

Raw voltages of labeled potentials relative to a post-stimulus baseline. All values are in μV as a result of RH median nerve stimulation. Top section represents values for left hand (LH) motor output. Bottom section for right hand (RH) motor output. C = Control, E BP = Early BP, L BP = Late BP, M = Movement, P-M = Post-Movement, P = P-value for contrasts for each potential epoch relative to its respective Control epoch. * represents p-value relative to E BP value.

CHAPTER 3 – STUDY 2: Non-dominant hand movement facilitates the frontal N30 somatosensory-evoked potential

3.1 Overview

Previous literature has shown that the frontal N30 is increased during movement of the hand contralateral to median nerve stimulation. This finding was a result of non-dominant left hand movement in right-handed participants. It is unclear however if the effect depends upon non-dominant hand movement or if this is a generalized phenomenon across limbs. This study tests the effect of dominant and non-dominant hand movement upon contralateral frontal and parietal SEPs and further if this relationship persists in left hand dominant participants. Median nerve SEPs were elicited from the left wrist of right handed participants and both right and left wrists of left hand dominant participants in separate blocks. Participants were required to quickly and forcefully squeeze a pressure-sensitive bulb roughly every 3 seconds with the hand contralateral to median nerve stimulation. SEPs were averaged and quantified from both FCZ and CP3/4 scalp electrode sites during both the squeeze task and at rest.

The N30 is facilitated during non-dominant hand movement but not during dominant hand movement. This effect is similar for both right and left hand dominant individuals. There is no effect of non-dominant hand movement upon parietal potentials.

These data suggest that movement of the non-dominant upper-limb exclusively modulates sensory inputs to frontal motor areas. Cortical areas exclusive to non-dominant hand movement may mediate this effect.

3.2 Introduction

Somatosensory input is required for accurate motor performance and learning new motor skills. Patients with decreased somatosensory input due to peripheral deafferentation display abnormal motor behaviour (Rothwell et al., 1982) while somatosensory deficits in stroke patients are associated with a slower recovery of motor function (Reding & Potes, 1988). Somatosensory information from the hand is first processed cortically in contralateral S1 but also reaches classically defined motor areas in the frontal cortex (Wiesendanger et al., 1985). The N30 component of the median nerve SEP is a promising physiological index of somatosensory inflow to frontal motor cortical structures. It is maximal at frontal midline electrode sites and has therefore been hypothesized to be generated in the underlying cortex; most notably the SMA (Desmedt & Bourguet, 1985; Mauguiere et al., 1983).

The N30 has been investigated under various sensory-motor paradigms and generally been shown to behave similarly to parietal SEP components (Cheron et al., 2000). However, the N30 does display unique modulation independent of parietal SEP components under specific motor-related conditions such as mental imagery and ideation (Cheron & Borenstein, 1992; Rossini et al. 1996a) as well as a distinct attenuation in Parkinson's disease (Cheron et al., 1994; Rossini et al., 1989) and facilitation in dystonia (Reilly et al. 1992). As such, the N30 has been hypothesized to reflect activity of specific motor pathways linking basal ganglia to frontal cortex (Cheron 1999).

Interestingly, the N30 is also facilitated independently of parietal components during upper-limb movements contralateral to the stimulating site (Legon et al., 2008; Rossini et al. 1999a) which is suggestive that the N30 operates independently of parietal components. Legon et al. (2008) demonstrated that N30 facilitation only occurs during but not before or after movement, suggesting an influence of motor cortical activity on N30 facilitation. However, it is unclear from these two studies if facilitation of the N30 is dependant upon the dominance of the hand performing the motor output as neither investigated the reversal of sensory input and motor output across the upper limbs. It is hypothesized that the hand performing the movement affects N30 modulation because non-dominant hand movement results in unique recruitment of ipsilateral primary motor cortical activity (Kawashima et al. 1993; Kim et al. 1993; Cramer et al. 1999) and subsequent differences in inter-hemispheric inhibition between motor cortices (Kobayashi et al. 2003; Duque et al. 2007). In addition to primary motor cortex activity, differences based upon hand use have also been observed in pre-motor (Kawashima et al. 1993) and supplementary motor cortex (Babiloni et al., 2003). Most of these studies investigated right hand dominant individuals only and do not provide evidence if the ipsilateral (left) motor cortex activity is a result of general left hemisphere dominance for motor control as suggested by the stroke literature (Haaland & Harrington, 1989a) or if it is specific to the motor cortex contralateral to the dominant hand. Handedness may indeed affect this relationship as motor cortical activity has been shown to be less lateralized in left handed individuals as compared to right and with greater variability of cortical

activation depending upon the hand being used (Kawashima et al., 1993; Singh et al., 1998). For example, Kawashima et al. (1993) reported ipsilateral premotor activation during non-dominant hand movement in left hand dominant individuals whereas Singh et al. (1998) showed bilateral activation.

Despite the well-investigated motor cortical differences depending upon hand use and handedness, there is a dearth of work investigating how handedness and particularly dominant versus non-dominant hand use affect sensory input across the upper limbs. This is an important consideration as sensory dysfunction is thought to contribute to many classically defined motor pathologies (Abbruzzese & Berardelli, 2003). Sensory inputs from one arm have been shown to affect motor cortical excitability of the contralateral limb (Manganotti et al., 1997; Swayne et al., 2006), and interestingly, the removal of these inputs via transient cutaneous anaesthesia, shown to increase performance of the paretic hand in chronic stroke patients (Floel et al., 2004).

There are a few reports employing SEPs that have shown an effect of sensory-motor interaction across the upper limbs (Hoshiyama & Kakigi 1999; Kida et al. 2006; Wasaka et al. 2007). For example, Hoshiyama & Kakigi (1999) had both right and left-hand dominant participants perform a tracing task with either their dominant or non-dominant hand while recording SEPs from the contralateral hand. Non-dominant hand use resulted in an attenuation of N30 amplitude - a result at odds with the work of both Rossini et al. (1999) and Legon et al. (2008). This discrepancy is likely a result of increased demands associated with the tracing task employed – both Rossini et al. (1999) and Legon et al. (2008) had participants perform simple self-paced repetitive

hand movement. Despite this, modulation of the N30 in the Hoshiyama & Kakigi (1999) study only occurred for tracing performed with the non-dominant hand suggesting a specific relationship for N30 modulation during non-dominant upper-limb motor output. The purpose of the current study is to determine if the N30 facilitation observed by Legon et al. (2008) is exclusive to movement of the non-dominant upper-limb and further if this relationship persists in left-hand dominant individuals. It is hypothesized that N30 facilitation may be specific to movement of the non-dominant hand in right hand dominant individuals due to the aforementioned increase in ipsilateral motor cortex activity. This may not be so in left hand dominant individuals as their ipsilateral motor cortical activation is more variable and motor cortical activity in general is less lateralized.

3.3 Methods

3.3.1 Participants

Sixteen subjects participated in one of two experiments performed on separate days. Experiment 1 studied eight right-handed participants (3 Female, Age 26 ± 4.6yr) and Experiment 2, eight left-handed (2 female, Age 24 ± 2.2yr). All participants' handedness was assessed by the Waterloo Handedness Inventory (Right Handed +36 ± 2.8; Left Handed -28 ± 5.5) (Bryden 1977). Participants provided written informed consent to participate in the study. None of the participants reported any history of neurological or musculoskeletal impairments, and all were paid a nominal fee for their participation. The University of Waterloo, Office of Research Ethics approved all experimental procedures.

3.3.2 Behavioural Task

For both experiment 1 and experiment 2, participants were seated comfortably in a desk chair, with arms supported upon a table top, in a sound-attenuating booth and instructed to perform a non-maximal (~ 20% of their maximum) squeeze and hold (1-2 s) voluntary contraction against a pressure-sensitive bulb held in either their right or the left hand while fixating straight ahead. Participants were instructed to initiate squeezes roughly every 3 s but were allowed to perform successive movements at their own pace. The hand with which they squeezed was alternated in 3 min blocks repeated five times for each hand with a 1 min break between successive trials. Motor and rest periods were indicated by a verbal cue.

3.3.3 Stimulation and Recording

Stimulation and recording details are similar for both experiment 1 and 2 except during experiment 1 SEPs were derived from electrical stimulation of the median nerve of the non-dominant (left) wrist only. (Dominant (right) wrist stimulation has been reported elsewhere; Legon et al. (2008). For experiment 2, SEPs were derived from the electrical stimulation of the median nerve of both the non-dominant (right) and dominant (left) wrist on alternating blocks. Stimulation employed square wave pulses of 0.2 ms duration (GRASS S88 stimulator with SIU5 stimulus isolation unit; West Warwick, Rhode Island, USA) delivered through a surface bar electrode, with the anode distal, fixed over the median nerve. Median nerve stimuli were delivered during task performance (2 Hz) at a voltage sufficient to elicit a noticeable thumb twitch and recordable M-wave recorded via surface electromyography (EMG) from the thenar musculature. Surface EMG was also recorded from flexor digitorum superficialis of the hand performing the squeeze to monitor behavioural performance. EMG recordings were amplified (2000X), band-pass filtered (DC–200 Hz), digitized and stored for later analysis, using customized LabVIEW software (National Instruments; Austin, Texas, USA). Thenar electrodes were used to record the M-wave, an EMG wave resulting from the direct stimulation of the motoneuronal axons serving the thenar musculature. M-wave amplitude, measured peak-to-peak, was used to confirm the consistency of stimulus intensity. The onset of the squeeze was evidenced by the onset of flexor digitorum superficialis EMG activity. SEPs were elicited continuously throughout the squeeze blocks and rest periods. Electroencephalographic (EEG) data were recorded

from 7 electrode sites (FC2, FZ, FC1, C4, C3, CP4 and CP3), in accordance with the international 10–20 system for electrode placement referenced to the linked mastoids (impedance <5kΩ). EEG data were amplified (40000x), filtered (DC–200 Hz) and digitized at 1000 Hz (NeuroScan 4.3; Compumedics; El Paso, Texas, USA), before being stored on a computer for subsequent analysis. SEPs were extracted by averaging epochs time-locked to the median nerve stimulation (-50 to 300 ms). Individual traces were high-pass filtered (2 Hz) and visually inspected for artefacts (i.e. from blinks, eye movements or contraction of scalp musculature). Any contaminated epochs were eliminated before averaging.

3.3.4 Data Analysis

For Experiment 1, median nerve stimulations were averaged in bins time-locked to EMG onset (time 0ms) in flexor digitorum superficialis, according to predetermined movement epochs corresponding to the different known components of the Bereitschaftspotential (BP): Early BP (-2000ms to -500ms); Late BP (-500ms to 0ms); Movement (0ms to +250ms); Post-Movement (500ms after EMG offset). The timing of epochs for Experiment 2 was slightly different in that the Movement epoch was extended (1000ms rather than 250ms) in order to lengthen the time window in which to capture stimulations used for averaging (see figure 1). SEP traces for each time epoch were a result of at least 180 stimulations. Median nerve stimulations that did not fall within the pre-determined epochs were averaged and used as control. Latencies and amplitudes of the frontal and parietal SEPs were measured from individual participant averages for each movement epoch from the electrode sites that displayed the maximal

amplitudes, FCZ and CP3/4, respectively. Latencies were measured from stimulus onset to the peak of each SEP (frontal P18, N30 and N60; parietal P18, N20, P27 and P50). Amplitudes of the frontal N60 and parietal P50 were measured as peak voltage relative to a post-stimulus baseline; all other potentials of interest were measured and quantified as peak-to-peak voltages (eg. P18-N30; P18-N20 and N20-P27). A clearly defined peak was necessary for inclusion.

For experiment 1, a one-way repeated measures analysis of variance (ANOVA) was performed for each SEP component of interest with Timing Epoch relative to EMG onset as factor (Control/Early Bereitschaftspotential/Late Bereitschaftspotential/Movement/Post-Movement) during dominant (right) hand movement. Results of non-dominant (left) hand movement have been previously reported (Legon et al. 2008). For Experiment 2, two separate one-way ANOVAs were performed for each side of hand movement (dominant and non-dominant) using Timing Epoch as factor. A two-way ANOVA using Movement Hand and Timing Epoch as factors was not performed as an interaction was not hypothesized. For all three ANOVAs, pre-planned contrasts were conducted between the control value and the movement epoch.

3.4 Results

3.4.1 Controls

All eight left-handed and right-handed participants showed clear frontal and parietal SEPs. No latency differences were observed for any of the SEPs measured. M-wave amplitudes were measured to ensure stimulus consistency and also displayed no significant differences across any of the conditions.

3.4.2 Frontal Components

N30

Experiment 1: Right Hand Dominant.

There was no effect of Timing Epoch for dominant (right) hand movement upon N30 amplitudes ($F(4,28) = 1.95$, $p = 0.15$).

Experiment 2: Left Hand Dominant.

There was no effect of Timing Epoch for dominant (left) hand movement upon N30 amplitudes ($F(4,28) = 0.81$, $p = 0.94$). Non-dominant movement (right) revealed an effect of Timing Epoch ($F(4,28) = 4.08$, $p = 0.01$). Pre-planned contrasts revealed an increase in N30 amplitude for the movement epoch as compared to control ($p < 0.05$). There were no differences between any of the other epochs from control (see Table 1).

N60

Experiment 1

There was no effect of Timing Epoch for dominant right hand movement ($F(4,28) = 1.67$, $p = 0.22$).

Experiment 2

There was no effect of Timing Epoch for dominant left hand movement ($F(4,28) = 1.81$, $p = 0.21$). The ANOVA for non-dominant (right) hand movement revealed a main effect of Timing Epoch ($F(4,28) = 3.26$, $p = 0.05$). Contrasts revealed a significant difference between the Control and Movement epochs ($p = 0.01$). Further exploration revealed the Movement epoch significantly differed from both the EBP ($p = 0.01$) and Post-Movement ($p = 0.02$) epochs. The LBP epoch did not differ from any of the other epochs. (See Table 1).

3.4.3 Parietal Components

There were no significant effects of Timing Epoch on the amplitudes of any of the measured potentials (P18-N20; N20-P27 or P50) for either experiment 1 or 2 (see Table 1).

3.5 Discussion

The main finding of this study is for facilitation of the frontal N30 SEP component during non-dominant hand movement in left hand dominant individuals as well as the finding that dominant hand movement in both groups had no effect upon N30 amplitude. These results, in combination with previous results (Chapter 2 - Legon et al. 2008) - which found a similar increase in the frontal N30 during non-dominant hand movement in right hand dominant participants – lead to the conclusion that non-dominant hand movement facilitates the frontal N30 derived from contralateral dominant median nerve stimulation. It was originally hypothesized that the handedness of the participants may influence sensory-motor interaction across the upper-limbs because of the reported differences in motor cortical activity between right and left hand dominant individuals - specifically a decreased lateralization of motor cortical function for left hand dominant individuals (Dassonville et al. 1997), but this did not influence the results. This may be so because ipsilateral pre-motor activation has been reported in a left hand dominant group during non-dominant hand movement (Kawashima et al., 1997).

The purpose of N30 facilitation and the cortical areas mediating it is difficult to exactly define, chiefly because a concrete N30 generator is lacking and as such, provides no evidence for a specific population of cells that contributes to its amplitude or even the type of somatosensory information it represents This is in contrast to the early parietal potentials (N20 and P27) derived from median nerve stimulation that

have been source localized to Brodmann areas (3b and 1) within primary somatosensory cortex; areas shown to represent cutaneous peripheral afferent information (Allison et al. 1991). Work by Restuccia et al. (1999; 2002) has provided some evidence that the N30 may represent proprioceptive sensory information as direct stimulation of muscle afferents produced an N30 whereas purely cutaneous stimulation did not. Understanding this, it could be conjectured that the increase in N30 amplitude during hand movement is simply a result of a convergence of re-afferent input from the moving hand with that of the stimulated hand and therefore merely represents an increase in total afferent input. This is a possibility as midline electrode FCZ was used to record N30 amplitudes and hence would likely record activity from both right and left SMA. Convergence of afferent inputs has been shown for the same limb as well as across the upper limbs (Kakigi, 1986) but typically motor influence upon sensory input is inhibitory and this effect is site specific and absent across the upper limbs as evidenced by the movement-related gating literature (Cohen & Starr 1987; Tapia et al. 1987). Furthermore, for this to be true it should occur regardless of the hand performing the movement. N30 amplitude was not significantly different from control during dominant hand movement. In light of this, it seems reasonable to speculate that cortical motor activity specific to non-dominant hand movement may contribute to N30 facilitation.

As mentioned previously, the most notable difference between non-dominant and dominant hand movement is for increased ipsilateral primary motor cortical activity during the former (Kawashima et al. 1993; Kim et al. 1993; Cramer et al. 1999). A

prospective cause for this increased ipsilateral motor activity has been provided by Duque et al. (2007) who had right handed participants perform both right and left hand movements while investigating inter-hemispheric inhibition. They reported that motor cortical activity contralateral to dominant hand movement inhibits ipsilateral motor cortex whereas motor cortical activity contralateral to non-dominant hand movement does not. Assuming the N30 is generated in the supplementary motor area, its facilitation may be mediated by the rich recurrent projections between ipsilateral motor cortex and supplementary motor area (Jurgens 1984; Luppino et al. 1993). A repetitive transcranial magnetic stimulation (rTMS) study further supports this contention as rTMS of left M1 in right handed participants increased blood oxygenation level in SMA (Bestmann et al., 2003). In addition, the SMA has been shown to respond to somatosensory inputs but only to stimulation that is attended to or used to enact a motor output (Romo et al. 1993; Staines et al. 2002).

The specific attenuation of N30 amplitude in Parkinson's disease (Rossini et al. 1989; Cheron et al. 1994) suggests a significant link between the N30 and basal ganglia thalamo-cortical loops (Cheron 1999). Interestingly, recent research has demonstrated differences in basal ganglia activity as a result of hand use. Francois-Brosseau et al. (2009) demonstrated reduced activation of the putamen during self-initiated left hand movement as compared to right hand movement. However, under an externally cued condition right putamenal activation was demonstrated during left hand movement. As is well understood, Parkinson's patients have considerable difficulty with voluntary

action as compared to cued tasks. The specific link between these findings and N30 amplitude is speculative but nevertheless intriguing to speculate.

Lastly, there were no influences of movement contralateral to median nerve stimulation upon early parietal potentials known to be generated in primary somatosensory cortex (Allison et al. 1991). If indeed M1 activity ipsilateral to the non-dominant hand does influence N30 modulation, it would seem that this could also affect S1 activity as M1 has dense connections and well-established influence over somatosensory processing (Canedo 1997). This was not apparent for the left hand dominant participants in this study but does agree with the known specificity of movement related effects upon parietal SEP components (Cohen & Starr 1987; Tapia et al. 1987).

The purpose or cause of N30 facilitation in isolation of parietal modulation during non-dominant hand movement is currently unclear but lends indirect evidence for a distinct cortical generator and a likely difference in the role these distinct populations play in a somatosensory processing stream during movement.

3.6 Conclusions

The frontal N30 SEP is facilitated independently of parietal components during non-dominant hand movement. Dominant hand movement in both right and left hand dominant individuals does not influence N30 amplitudes.

3.7 Figures & Tables

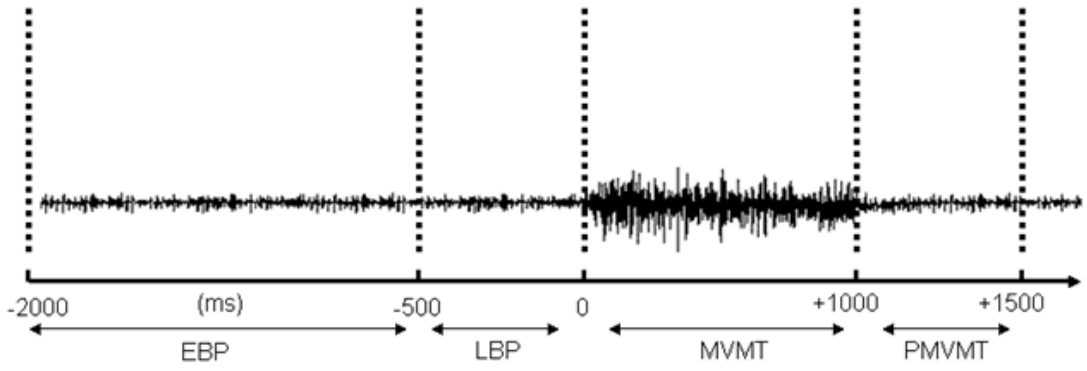

Figure 1

Example of raw EMG from flexor digitorum superficialis of the hand performing the voluntary squeeze and hold. Timing windows used to divide median nerve stimulations into respective epochs relative to the onset (0ms) of EMG are shown. (EBP) Early Bereitschaftpotential (-2000ms to -500ms); (LBP) Late Bereitschaftpotential (-500ms to 0ms); (MVMT) Movement (0ms to +1000ms); (PMVMT) Post-Movement (500ms after EMG offset).

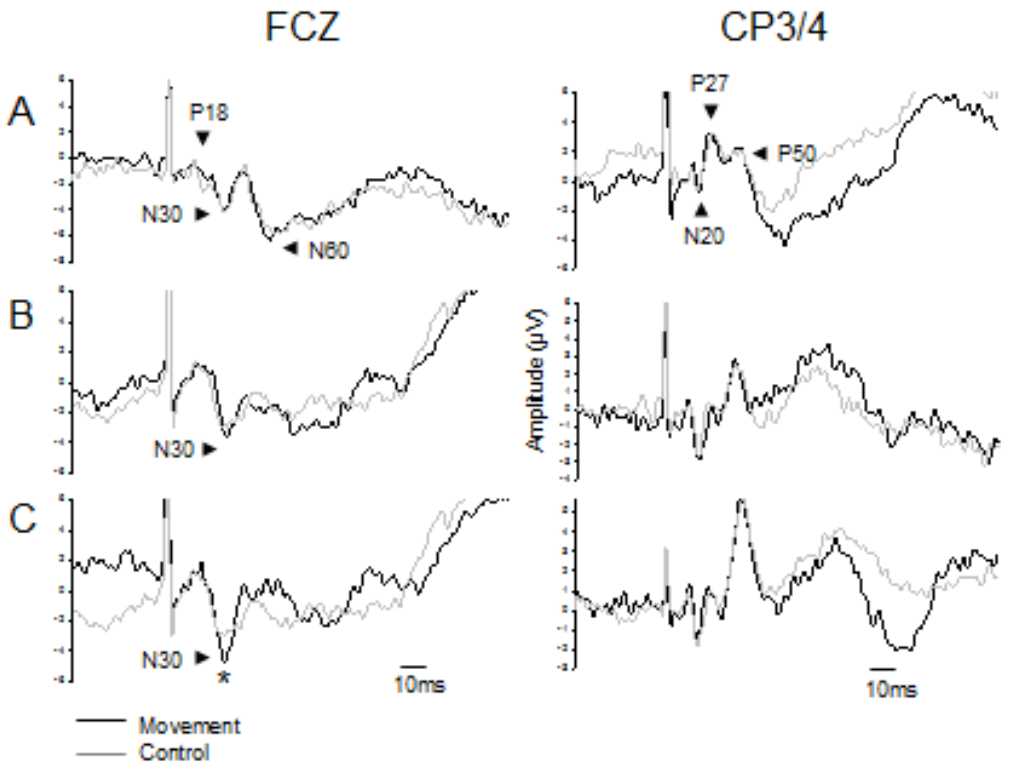

Figure 2

Representative somatosensory-evoked potential (SEP) trace from electrode sites FCZ and CP3/4 for one right-handed subject from Experiment 1 (A) and from one left-handed subject from Experiment 2 (B & C). Traces a result of median nerve stimulation contralateral to hand movement for two time epochs: Control (light trace) and Movement (Dark trace). A) Exp 1. Right hand dominant - movement of the dominant (right) hand. B) Exp 2. Left hand dominant - movement of the dominant (left) hand. C) Exp 2. Left hand dominant - movement of the non-dominant (right) hand. Potentials of interest are marked. Ordinate amplitude in microvolts (μV). * denotes significance $p < 0.05$.

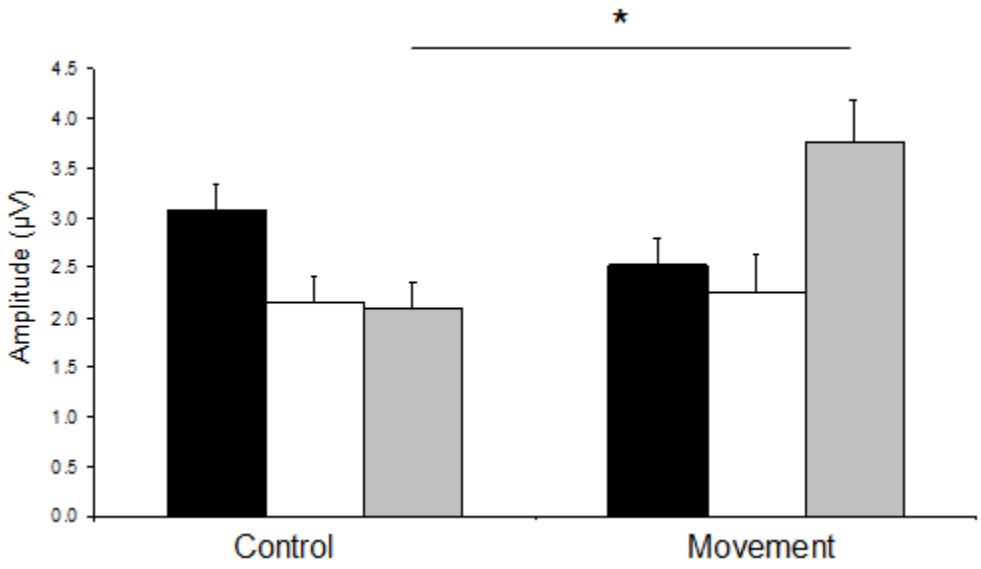

Figure 3

Grand average (n=8) P18-N30 amplitude bar graph showing data from both experiment 1 (Right hand dominant) Black bars denote right hand movement & 2 (Left hand dominant) White bars denote left hand movement. Grey bars denote right hand movement. Ordinate amplitude in microvolts (μV). Error bars are ±SEM. * denotes significance $p < 0.05$.

Table 1

Experiment 1 Right Hand Dominant

	FCZ		CP4		
	P18-N30	N60	P18-N20	N20-P27	P50
RH					
Control	3.08 (0.27)	2.98 (0.9)	2.28 (0.28)	3.79 (0.64)	3.28 (0.49)
EBP	2.92 (0.29)	2.93 (1.10)	2.35 (0.31)	3.93 (0.73)	3.13 (0.49)
LBP	3.02 (0.24)	2.65 (1.05)	2.35 (0.19)	4.51 (0.65)	2.72 (0.48)
MVMT	2.52 (0.28)	3.51 (1.05)	2.04 (0.23)	4.10 (0.55)	3.25 (0.73)
PMVMT	2.79 (0.24)	2.52 (1.07)	2.50 (0.20)	4.76 (0.83)	3.52 (0.55)

Experiment 2 Left Hand Dominant

	FCZ		CP3		
	P18-N30	N60	P18-N20	N20-P27	P50
LH					
Control	2.57 (0.38)	1.80 (0.56)	1.93 (0.45)	2.15 (0.38)	2.89 (0.54)
EBP	2.70 (0.45)	2.70 (0.54)	1.92 (0.55)	2.50 (0.67)	2.43 (0.55)
LBP	2.86 (0.20)	2.28 (0.29)	2.03 (0.38)	2.42 (0.36)	3.10 (0.46)
MVMT	2.77 (0.44)	2.55 (0.46)	1.66 (0.27)	2.24 (0.33)	2.53 (0.54)
PMVMT	2.40 (0.64)	2.03 (0.56)	1.56 (0.37)	2.72 (0.39)	2.64 (0.52)
RH			CP4		
Control	2.57 (0.33)	2.30 (0.56)	1.37 (0.20)	1.96 (0.37)	2.04 (0.55)
EBP	2.59 (0.43)	2.36 (0.32)	1.66 (0.11)	2.09 (0.28)	1.74 (0.59)
LBP	2.80 (0.40)	2.58 (0.53)	1.84 (0.28)	2.20 (0.28)	2.13 (0.71)
MVMT	4.17 (0.53)	3.37 (0.43)	2.01 (0.42)	1.91 (0.37)	1.22 (0.56)
PMVMT	3.32 (0.78)	2.20 (0.50)	1.61 (0.31)	1.71 (0.38)	2.07 (0.62)

Table 1.

Mean (± SE) voltages of labeled potentials. All values are in μV recorded from labeled electrode sites (FCZ, CP3/4) as a result of median nerve stimulation contralateral to hand movement. (RH) Right hand movement. (LH) Left hand movement. (EBP) early Bereitschaftspotential; (LBP) late Bereitschaftspotential; (MVMT) movement; (PMVMT) post movement. * represents $p = 0.05$ as compared to control.

CHAPTER 4 – STUDY 3: Continuous theta-burst stimulation of the left motor cortex removes N30 facilitation from ipsilateral hand movement.

4.1 Overview

Movement of the left hand is often associated with an increase in activation of the ipsilateral motor cortex, a phenomenon that is less common during right hand movement. Similarly, non-dominant but not dominant hand movement has been shown to increase the N30 SEP derived from contralateral median nerve stimulation. It is hypothesized that ipsilateral motor cortex activity exclusive to left hand movement mediates the amplitude increase of the N30 SEP during non-dominant left handed movement. To test this, continuous TBS was delivered over the hot spot for both right and left first dorsal interosseous (FDI) for 40 s (600 pulses) of 3 stimuli at 50 Hz repeated at 5 Hz at 90% of resting motor threshold (RMT) in separate experiments. In experiment 1, subjects performed two separate non-cued volitional motor tasks with their left hand in addition to rest: 1) 20% maximum voluntary contraction grip and hold (~2s) and 2) sequential finger thumb opposition in 3 min blocks repeated twice both before and after TBS to the left motor cortex. The same tasks were performed in experiment 2, but with the right hand both before and after TBS to the right motor cortex. Average motor evoked potentials (20 pulses at 120% RMT) were recorded before and after TBS to test motor cortical inhibition. Median nerve SEPs were elicited from the wrist contralateral to the movement hand via electrical stimulation (0.2 ms pulse) at 2 Hz. SEPs were averaged and potential amplitudes quantified from scalp electrode sites FCZ, FC3 and CP3. Results suggest that gripping of the left hand

increases the frontal N30 but that this facilitation is removed after cTBS to ipsilateral M1. cTBS of the right motor cortex does not affect the N30. These results provide evidence that inhibition of the ipsilateral left motor cortex affects the frontal N30 SEP. Furthermore, these results depend upon movement of the ipsilateral limb.

4.2 Introduction

Sensory afference to the primary somatosensory cortex is inhibited as a result of ipsilateral movement. This does not occur when sensory input and motor output are dissociated across the upper limbs such that movement of the contralateral limb does result in inhibition of somatosensory evoked potential components (Tapia 1987; Cohen & Starr 1987). Recent research has demonstrated however that non-dominant hand movement facilitates the frontal N30 SEP derived from contralateral median nerve stimulation (Rossini et al. 1999; Legon et al. 2008). Curiously, N30 facilitation does not occur for the reverse (during similar dominant hand movements) (Chapter 3; Legon et al. submitted). It is unclear why this is so. A potential reason for this difference is the well-documented increase in ipsilateral motor cortical activity reported during non-dominant hand movement (Kawashima et al. 1993; Kim et al. 1993; Kobayashi et al. 2003; Horenstein et al., 2009); a phenomenon that is not common for dominant hand movements (Hanakawa et al., 2005; Kansaku et al., 2005; Verstynen et al., 2005).

The frontal N30 SEP is maximally recorded from scalp electrodes over fronto-central sites and as such has been postulated to be generated in the underlying cortex; most notably the SMA (Desmedt & Bourguet, 1985; Mauguiere et al., 1983). The SMA has been implicated in both the preparation and execution of voluntary movements of varying complexity, as well as being particularly responsive to somatosensory inputs (Roland et al., 1980; Romo et al., 1993). The SMA has dense connectivity with ipsilateral M1 (Jurgens 1984; Luppino et al. 1993) and therefore may be specifically modulated during movement that preferentially recruits ipsilateral M1

activity. It is the purpose of this study to test the hypothesis that M1 activity ipsilateral to the non-dominant hand contributes to the facilitation of N30 amplitude as derived from contralateral median nerve stimulation. This was tested by applying continuous TBS (Huang et al., 2005) to the ipsilateral motor cortex before dominant and non-dominant hand movement in two separate experiments. In addition, a sequence finger-thumb opposition movement was performed to test if the type of movement is a factor in contralateral N30 facilitation as a sequence movement has been previously reported to increase ipsilateral M1 activity (Verstynen et al. 2005) and subsequently been shown to be disrupted by repetitive transcranial magnetic stimulation to left M1 (Avanzino et al., 2008; Chen et al., 1997). It is hypothesized that continuous TBS of M1 ipsilateral to non-dominant hand movement will remove the N30 facilitation resulting from this movement. This effect is not hypothesized to be movement specific though behaviour of the sequence task is hypothesized to be disrupted. Continuous TBS to ipsilateral M1 for dominant hand movement is not hypothesized to affect N30 amplitude as dominant hand movement has not been reported to have an effect on this potential.

4.3 Methods

4.3.1 Participants

Experiment 1 studied ten right-handed participants (5 female, Age 24 ± 3.5yr). Handedness was assessed using the Edinburgh Handedness Scale (Mean laterality: +77.77 ± 22.24; range: +40 to +100). Experiment 2 studied five right-handed participants (2 female, Age 23 ± 1.9yr). All participants were right handed (mean: +94 ± 5.5; range: +90 to +100). Participants provided written informed consent to participate in the study. None of the participants reported any history of neurological or musculoskeletal impairments, or any contra-indicators for TMS and all were paid a nominal fee for their participation. The University of Waterloo, Office of Research Ethics approved all experimental procedures.

4.3.2 Behavioural Task

For experiment 1, participants performed the motor tasks with their non-dominant left hand and for experiment 2 participants performed the motor tasks with their dominant right hand. For both experiments, participants were seated comfortably in a desk chair with elbow, forearm and hand resting upon a custom-made armrest. Participants were instructed to perform two tasks in addition to a resting task. The first task (Gripping Task) consisted of a non-maximal (~20% MVC) squeeze and hold (1-2 s) voluntary contraction of a pressure-sensitive bulb held in their left hand. The second task consisted of a finger-thumb opposition sequence (Sequence Task) whereby subjects were instructed to touch their left thumb to each of their fingers sequentially –

starting with the index finger and returning. For this task, participants were instructed to perform the sequence as quickly but as accurately as possible at "a rate that maximized the total number of touches but the least numbers of errors." Force sensing resistors were attached to the pad of the thumb and 3rd finger during this task to record behavioural data. There were no force instructions/requirements for this task. During both motor tasks and the rest task, participants were instructed to fixate straight ahead and to not look at their hand. Each of the movement tasks lasted 4 min. The rest task lasted 3 min. Each of these tasks was conducted pseudo-randomly pre and post TMS. Participants were allowed to pause during the motor tasks if they felt fatigued. None ended up doing so (see Figure 1).

4.3.3 Stimulation and recording

Stimulation and recording parameters were the same for both experiments. SEPs were derived from electrical stimulation of the median nerve of the wrist contralateral to movement (Experiment 1: Move left hand; MN right hand. Experiment 2: Move right hand, MN left hand) (square wave pulse 0.2 ms duration) using a GRASS S88 stimulator with SIU5 stimulus isolation unit (GRASS Instr., West Warwick, Rhode Island, USA), delivered through a surface bar electrode (anode distal) fixed over the median nerve. Median nerve stimuli were delivered during task performance at a constant rate of 2 Hz and at a voltage sufficient to elicit a noticeable thumb twitch and recordable M-wave. Electromyography (EMG) was recorded via surface electrodes placed over the thenar musculature of the hand receiving median nerve stimulation to record M-waves and flexor carpi ulnaris (FCU) of both arms to

monitor EMG activity from both arms. EMG recordings were amplified (2000X), band-pass filtered (DC–200 Hz), digitized and stored for later analysis, using customized LabVIEW software (National Instruments; Austin, Texas, USA). Thenar electrodes were used to record the M-wave, an EMG wave resulting from the direct stimulation of the motoneuronal axons serving the thenar musculature. M-wave amplitude, measured peak-to-peak, was used to confirm the consistency of stimulus intensity. The onset of the motor activity was evidenced by the onset of FCU EMG activity and confirmed from both pressure and force profiles collected from the bulb and force-sensing resistors respectively. SEPs were elicited continuously throughout the motor and rest tasks. Electroencephalographic (EEG) data were recorded from 3 electrode sites FC3, FCZ and CP3 in accordance with the international 10–20 system for electrode placement referenced to the linked mastoids (impedance <5kΩ). EEG data were amplified (40000x), filtered (DC–200 Hz) and digitized at 1000 Hz (NeuroScan 4.3; Compumedics; El Paso, Texas, USA), before being stored on a computer for subsequent analysis. SEPs were extracted by averaging epochs time-locked to the median nerve stimulation (-50 to 300 ms). Individual traces were high-pass filtered (2 Hz) and visually inspected for artefacts (i.e. from blinks, eye movements or contraction of scalp musculature). Any contaminated epochs were eliminated before averaging.

4.3.4 Transcranial Magnetic Stimulation

For both experiments, continuous TBS for 40 s (600 pulses) of 3 stimuli at 50Hz repeated at 5Hz (Huang et al. 2005) was applied to the motor cortex (Experiment

1 - Left motor cortex; Experiment 2 – Right motor cortex) representation of the FDI at an intensity of 90% resting motor threshold (RMT) using a MagPro stimulator (Medtronic, Minneapolis, MN, USA) and 'figure of eight' coil (model No. MCF-B65). Each participant's RMT for FDI was determined with coil handle pointing backwards and laterally at 45 degrees from midline using a neuronavigational system (Brainsight, Rogue Research, Montreal, Canada) to ensure exact repositioning of the coil. RMT was determined as the lowest stimulus intensity at which 5 of 10 consecutive stimuli elicited a reliable MEP of at least 50 mV. A total of 20 MEPs (single-pulses delivered every 3sec) were recorded both pre- and post-TBS (~ 20 min) and used for averaging and analysis.

4.3.5 Data Analysis

4.3.5.1 Behavioural

Behavioural data was quantified from the gripping and sequence task to assess behavioural effects of TBS. For the gripping task, peak force of each grip was measured to ensure consistency. For the sequence task, due to the high number of total opposition movements made, blocks of 15 movements were analyzed from a portions (early (~ 30 s), middle (~ 120 s) and end (~ 200 s)) of the 240 s block to assess the frequency of the behaviour. This was done for tasks both before and after TBS. Data for the gripping task was averaged for each individual both pre- and post-TBS and subjected to a paired Student's *t*-test. Data for the sequence task was averaged for each timing window (early (30s), middle (120s), late (240s)) for each participant both pre-

and post-TBS and subjected to a two-way repeated measures analysis of variance (ANOVA) with factors TBS (pre, post) and Timing during block (early, middle, late).

4.3.5.2 MEPs

MEPs were measured peak-to-peak from individual participants and averaged (20 total) both before (~ 20 min before cTBS) and after TBS (~ 20 min after cTBS). MEP amplitudes were subjected to a paired Student's *t*-test.

4.3.5.3 Somatosensory evoked potentials

Latencies and amplitudes of the frontal and parietal SEPs were measured from individual participants' averages for each task. For the squeeze and hold task, only the median nerve stimulations that fell during EMG activity as a result of the squeeze were used. On average this consisted of 64 ± 12% or 307 ± 58 total stimulations. Stimulations in the first and last 15 s of the sequence task were excluded from averaging. This resulted in a total of ~ 420 stimulations. The rest task consisted of ~ 340 stimulations. Electrode sites that displayed maximal amplitudes (FCZ and CP3) were used to quantify potentials of interest. A clearly defined peak was necessary for inclusion. All participants from both experiments displayed clear frontal and parietal potentials.

For each experiment a two-way repeated measures ANOVA was performed for each SEP component of interest with Timing relative to TBS (pre, post) and Task (Control, Grip, Sequence) as factors. Pre-planned contrasts were conducted between the control value and motor tasks pre- and post-TBS.

M-wave amplitudes were subjected to a similar two-way repeated measures ANOVA to ensure stimulus consistency across task.

4.4 Results

4.4.1 Experiment 1
Left M1 TBS, Left Hand Movement

4.4.1.1 Behavioural

Sequence Task

The two-way repeated measures ANOVA for frequency of sequence movements did reveal any statistical differences ($F(2, 18) = 2.22$, $p = 0.13$) (see Figure 5).

4.4.2.2 Frontal potentials

P18-N30

The two-way repeated measures ANOVA revealed a main effect of Task ($F(2,18) = 4.25$, $p = 0.03$), and a Timing x Task interaction ($F(2,18) = 7.00$, $p = 0.006$). Pre-planned contrasts revealed a difference between the gripping task and rest pre-TBS ($p<0.05$). Gripping resulted in a facilitation of N30 amplitude. To assess the effect of TBS, a further pre-planned contrast between post-TBS gripping and pre-TBS gripping revealed a difference ($p<0.05$). Post-TBS gripping had no effect upon N30 amplitude. There was no effect of TBS upon N30 amplitudes during either rest or the sequence task (see Figures 2 & 4).

P40-N60

The two-way repeated measure ANOVA revealed a main effect of Task ($F(2,18) = 5.81$, $p = 0.01$). Contrasts revealed this was due to an increase in N60 amplitude for the sequence task ($p < 0.05$). There was no effect of TBS.

4.4.2.3 Parietal potentials

P18-N20

The two-way repeated measures ANOVA revealed a main effect of Task ($F(2,18) = 4.72$, $p = 0.02$). Contrasts revealed this was due to an increase in the P18-N20 during the sequence task ($p < 0.05$).

N20-P27; P27-N33; N33-P50

There were no significant effects for any of the other parietal potentials.

4.4.2.4 MEPs

There was no significant difference in MEP amplitude after TBS, $t(8) = 1.23$, $p = NS$.

4.4.2 Experiment 2
Right M1 TBS, Right Hand Movement

4.4.3.1 Behavioural

The two-way repeated measures ANOVA for frequency of sequence movements did reveal any statistical differences ($F(2, 18) = 1.46$, $p = 0.26$).

4.4.3.2 Frontal potentials

P18-N30

The two-way repeated measures ANOVA revealed no main effect of TBS ($F(1,4) = 0.18$, $p = NS$) or Task ($F(2,8) = 0.64$, $p = NS$). The interaction of Task x TBS was also not significant ($F(2,8) = 0.92$, $p = NS$).

P40-N60

The two-way repeated measure ANOVA revealed no main effect of TBS ($F(1,4) = 3.92$, $p = 0.11$) and no main effect of Task ($F(2,8) = 0.56$, $p = 0.61$).

4.4.3.3 Parietal potentials

P18-N20

The two-way repeated measures ANOVA revealed a main effect of TBS ($F(1,4) = 18.23$, $p = 0.01$) and an interaction of TBS x Task ($F(2,8) = 10.81$, $p = 0.05$). Post-hoc analysis revealed that the P18-N20 was facilitated before TBS during the sequence task but that this facilitation was removed post TBS ($p<0.05$) (see Figure 4).

N20-P27

The two-way repeated measures ANOVA revealed an interaction of TBS x Task ($F(2,8) = 6.83$, $p = 0.02$). Post-hoc analysis revealed a decrease in N20-P27 amplitude during the sequence task post-TBS ($p<0.05$) (see Figure 4).

P27-N33; N33-P50

There were no significant effects on any of the later parietal potentials.

4.4.3.4 MEPs

There was no significant effect upon MEP amplitude post TBS $t(4) = 0.87$, $p = 0.29$.

4.5 Discussion

The main finding of this study is that in support of the hypothesis there was a removal of the movement-related facilitation of the frontal N30 after continuous theta-burst stimulation to the left motor cortex; ipsilateral to non-dominant hand movement. Previous reports have shown that the frontal N30 SEP derived from right median nerve stimulation is increased during movement of the left hand (Rossini et al. 1999; Legon et al. 2008) and that this increase is exclusive for non-dominant hand movement (Chapter 3; Legon et al. submitted). Many previous reports have shown that non-dominant hand movement is associated with an increase in ipsilateral motor cortical activity despite no overt electromyographic activity (Bastings et al., 1998; Cramer et al., 1999; Kansaku et al., 2005; Kobayashi et al., 2003; Singh et al., 1998; Verstynen et al., 2005), a phenomenon that is commonly absent during dominant hand movement (Kawashima et al. 1998; Kobayashi et al. 2003; Hanakawa et al. 2005). In a separate experiment, continuous TBS was delivered to the right motor cortex during right hand movement but did not result in any effect upon the N30 potential lending evidence for a specific

functional relationship between left motor cortical activity and N30 amplitude during ipsilateral non-dominant hand movement.

The functional significance of ipsilateral motor cortical activity during non-dominant hand movement is currently unclear. Hypotheses suggest it may be a result of uncrossed descending corticofugal fibers (Ziemann et al., 1999) or inter-hemispheric interactions via contralateral non-dominant motor cortex (Kobayashi et al. 2003; Duque et al. 2007). The former seems unlikely as this was directly tested by Bastings et al. (1998) who using co-registration of functional magnetic resonance imaging (fMRI) and TMS delivered TMS directly to the ipsilateral M1 area activated by ipsilateral left hand movement and failed to produce ipsilateral MEPs. In support of the latter hypothesis, Kobayashi et al. (2003) showed that individuals who display ipsilateral M1 activity on fMRI during non-dominant left hand movement also show a significant inhibition of the left motor cortex by the right as tested by inter-hemispheric paired-pulse stimulation. In contrast, those that did not display ipsilateral M1 showed no inter-hemispheric inhibition. Duque et al. (2007) further investigated this phenomenon during voluntary movement and found that inhibition of M1 contralateral to the moving limb is released during dominant hand movement but not during non-dominant hand movement. It is presumed from these results that ipsilateral left motor cortical activity seen in imaging studies reflects inhibition from contralateral motor cortex to supposedly prevent mirror or interfering movement of the contralateral limb; a contention supported by a patient with agenesis of the corpus callosum who displayed mirror movements and a lack of inter-hemispheric inhibition (Rothwell et al. 1991).

The inhibitory tone from one motor cortex upon the other may be the basis for handedness and the differences seen in manual dexterity between the two hands.

Be this as it may, the specific relationship between ipsilateral motor cortical activity during non-dominant left hand movement and the frontal N30 is functionally indeterminate. Support for a frontal N30 generator in the supplementary motor area has come from clinical reports (Mauguiere et al., 1983; Mauguiere & Desmedt, 1991; Rossini et al., 1989), functional studies (Cheron et al., 1994; Rossini et al., 1991) and from the Parkinson's literature (Rossini et al. 1989,1991; Cheron 1994). However, it is acknowledged that a specific generator is difficult to localize (Barba & Valeriani, 2004) and as such other sites including M1 (Waberski et al., 1999) and pre-motor cortex (Kanovsky et al., 2003) have been proposed. Nevertheless, the frontal N30 but not parietal potentials is specifically attenuated or absent in PD groups (Rossini et al. 1991) but transiently facilitated with either apomorphine administration (Cheron 1994) or deep brain stimulation (Pieriantozzi 1999); evidence for a specific link between the N30 and thalamo-cortical basal ganglia loops and SMA (Cheron 1999). The SMA, M1 and premotor cortex (PM) all project to the basal ganglia and also receive dense efferents from the thalamus via the basal ganglia in the traditionally defined motor loop (Akkal et al., 2007; Middleton & Strick, 2000). In addition, the SMA has been demonstrated to have dense reciprocal connectivity with ipsilateral M1 (Ghosh et al. 1987; Jurgens 1984; Luppino et al. 1993) that is likely inhibitory in nature as stimulation of post-arcuate neurons in the monkey has been shown to result mainly in IPSPs in pyramidal neurons (Ghosh & Porter, 1988) suggesting a modulatory or tuning

role of SMA upon M1. Because the N30 is often absent in PD, it is possible that a normal N30 reflects basal-ganglia tone upon SMA or more generally the proper functioning of the basal-ganglia, thalamo-cortical motor loops and may be an index of inhibitory tone to M1 such that an increase in N30 represents an increase in this inhibitory tone. This contention is supported by evidence that short intra-cortical and inter-hemispheric inhibition is dysfunctional in PD patients but subsequently improved upon L-dopa medication (Ridding et al., 1995) and that short-latency (Tamburin et al., 2003) and long-latency afferent inhibition (Sailer et al., 2003) are abnormal in PD.

Further support for an inhibitory tone hypothesis comes from Urushihara et al. (2006) who delivered low frequency TMS to left pre-motor cortex that resulted in an increase in N30. This has implications for these results as it has been demonstrated that ipsilateral motor cortical activity is slightly shifted anterior (Cramer et al. 1999) and as such has been postulated to be have pre-motor cortex contributions. Furthermore, recent work by the Cheron lab (Cebolla et al., 2009; Cheron et al., 2007) have reported that the N30 may be a result of a power increase of the beta-gamma frequency and/or a stimulus dependant phase-locking and suggest that their results may support an inhibition-timing hypothesis such that an increase in N30 amplitude reflects increasing inhibition and a N30 decrease reflects excitation as a result of motor execution.

An inhibition hypothesis for N30 amplitude increase fits well with the results of Legon et al. (2008) and this study such that during non-dominant left hand movement ipsilateral left motor cortex is inhibited (Kobayashi et al. 2003; Duque et al. 2007) and N30 is increased. Recent work from this lab (Chapter 3; Legon et al. submitted) has

demonstrated that the N30 is not increased for dominant hand movement and that this phenomenon is stable regardless of the handedness of the participants. Experiment 2 further supports this as dominant right hand movement does not result in N30 facilitation with continuous TBS of right motor cortex having no effect as hypothesized.

A question remains however as to what continuous TBS to ipsilateral motor cortex is actually doing during this study due to the MEP results. Unlike the results of Huang et al. (2005), we did not report inhibition of the MEP post TBS at the group level. This may have been due to the movements performed either before or after the TBS intervention. Motor training has been shown to increase MEP size (Garry et al., 2004; Ziemann et al., 2001) and to affect repetitive TMS results (Stefan et al. 2006). Gentner et al. (2008) recently reported that prior isometric contraction of the targeted muscle changes the effects of continuous theta-burst stimulation such that when their TBS intervention was preceded by isometric voluntary contraction, original facilitation was turned into inhibition. In addition to prior execution, contraction of the target muscle immediately after TBS also reverses the inhibitory effects of continuous theta burst stimulation (Huang et al., 2008). The mechanisms mediating this reversal are speculative, however low frequency repetitive stimulation is not usually affected by contraction (Ragert et al., 2003; Siebner et al., 1999) which may be due to the different intracortical circuits TBS and low frequency TMS preferentially affect (Di Lazzaro et al., 2005, 2008). It was originally thought that the interaction of movement and continuous TBS would not be of concern here, firstly because TBS was delivered to the

motor cortex ipsilateral to movement and secondly was delivered at higher stimulation intensity (90% RMT vs. 80% AMT) than that used by Huang et al. (2008). This was done under the hypothesis that 1 Hz rTMS does not seem to be affected by voluntary contraction due to the higher stimulation intensities employed which activate larger populations of neurons (Huang et al. 2008).

It is inconclusive from our results if movement ipsilateral to continuous TBS also has potentially reversing effects upon motor cortical excitability as this was not the specific purpose of this study. The group data would suggest not and examination of individual subjects revealed that MEP inhibition/facilitation post-TBS was 50/50 for left motor cortical stimulation. The MEP data for right motor cortical TBS also revealed no change in MEP size at the group level with three of the five participants displaying inhibition. It would be interesting to see if indeed TBS effects can be manipulated during ipsilateral motor cortical stimulation and further if this depends upon the cortex stimulated. The movements used and their timing relative to TBS were not explicitly controlled here and we only tested five participants in experiment two. Specific control of motor demands and more participants are obviously required to adequately test this. As such, it is indeterminate whether ipsilateral movement interacts with TBS to the ipsilateral motor cortex.

There was no effect of continuous TBS delivered over the right motor cortex on N30 amplitude. During dominant right-hand movement, inhibition of the left motor cortex is released (Duque et al. 2007) and may be the reason ipsilateral motor cortical activity is not often seen under these conditions. As such, during movement there is

regular inhibitory tone and the N30 has similar amplitude to rest conditions. Increasing inhibition via continuous TBS essentially has no effect as there is no additional inhibition to remove and as such no effect upon the N30.

Continuous theta burst stimulation to the left motor cortex did not result in any behavioural changes in either the gripping task or the sequence task. It was originally hypothesized that the timing or frequency of the sequence task would be disrupted as 1Hz rTMS to left motor cortex has been reported to disrupt left handed behaviour (Avanzino et al., 2008; Chen et al., 1997). The lack of behavioural effect may be related to the lack of MEP inhibition.

Interestingly, an increase in the P18-N20 complex was found for the sequence task performed with the left hand. The P18 is thought to reflect thalamic synaptic activity in sensory nuclei and the N20 to reflect the arrival of peripheral input to somatosensory cortex area 3b (Allison et al., 1989). Typically, these potentials are not affected in classic movement-related gating paradigms or by TMS interventions of either motor or sensory cortex. We can only speculate on a reason for this increase but it may be that the drive from basal ganglia through motor thalamic nuclei to SMA which serves to inhibit left motor cortex is suppressed during a sequence task due to the known involvement of it during sequencing (Halsband et al., 1994; Shima & Tanji, 1998). Indeed, the N30 was suppressed during the sequence task as compared to rest, though not significantly, and this lack of inhibitory drive may release inhibition of thalamic sensory nuclei (Morel et al., 2005) to provide an increase in the fidelity of sensory input from the dominant hand to left sensory cortex during a complex task

performed with the non-dominant hand. During right hand movement, the P18-N20 from left median nerve stimulation was increased during the sequence movement but suppressed after continuous TBS to right motor cortex. Right motor cortex is not inhibited during right hand movement (Duque et al. 2007), but after TBS suppresses the P18-N20 suggesting that ipsilateral M1 inhibition via TBS suppresses input to ipsilateral S1 during dominant hand movement but does not during non-dominant because of the already existent SMA inhibitory tone.

Finally, in addition to a simple gripping movement we added a sequence type finger/thumb opposition because it had previously been reported to increase ipsilateral motor cortical activity (Verstynen et al. 2005). We cannot be certain that this task resulted in increased ipsilateral activation and under our hypothesis of an N30 increase reflecting increased inhibition, the sequence task may have disinhibited ipsilateral M1 as the N30 amplitude tended to be reduced for this task as compared to rest; the opposite of the gripping task. The SMA has been implicated in sequencing tasks (Halsband et al., 1994; Tanji, 2001) and as such its activity may result in increased excitatory activity driving down inhibitory tone. These contentions need further exploration.

4.6 Conclusions

The frontal N30 derived from dominant median nerve stimulation is increased during simple contralateral non-dominant hand movements. Continuous theta burst stimulation of the ipsilateral left motor cortex removes this. It is postulated that the

N30 reflects inhibitory tone of a BG-thalamic-SMA motor loop that is removed with modulation of motor cortical activity of left M1.

4.7 Figures

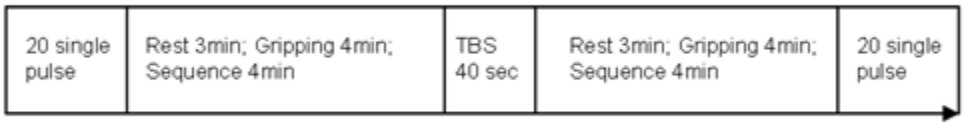

Figure 1

Schematic time line of testing. MEP testing (20 single pulse) followed by tasks (Rest, Gripping, Sequence) and then TBS intervention. Tasks were repeated, and MEPs re-tested at the end. Times indicated during task intervals reflected the time taken to complete each task.

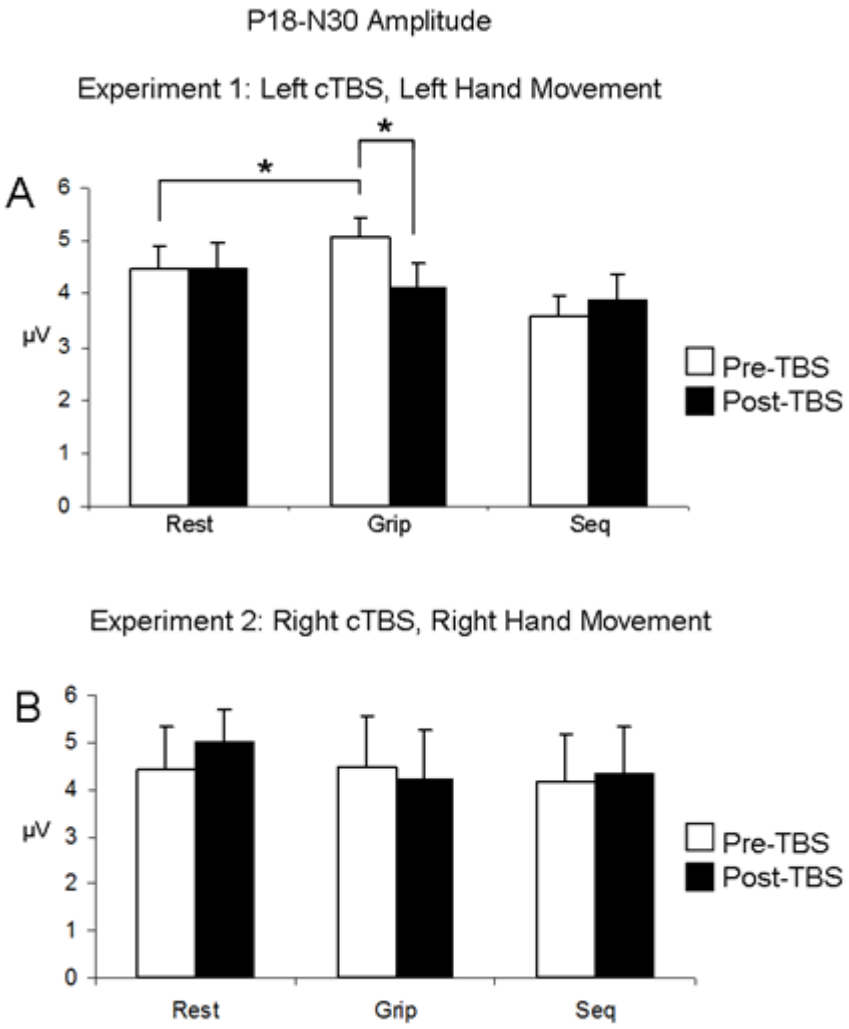

Figure 2

Group mean averages of P18-N30 SEP amplitude in μV for the Rest, Gripping task (Grip) and Sequence task (Seq) for both experiment 1 (A) (n=9) tasks performed with the left hand, TBS to left M1 and experiment 2 (B) (n=5) tasks performed with the right hand, TBS to right M1. White bars = before TBS; Black bars = after TBS. Values are in uV. Bars represent ± SEM. * denotes significance $p < 0.05$.

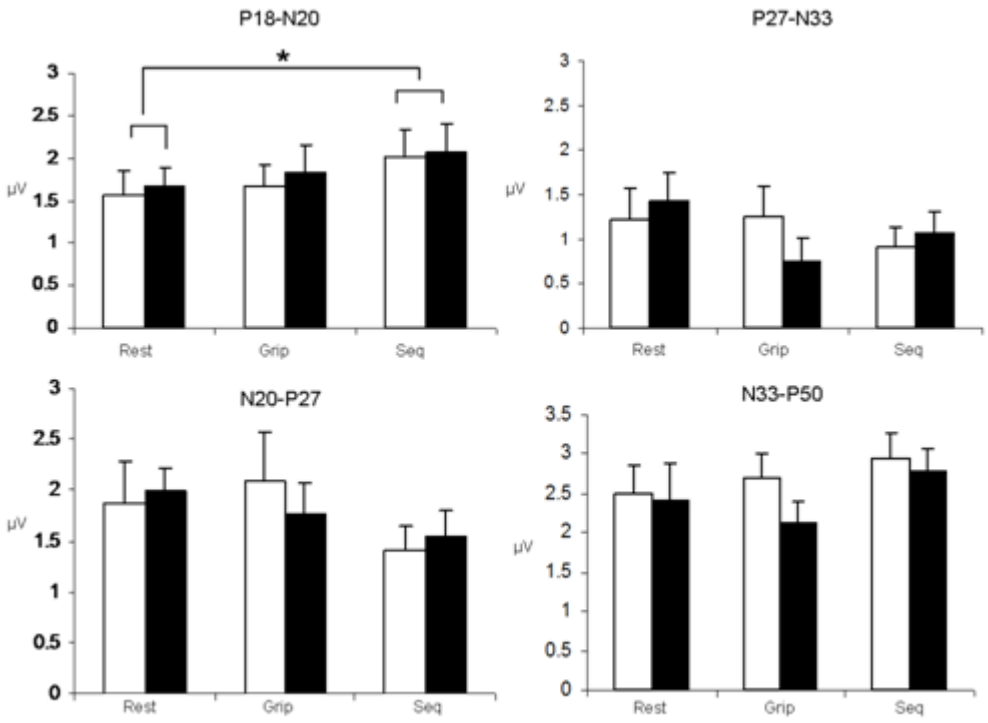

Figure 3

Group mean averages of labeled potentials from experiment 1 (n=9) for the Rest, Gripping task (Grip) and Sequence task (Seq). White bars = before TBS; Black bars = after TBS. Values are in uV. Bars represent ± SEM. * denotes significance $p < 0.05$.

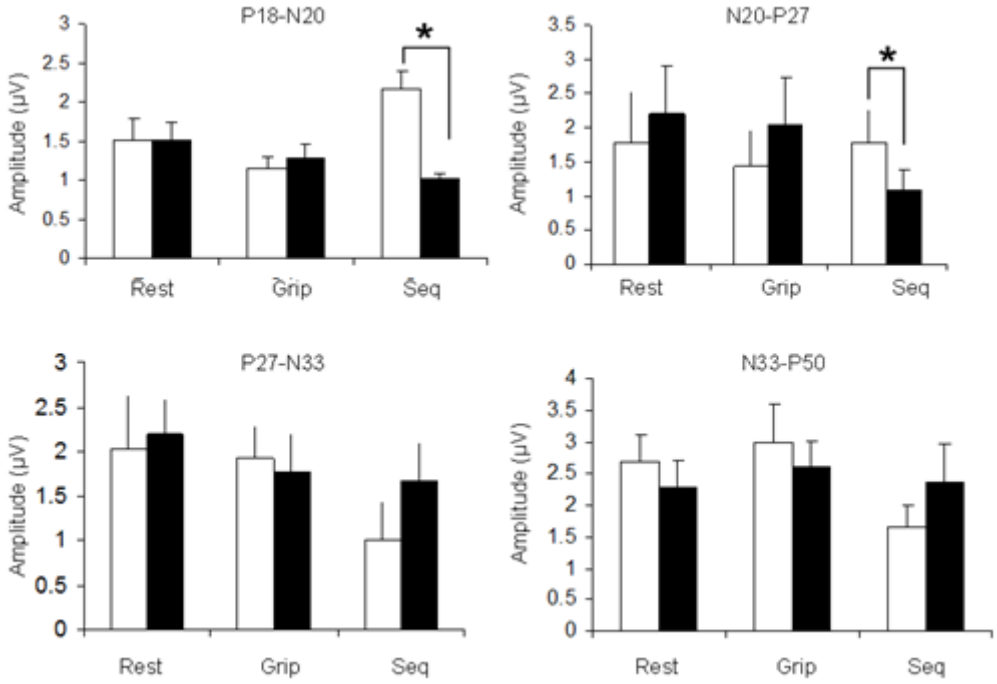

Figure 4

Group mean averages of labeled potentials from experiment 2 (n=5) for the Rest, Gripping task (Grip) and Sequence task (Seq). White bars = before TBS; Black bars = after TBS. Values are in uV. Bars represent ± SEM. * denotes significance $p < 0.05$.

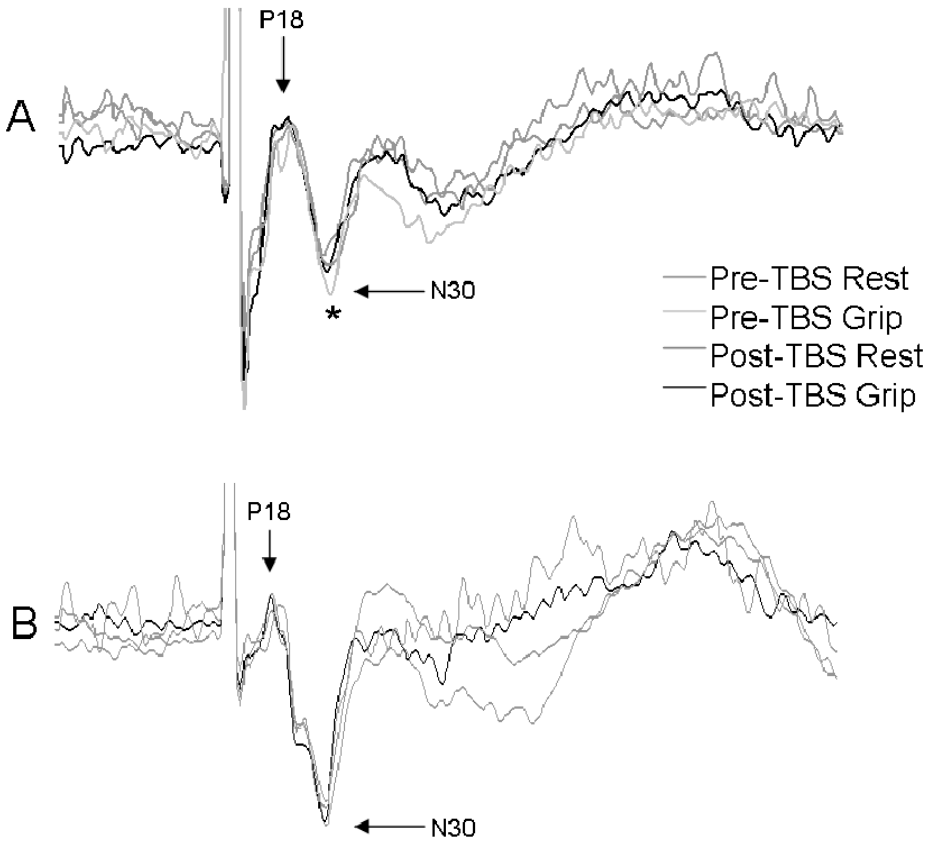

Figure 5

Representative trace from one subject from experiment 1 (A) and experiment 2 (B) recorded from electrode site FCZ. * denotes significant difference of pre-TBS grip as compared to post-TBS grip ($p < 0.05$).

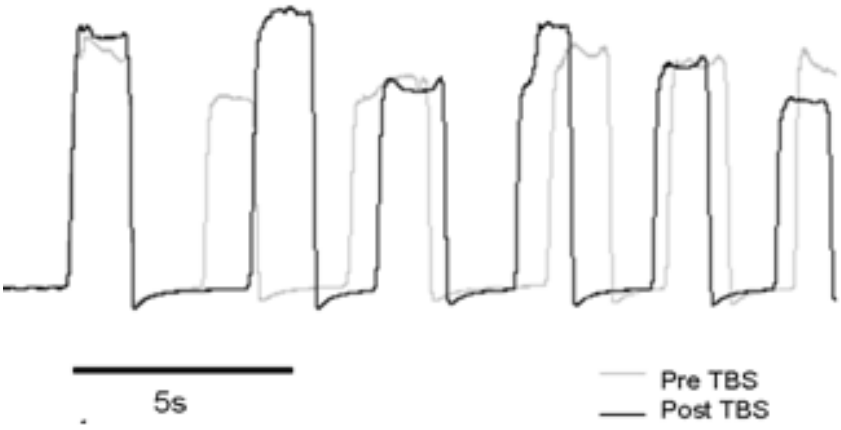

Figure 6

Representative sample of behavioural data from the gripping task of one subject in experiment 1. Light line = before TBS, dark line = after TBS.

CHAPTER 5 – STUDY 4: Continuous theta burst stimulation of the SMA attenuates the frontal N30 and raises tactile perception threshold.

5.1 Overview

The SMA has been implicated in a myriad of different aspects of movement preparation and execution. In addition to its purported motor roles, the SMA receives peripheral afferent input and is responsive to somesthetic stimuli though it is unclear exactly what role the SMA plays in a somatosensory network. It is the purpose of this study to assess how disruption of the SMA affects SEP amplitudes in both frontal and parietal cortices and in turn if this disruption affects tactile perception threshold. Continuous theta burst stimulation was delivered over scalp sites FCZ (n=10) and CZ (n=10) in separate groups. The TBS protocol consisted of 3 stimuli delivered at 50 Hz repeated at 5 Hz for 40 s delivered at 90% of participants' resting motor threshold. For both groups, median nerve SEPs were elicited from the right wrist at rest via electrical stimulation (0.2 ms pulse) before and at 10 min intervals post TBS out to 30 min (t= pre-TBS, 10, 20, 30). SEPs were averaged and potential amplitudes quantified from scalp electrode sites FCZ and CP3. Subjects' perceptual threshold was assessed at similar time intervals as the SEP data (though not at the same time) using a Vibratron II biothesiometer (120 Hz vibration). Results demonstrate that TBS to scalp site FCZ reduces both the frontal N30 and parietal N20-P27 complex as well as increases perceptual thresholds. Results were maximal 30 min post TBS. TBS to stimulation site CZ did not result in any significant physiological or behavioural changes. These data imply that the SMA plays a critical role in somatosensory processing and disruption of

it influences early processing of somatosensory information in primary somatosensory cortex.

5.2 Introduction

The supplementary motor area has been implicated in a myriad of different aspects of movement preparation (Alexander & Crutcher, 1990; Tanji, 1985) and execution including bimanual (Brinkman, 1984), sequential (Halsband et al., 1994; Roland et al., 1980), and internally generated or volitional movements (Chen et al., 1995; Thaler et al., 1995). In addition to its purported motor roles, the SMA receives peripheral afferent input (Hummelsheim et al., 1988; M. Wiesendanger et al., 1985) and is responsive to somesthetic stimuli as evidenced by single-cell studies (Matsuzaka et al., 1992; Romo et al., 1993) and inferred by the frontal N30 somatosensory evoked potential (Desmedt & Bourguet, 1985; Mauguiere et al., 1983). In addition to the dense connections with motor cortical areas, SMA also has rich connectivity with post-rolandic parietal areas, including primary and secondary somatosensory cortex (Jurgens 1984; Luppino et al. 1993). It is unclear however exactly what role the SMA plays in a somatosensory network. The SMA has been hypothesized to link somatic sensation to action (Romo & Salinas 2001) and interestingly, lesion of the SMA has been shown to affect tactile discrimination (Lacruz et al. 1991).

Transcranial magnetic stimulation of the SMA has been shown to disrupt various aspects of motor performance (Cunnington et al., 1996; Gerloff et al., 1997; Obhi et al., 2002; Serrien et al., 2002; Steyvers et al., 2003; Verwey et al., 2002) and to affect motor cortex excitability (Civardi et al., 2001; Matsunaga et al., 2005; Oliveri et al., 2003) but no literature to date has explored how SMA disruption using TMS affects somatosensory processing and tactile perception, although Kanda et al., (2003) showed

that double-pulse stimulation of medial frontal cortex suppresses pain perception. In contrast, there are numerous papers exploring how magnetic stimulation of the primary somatosensory (Cohen et al., 1991; Hannula et al., 2005; Harris et al., 2002; Knecht et al., 2003; Koch et al., 2006; McKay et al. 2003b; Meehan et al., 2008; Morley et al., 2007; Satow et al., 2003; Seyal et al., 1992; Tegenthoff et al., 2005), parietal (Nager et al., 2004; Oliveri et al., 1999, 2000), and motor cortex (Cohen et al., 1991; McKay et al. 2003a; Yoo et al., 2008) affects tactile perception. TMS protocols similar to those that affect behavioural performance delivered to both M1 and S1 also modulate somatosensory evoked potentials (Kujirai et al. 1993; Seyal et al. 1993; Enomoto et al. 2001; Meehan et al. 2008). The recently developed continuous theta-burst protocol (Huang et al. 2005) delivered over both primary motor and sensory cortex has been shown to also affect median nerve somatosensory evoked potentials but with differing effects. Continuous theta-burst over M1 resulted in an increase of SEP components whereas stimulation of S1 suppressed the same components (Ishikawa et al. 2007). Unfortunately, none of the above studies investigated both tactile perception thresholds and SEP effects.

It is the purpose of this study to investigate how disruption of the SMA using continuous TBS affects the frontal N30 somatosensory evoked potential and further, to determine if this results in any perceptual consequences. It is hypothesized that inhibitory stimulation of the SMA will attenuate the frontal N30. It is unclear whether this will have any affect on tactile perception thresholds, but the same mechanisms that

attenuate the N30 may also affect parietal activity and therefore increase perceptual detection thresholds similar to the research employing TMS over S1.

5.3 Methods

5.3.1 Participants

All subjects participated in one of two experiments performed on separate days. Both experiment 1 (4 Female, Age 24 ± 3.6yr) and experiment 2 (3 Female, Age 23 ± 3.3yr) studied ten participants. Three individuals participated in both experiments and all were right-handed as assessed by the Modified Edinburgh Handedness Scale. All subjects provided written informed consent to participate. None reported any history of neurological or musculoskeletal impairments or any contra-indicators for TMS. All were paid a nominal fee for their participation. The University of Waterloo Office of Research Ethics approved all experimental procedures.

5.3.2 Behavioural Task

For both experiment 1 and 2, participants were seated in a desk chair with elbow and forearm of both arms resting on a raised platform upon a table top. The raised platform allowed for the hand to rest over the far edge of the platform with slight flexion of the wrist and allowed for a comfortable resting of the right index finger upon a vibrating posts placed at the end of the raised platform.

A Vibratron II biothesiometer (Physitemp Instruments, Clifton NJ USA) (120Hz vibration) was used to test perceptual thresholds of the right index finger (the hand being probed by median nerve stimulation). This was the dominant hand in all

cases. For all time points of testing (pre TBS, 10 min, 20 min, 30 min post TBS), the experimenter slowly increased the displacement of the post from zero μM until the subjects indicated verbally that they felt it. All subjects performed the tactile judgment task with their eyes closed. Participants were familiarized with the vibration before testing and instructed not to move their finger or arm and to be sure they felt the vibration before reporting it. To establish a pre-testing baseline, participants repeated the threshold testing until three consecutive trials were within one vibration unit of each other. Display readings are in Vibration Units (X) that are related to true amplitude in microns of the vibration (A) by the following formula: $A=(0.5)X^2$. Participants were not informed of these values at any point of the testing and were naïve to the purposes of the study. For each time point of testing post TBS, 3 trials were repeated for each finger. Vibration threshold testing was performed pre-TBS (10 min prior) and at time points 10, 20 and 30 min post TBS. Five subjects in experiment 1 performed this task post TBS at 10 min intervals out to 60 min.

5.3.3 Stimulation and Recording

SEPs were derived from the electrical stimulation of the median nerve of the dominant right wrist. Square wave pulses of 0.2-ms duration (GRASS S88 stimulator with SIU5 stimulus isolation unit; West Warwick, Rhode Island, USA) were delivered through a bar electrode, with the anode distal, fixed over the median nerve at a stimulation rate of 1 Hz at an intensity sufficient to produce a small but noticeable thumb twitch. Surface electromyography (EMG) was recorded from the thenar musculature to record the M-wave, an EMG wave resulting from the direct stimulation

of the motoneuronal axons serving the thenar musculature to ensure stimulation consistency. EMG recordings were amplified (2000x), band-pass filtered (DC–200 Hz), digitized and stored for later analysis. Electroencephalographic (EEG) data were recorded from two Ag-AgCl cup electrodes fixed to the scalp and referenced to the linked mastoid. One electrode was placed 3 cm anterior to site Cz and the other over a spot corresponding to electrode site CP3/4 (contralateral to MN stimulation) in accordance with the international 10-20 system for electrode placement. Data were amplified (40 000x), filtered (DC-200 Hz) and digitized at 1000 Hz (NeuroScan 4.3; Compumedics; El Paso, Texas, USA). SEPs were extracted by averaging epochs time-locked to median nerve stimulation (-50 to 300 ms). All traces were visually inspected for artefact (blinks, eye movements or contraction of scalp musculature) and any contaminated epochs were eliminated before averaging. All traces were the result of at least 200 stimulations.

5.3.4 Transcranial Magnetic Stimulation

Continuous theta burst stimulation for 40s (600 pulses) of 3 stimuli at 50Hz repeated at 5Hz (Huang et al. 2005) was applied using a MagPro stimulator (Medtronic, Minneapolis, MN, USA) and 'figure of eight' coil (model No. MCF-B65). Prior to theta burst stimulation, each participant's resting motor threshold (RMT) over M1 for the first dorsal interosseous (FDI) was determined with the coil handle pointing backwards and laterally at 45 degrees from midline. RMT was determined as the lowest stimulus intensity at which 5 of 10 consecutive stimuli elicited a reliable MEP. For experiment 1, the intersection of the coil was placed over the mid-line scalp site

3cm anterior to Cz (site for SMA). For experiment 2, the intersection of the coil was placed over scalp site Cz (control) in accordance to the international 10-20 system for electrode placement. For both experiments the handle of the coil was directed posteriorly along the mid-line providing a posterior-anterior current at an intensity of 90% individual RMT.

5.3.5 Data Analysis

5.3.5.1 Somatosensory evoked potentials

Latencies and amplitudes of the frontal and parietal SEPs were measured from the individual participant averages for each time point of interest from both electrode sites FCZ and CP3/4. Latencies were measured from onset of stimulation to the peak of each SEP component of interest (frontal P18; N30; P40 and N60) and (parietal P18; N20; P27; N33 and P50). A clearly defined peak was necessary for inclusion. Amplitudes were measured as both peak-to-peak and relative to a post-stimulus baseline to account for any baseline shifts. For experiment 1, a one-way repeated-measures analyses of variance (ANOVA) was performed for each SEP component of interest with Time as factor (pre, 10, 20, 30). An additional one-way repeated measures ANOVA was conducted on the 5 subjects who had data out to 60 min post TBS with Time as factor (30, 40, 50, and 60) to assess duration of TBS effects for any potentials that displayed a difference. For experiment 2, a one-way repeated-measures ANOVA was performed with Time as factor (pre, 10, 20, 30).

5.3.5.2 Behavioural Threshold

For experiment 1, a one-way repeated measures ANOVAs was performed with Time as the factor (pre, 10, 20, 30). For experiment 2, similar one-way repeated measures ANOVAs was performed with Time (Pre, 10, 20, 30) as factor.

5.4 Results

5.4.1 Latencies and M-wave

All participants displayed clear frontal and parietal potentials. There were no differences in the latencies of any of the potentials of interest or M-wave amplitude across time for both experiment 1 and experiment 2.

5.4.2 Behavioural Detection Threshold

Experiment 1:TBS over FCZ

The one-way repeated measures ANOVA for vibration thresholds from the right hand revealed an effect of Time ($F(3, 27) = 6.92$, $p < 0.05$). Contrasts revealed a significant difference between the 30 min time point and each of the others (pre, 10 min, 20 min; $p < 0.05$) (see Figure 1).

Experiment 2: TBS over CZ

The one-way repeated measures ANOVAs for vibration thresholds from the right hand revealed no significant effect of Time ($F(3, 27) = 2.25$, $p = 0.10$). (see Figure 1).

5.4.3 Frontal potentials

N30

Experiment 1: TBS over FCZ

The one-way repeated measures ANOVA revealed an effect of Time ($F(3, 27) = 3.41$, $p < 0.05$). *A priori* contrasts revealed a significant difference between pre and 30 min post ($p < 0.05$). (see Figures 2 & 3). The one-way repeated measure ANOVA conducted upon the five participants who had data out to 60 min revealed no significant difference of Time between time point 30 min and any later time points $F (3, 12) = 0.74$, p = NS.

Experiment 2: TBS over CZ

The one-way repeated measures ANOVA revealed no significant difference for Time ($F(3,27) = 1.09$, p = NS). (see Figures 2 & 3).

Frontal P18, P40 & N60

Experiment 1: TBS over FCZ

There was no effect of Time on any of the raw potentials. However, peak-to-peak measures of the P18-N30 ($F (3, 27) = 6.27$, $p < 0.05$), N30-P40 ($F (3, 27) = 5.69$, $p < 0.05$) and P40-N60 ($F (3, 27) = 9.12$, $p < 0.05$) revealed an effect of Time for each. Contrasts revealed a significant difference between time 30 min post-TBS and pre-TBS for both the P18-N30 and N30-P40 transitions ($p < 0.05$) – differences driven by the raw amplitude change of the N30. Contrasts on the P40-N60 also revealed a significant difference between time 30 min and pre-TBS ($p < 0.05$).

Experiment 2: TBS over CZ

There was no effect of Time on any of the raw or peak-to-peak potentials.

5.4.4 Parietal potentials

Experiment 1: TBS over FCZ

There were no effects of Time on any of the raw amplitude parietal potentials of interest. However, the one-way repeated measures ANOVA on peak-to-peak N20-P27 values revealed a significant effect of Time ($F(3, 27) = 3.67$, $p < 0.05$). Contrasts revealed this was due to a significant difference between pre and each of 20min and 30min ($p < 0.05$).

Experiment 2: TBS over CZ

There were no effects for any of the raw amplitude parietal potentials of interest or for any of the peak-to-peak transitions including N20-P27.

5.5 Discussion

The results suggest that continuous theta-burst stimulation over the scalp region corresponding to the 10-20 international system for electrode placement site FCZ results in an attenuation of both the frontal N30 and parietal N20-P27, 30 min after stimulation and further that this coincides with a decrease in tactile perception thresholds of the right index finger. Stimulation of a cortical site 3 cm posterior to this did not result in similar physiological nor behavioural consequences. It has previously been suggested that a scalp site 1-4 cm anterior to CZ electrode site preferentially stimulates the supplementary motor area (Cunnington et al., 1996; Matsunaga et al., 2005; Oliveri et al., 2003; Serrien et al., 2002; Terao et al., 2001; Verwey et al., 2002) and that the hand area of the SMA proper is 2-3 cm anterior to CZ (Hikosaka et al., 1996; Lee et al., 1999), although others (Gerloff et al., 1997) suggest that electrode site CZ is the preferential scalp location for activating SMA. We purposely chose site CZ as our 'control' to test this discrepancy, and specifically the effects of these two stimulation sites on N30 amplitude changes. Previous research has shown that a change of coil site of only 8-13 mm over S1 was sufficient to affect changes in perception (Hannula et al., 2005) and therefore we were confident that the 3 cm difference in stimulation sites would not result in similar effects at least upon behavioural perceptual thresholds. As for effects upon the N30, coil placement over CZ did not affect N30 amplitude at any time point post-stimulation. Despite the conjecture about an N30 generator site, our results support the view that TBS over scalp site 3 cm anterior to CZ preferentially affects the N30 and that this coil location is in

line with previous TMS studies of the SMA shown to affect motor aspects thought to be mediated by SMA (Verwey et al. 2002; Serrien et al. 2002). These results support the contention that the N30 has at least a partial generator site in or around the SMA. Be this as it may, the type of sensory information the N30 represents is also debatable. Resutccia et al. (1999, 2000) suggest that the N30 is a result of proprioceptive afference whereas single-cell studies suggest that somatosensory cells within SMA are responsive to cutaneous stimuli (Romo et al. 1993). Single-cell and SEP studies are difficult to rectify and our results do not lend any direct evidence to the type of somatosensory information the N30 represents, but do suggest that the population of cells contributing to N30 amplitude likely contribute to coding cutaneous afferent information as a reduction in amplitude of the N30 coincides well in time with a decrease in perceptual threshold of a 120 Hz vibration – a frequency shown to preferentially activate Pacinian corpuscles (Mountcastle et al., 1972; Talbot et al., 1968).

It is possible that the effects on both N30 amplitude and detection threshold are a result of indirect inhibition of primary motor cortex. It is well-established that M1 asserts considerable control over peripheral afference (Canedo, 1997; Chapman, 1994; Nelson, 1996a), that motor execution may increase cutaneous thresholds (Chapman et al., 1987; Milne et al., 1988; Williams et al., 1998), and that TMS of M1 directly affects detection threshold (MacKay et al. 2003; Yoo et al. 2008). Research in our lab has demonstrated that continuous theta-burst stimulation to the SMA does not affect motor evoked potential amplitudes or short interval intracortical inhibition of both the abductor pollicis brevis or extensor carpi radialis muscles (unpublished observations)

and as such lends evidence that M1 activity as a result of SMA stimulation does not account for our results.

In addition to the N30 effects, there was a peak-to-peak N20-P27 effect of stimulation to a cortical site 3 cm anterior to CZ but not to CZ. There was no effect on either of these parietal potentials in isolation as measured from a post-stimulus baseline; only the peak-to-peak analysis revealed this. Further inspection made it clear why this is so. Both the N20 and P27 displayed attenuation (20% ± 36% and 25% ± 24% respectively) that became statistically significant with the peak-to-peak analysis that essentially captured the combined attenuation (22% ± 8%). The raw amplitude difference for either the N20 or P27 did not reach significance likely because the theta-burst intervention was delivered over SMA and not S1 and effects downstream are likely to be less robust than those lying directly under the stimulation site. We suggest that the parietal effect is a result of connectivity between the SMA and S1 as the effect of TMS on remote connected cortical regions has recently been demonstrated (Bestmann et al., 2008). The specific route by which SMA inhibition influences S1 activity is uncertain. S1 sends relatively sparse projections to SMA (Luppino et al. 1993) and there are no known direct connections from SMA to S1 (Jones & Powell, 1969a; Jurgens, 1984; Vogt & Pandya, 1978). It is possible then that SMA-S1 influence is asserted via the thalamus. The SMA receives and sends the majority of its thalamic connections to and from the ventro-lateral nucleus (Matelli & Luppino, 1996; Morel et al., 2005) whereas S1 receives it thalamic input from ventro-posterior-lateral nucleus (Darian-Smith & Darian-Smith, 1993). There is no direct anatomical evidence that lemniscal input

terminates in VL (Mackel & Miyashita, 1992) nor is there evidence for any direct connections between VPL and SMA (Barba et al., 2003; Morel et al., 2005), however there is increasing evidence for overlap of sensory and motor projections in classically defined motor thalamic nuclei (Morel et al., 2005; Stepniewska et al., 2003). Morel et al. (2005) point out that SMA thalamo-cortical connections are closely related to those of M1, which is of interest here as there is evidence of short-latency relay of somatosensory inputs from thalamus to motor cortex (Asanuma et al., 1980; Evarts, 1973; Lemon & Porter, 1976), and Stepniewska et al. (2003) suggest that sensory inputs to the VL nucleus may come from sources other than lemniscal inputs such as the cerebellum, which itself receives input from muscle spindles, golgi tendon organs and cutaneous receptors (Ebner & Bloedel, 1981). Recent tracing work (Akkal et al. 2007) reported that the thalamic nuclei that sends projections to SMA receive their densest afferents from the globus pallidum of basal ganglia which fits well with single-cell (Romo et al. 1993) and imaging work (Staines et al., 2002) that report the SMA does not respond to passive somesthetic input, but rather only to input attended to or required for a motor response – suggestive of basal ganglia involvement. The N30 is uniquely attenuated in Parkinson's disease (Cheron et al., 1994; Rossini, 1996) and as such has been hypothesized to reflect the activity of basal-ganglia-thalamo-cortical connections (Cheron 1999).

The relation between SEP amplitude and perceptual thresholds is tenuous and speculative and we do not suggest a direct cause and effect between the two, however because both the N30 and the N20-P27 amplitudes displayed attenuation concomitant

with a perceptual threshold increase it is important to comment upon whether both or each is related to the threshold increase. It is likely that an S1 inhibition (N20-P27) is responsible for a perceptual threshold increase as TMS to S1 has previously reported this. These reports show that TMS delivered 20 ms post peripheral stimulus, is most effective at reducing perception of that stimulus (Andre-Obadia et al., 1999; Hannula et al., 2005; Koch et al., 2006; Meehan et al., 2008). Unfortunately none of these studies measured the frontal N30 SEP. Though SMA seems an unlikely source for mediating perceptual threshold change, lesion of it has been reported to affect tactile detection thresholds (LaCruz et al. 1991), a decrease in left SMA activation has been associated with an increase in sensory threshold (Yoo et al., 2008), and before movement, at timings similar to those shown for SMA involvement, tactile detection thresholds are raised (Williams et al., 1998).

Finally, the timing of N30 effects is at odds with other research investigating the effect of continuous theta-burst stimulation on SEPs. Ishikawa et al. (2007) reported effects as early as 3 min post stimulation. The discrepancy in the timing of effects may be due to the location of the SMA relative to the stimulating coil as it is located on the mesial wall of the longitudinal fissure and not directly on the cortical surface under the coil. This may therefore delay the continuous TBS effects as a delay in TBS effect has been shown for stimulation of a remote site (Huang et al., 2009).

5.6 Conclusion

Theta-burst stimulation to a scalp site overlying the supplementary motor area raises tactile perceptual thresholds. These behavioural effects are concomitant with a

physiological change in both the frontal N30 and parietal N20-P27 amplitudes. The SMA may play a more substantial role in a cutaneous somatosensory network then previously appreciated.

5.7 Figures

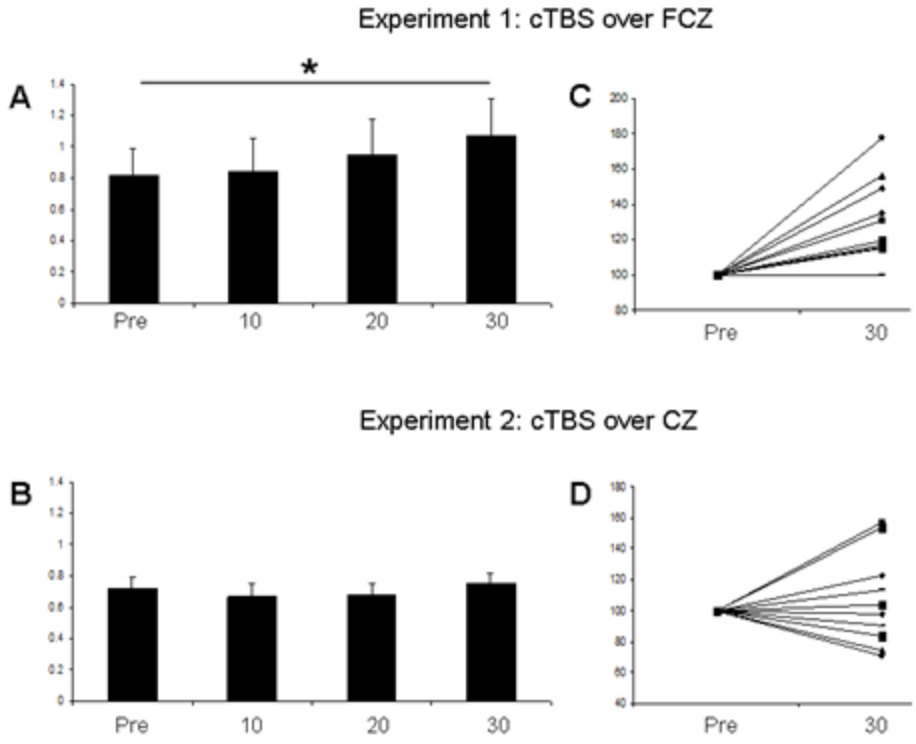

Figure 1

(A & B) Group mean data of behavioural perception thresholds in micrometers (μM) for dominant index finger. Top graph (A) are results from experiment 1 (n=10), bottom graph (B) from experiment 2 (n=10). Time points of testing are indicated: pre-TBS (pre) and at 10min, 20min and 30min post TBS. Ordinate units are in micrometers (μM). Bars are ± SEM. * denotes $p < 0.05$. n.s. denotes non-significant. (C & D) Individual data expressing the change in perceptual threshold between time point pre-TBS (pre) and 30min post (30) expressed as a percentage of pre-TBS value (100%). Top plot (C) is data from experiment 1 (n=10), bottom plot (D) is data from experiment 2 (n=10).

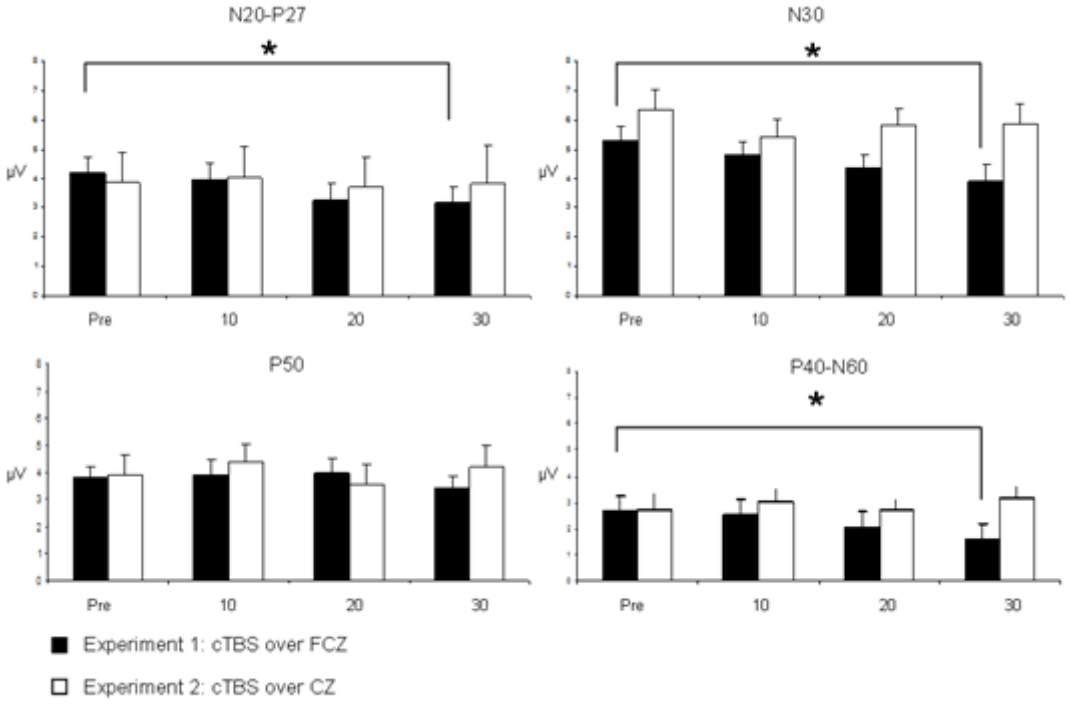

Figure 2

Group mean SEP amplitude data for experiment 1 (n=10) (Black bars) and experiment 2 (n=10) (White bars) for potentials of interest as marked. Time points of recording are indicated on abscissa (Pre = pre-TBS, 10, 20 and 30 indicate minutes post-TBS). Ordinate amplitude in microvolts (μV). Bars represent ± SEM. * denotes significance $p < 0.05$.

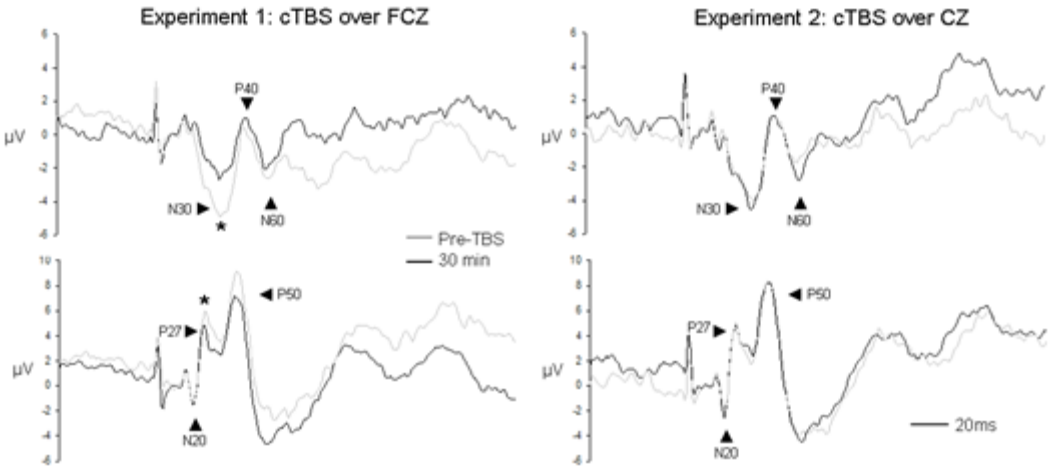

Figure 3

Representative example from one subject that participated in both experiment 1 (left) and experiment 2 (right). Traces recorded from electrode site FCZ (top). Traces recorded from electrode site CP3 (bottom). Light traces recorded pre-TBS, dark traces recorded 30min post TBS. Potentials of interest are marked. * denotes significant difference $p < 0.05$.

CHAPTER 6

6.1 General Discussion

It was the purpose of this thesis to understand how somatosensory input is modulated in the SMA and S1 during the preparation and execution of upper-limb voluntary movement contralateral to sensory input. The main results of this thesis describe how the N30 is increased during non-dominant hand movement as compared to dominant hand movement. It may be that differences in ipsilateral motor cortical activity contribute to the reported N30 differences.

The first study revealed that the N30 is increased during execution but not the planning of movement of the limb contralateral to median nerve stimulation. The second study further explored this phenomenon and found that N30 modulation is unique to movement of the non-dominant upper-limb. Studies three and four were aimed at probing how motor cortical areas contribute to the facilitation of the N30 and the potential behavioural consequences of this modulation. Study three revealed that inhibition of left motor cortex removes the previously observed N30 facilitation, and the fourth study provided evidence that the supplementary motor area contributes to generation of the N30 and may also play a role in tactile perception.

The results of Study 1 were initially surprising as an increase in amplitude of the frontal N30 during movement preparation rather than execution was originally hypothesized. This hypothesis was based on evidence that the SMA contributes to both the generation of the N30 (Desmedt & Bourguet, 1985; Mauguiere et al., 1983) and to the early and late phase of the Bereitschaftspotential (Shibisaki & Hallett 2006).

However, the observed increase in N30 amplitude during EMG activity only points to cortical events related to motor execution. It should be noted here that the SMA does contribute to the corticospinal tract but to a much lesser extent than M1 (Teitti et al., 2008), making the contribution of M1 significantly more likely as the mediator of N30 amplitude during movement execution. The results of this thesis cannot rule out the contribution of SMA corticospinal efferents to N30 modulation but two results point to M1 being the prime modulator: 1) the finding of Matsunaga et al. (2004) that the N30 is increased as a result of direct current stimulation to the left motor cortex and 2) the results of study 4 which found that continuous TBS to left M1 removed this facilitation.

The results of study 2 show that facilitation of the N30 is a product of non-dominant hand movement and not a generalized phenomenon when sensory input and motor output are dissociated across the upper limbs. Movement of the dominant hand does not result in any impact upon the frontal N30 and parietal potentials generated from the other limb – the typical finding for movement-related studies on SEP amplitude which repeatedly report site specific effects for the influence of movement upon sensory afference. It is unclear why movement of the non-dominant but not the dominant limb results in N30 facilitation though it may be related to differences in motor activity between the two primary motor cortices.

There are established differences in motor lateralization between left and right hand dominant individuals such that left hand dominant individuals in general display less laterality of motor activity and more bilateral activation during unilateral upper-limb movement (Dassonville et al., 1997; Kawashima et al., 1997; Singh et al., 1998;

Solodkin et al., 2001). Despite motor activation differences, handedness does not impact the relationship of non-dominant hand movement and N30 facilitation such that the N30 is only modulated during right hand movement in left hand dominant individuals. This result does not rule out a dominant left motor cortex hypothesis for N30 modulation because in both cases (right hand dominant – move left; left hand dominant – move right) the left motor cortex is active. It was mentioned previously that lesion of the left motor cortex affects both left and right hands but lesion of right motor cortex only affects the left hand, and this has led to certain groups attributing more importance to the left motor cortex than right for motor control (Haaland & Harrington, 1989a; Ziemann & Hallett, 2001). However from the results of this thesis, it does not seem that that the left motor cortex exerts similar control of sensory input for both limbs. If so, it would be expected that right hand movement in right-hand dominant individuals would modulate sensory input from the left hand – and this was not the case.

The literature suggests that in right hand dominant individuals non-dominant hand movement repeatedly results in ipsilateral motor cortical activity including left hand dominant individuals (Kawashima et al., 1997; Singh et al., 1998). The purpose for ipsilateral M1 activity is currently unclear but inter-hemispheric paired pulse TMS studies suggest that it is the result of contralateral M1 activity. At rest, inhibition is stronger from left to right motor cortex (Netz et al. 1995), and this is associated with an increase in ipsilateral BOLD response (Kobayashi et al. 2003). During voluntary

movement, Duque et al. (2007) reported that the right motor cortex is inhibited during right hand movement but the left motor cortex is not during left hand movement.

It is unclear if motor cortical differences such as those discussed above are the physiological underpinnings for hand preference but seem to also affect sensory-motor integration across the upper limbs as evidenced by the results of Study 3. Continuous TBS to the left motor cortex during left hand movement removed the N30 facilitation, whereas the same protocol delivered to the right motor cortex had no effect at rest or during movement.

Although the fourth study was somewhat tangential to the explicit purpose of this thesis and exploratory in nature, it was nonetheless purposeful as a means of confirming a contribution of the SMA to N30 amplitude. Interpretation of N30 modulation is obviously difficult when the cortical areas contributing to its generation are unknown and therefore too is the type of somatosensory information coded by this population although evidence for both cutaneous (Matsunaga et al. 1992; Romo et al. 1993) and proprioceptive (Restuccia et al. 1999; 2002) information exists. The results of Study 4 suggest that the SMA contributes at least in part to N30 amplitude and the cells contributing to its amplitude may code information from cutaneous mechanoreceptors. It is premature however to suggest the N30 represents a population of cells that code cutaneous somatosensory inputs and is not argued here with any vigour. However, this contention should be considered as the SMA does respond to tactile inputs monophasically, similar to those in 3b of S1 (Romo & Salinas 2001) with one critical difference. Cells in the SMA do not respond to passive tactile stimulation

as do cells in area 3b but rather only do so when either paired or associated with a motor response (Romo & Salinas 2001). Verbal response, as required in study 4, may satisfy these motor criteria and thus provides a link between N30 amplitude and cutaneous inputs. The results of study 4 are the first to report an inhibition of SMA effect upon early processing in S1. It is possible and likely that the suppression of the N20/P27 led to a decrease in tactile perception as suppression of these potentials has previously been associated with a decrease in perception but the link between the SMA and tactile perception has not been previously reported. The connections mediating this effect may be through parietal back projections to S1 as SMA does not send direct efferents to S1 (Jones et al., 1978; Vogt & Pandya, 1978; M. Wiesendanger, 1986), via M1 or through sub-cortical thalamic connections. The thalamic potential (P18) was not affected in this study, and TBS of SMA does not alter MEP amplitudes suggesting that SMA influence upon early S1 processing may be via its strong connections with area 1, 2 or S2. Either way, the link between SMA and early S1 processing of tactile inputs is intriguing and suggests a more important role for the SMA in sensory processing and sensory-motor integration across the upper-limbs then may have been previously appreciated.

It has been argued throughout this thesis that ipsilateral M1 influences SMA activity as demonstrated by modulation of N30 amplitude during movement execution of the non-dominant limb. However, the specific temporal relationship between SMA and ipsilateral M1 activity during movement execution is not clear and as such, it may very well be that an increase in N30 amplitude during movement execution reflects

SMA activity upon ipsilateral M1. Previous literature has suggested a modulatory role for the SMA both before and during movement and the results of this thesis may suggest that the SMA may play a critical role in coordinating inhibitory input to ipsilateral M1 during unilateral movements. The results of this thesis, under this hypothesis, may suggest that the SMA assumes a critical role in coordinating the inhibitory inputs to ipsilateral M1 that counteract the crossed facilitation that would otherwise be mediated by crossed-hemispheric interactions occurring upstream of primary motor cortex. As such, SMA activity, evident during movements of the ipsilateral limb, would not necessarily be contingent upon sensory inflow from the moving limb.

Somatosensory evoked potentials are not often studied under conditions involving bilateral upper-limb use or interaction, but the results of this thesis suggest that, at the very least, the N30 may be a fruitful index of differences in sensory inflow across the upper limbs during contralateral movement. The N30 has been demonstrated to act independently of parietal potentials under certain motor conditions and this thesis too finds this, lending further evidence to the separate generator theory for the frontal N30.

One of the specific conditions that affect the N30 is Parkinson's disease. It is often attenuated or absent in PD suggesting a link between it and the basal ganglia thalamic cortical motor loop. Parkinson's disease is characterized by impaired initiation of movement and reduced amplitude and velocity of voluntary movement, findings similar to non-dominant hand movement if compared to dominant hand

movement. Recent research has demonstrated an increase in putamenal activity during voluntary non-dominant hand movement. It is possible then that an increase in N30 amplitude during non-dominant hand movement is a reflection of a compensatory ramping up of the basal ganglia thalamic cortical motor loop. It is possible that his difference is initiated by the imbalance of inhibitory influence of the left motor cortex upon the right motor cortex. During left hand movement in right hand dominant individuals the right motor cortex is not released by the left motor cortex before or during voluntary movement. This lack of release may be a factor in instituting a ramping up of the basal ganglia motor loops thus increasing the amplitude of the N30. Interestingly, if movements are externally cued for non-dominant hand movement, the difference in putamenal activation for these movements versus dominant hand movements is lost. Parkinson's patients typically have less trouble initiating movements to external cues.

The results of this thesis warrant a further look into how the motor cortices interact during unilateral movement of both the dominant and non-dominant limb. Consideration of the limb performing the movement is important when conceptualizing protocols as it has differential effects upon SMA activity as reflected by N30 amplitude; differences which may be from specific SMA influence upon ipsilateral motor cortex or be the result of ipsilateral motor cortical activity during non-dominant hand movement or specific sub-cortical basal ganglia activity. The N30 provides a quantitative measure of differences in cortical activity depending upon hand use and

should be considered when examining inter-limb, bimanual and unilateral hand use function and recovery.

6.2 Conclusions

The frontal N30 is facilitated during non-dominant hand movement in both right hand and left hand dominant individuals. In both groups, dominant hand movement has no impact on the N30. Non-dominant hand movement is associated with ipsilateral motor cortical activity, likely as a result of inter-hemispheric connections with contralateral M1 that when disrupted, removes facilitation of the N30 during movement.

The results of this thesis suggest a functional lateralization of SMA-M1 interaction depending upon hand use. The functional consequence of this is currently not well-understood however it may be that the interaction between sensory input and motor output is functionally separate across the upper limbs.

The population(s) of cells contributing to N30 amplitude is not well-established, but the results of this thesis suggest it is intimately linked to specific motor cortical activity during non-dominant hand movement and also may represent cell populations that code cutaneous tactile information that is potentially used for the integration of sensory input and motor output across the upper limbs.

6.3 Limitations

This thesis suffers from the use of a dependant measure that is frustratingly enigmatic. The N30 is difficult to source localize due to the cortical convolutions of the frontal cortex and as such provides opportunity for hyperbole and conjecture about the meaning and interpretation of results. It is unlikely, but possible, that the SMA does not contribute to N30 amplitude. In addition, there is debate as to the physiological nature of SEP potentials themselves and what they specifically represent. The debate is whether event-related potentials are generated by fixed latency, fixed polarity responses or by a reset of oscillatory activity. This is of critical importance to this thesis given the recent work by Cebolla et al. (2009) and Cheron et al. (2007) who suggest that the frontal N30 is a result of β-gamma phase-locking. If so, this raises questions about the interpretation of amplitude differences of SEP components not only from this thesis but from the litany of previous SEP research this thesis was built upon.

Finally, transcranial magnetic stimulation is, relative to certainty, a poorly understood intervention. Many compelling papers reporting the beneficial effects of TMS in clinical populations are hampered only by the fact that physiologically, it is not understood how TMS actually works – especially in cortical areas outside of M1 (see Bestmann, 2008 for a discussion and some respite). Of course, sometimes that is not so important so long as it works – like anaesthesia. This uncertainty again makes interpretation of results a touch more speculative and difficult, but does at least provide for lengthy and fanciful discussions.

6.4 Future Directions

The results of this thesis suggest that contralateral non-dominant hand movement increases the response of SMA to sensory input. The functional impact of this is not yet clear but the results of Study #4 suggest that it may be beneficial, such that attenuation of the N30 was associated with impairments in tactile perception. It may be that movement of the non-dominant limb increases tactile perceptual acuity for the dominant hand. This is not unprecedented as transient anaesthesia of one limb has been demonstrated to improve tactile acuity of the other (Werhahn et al. 2002). If this assertion is true, it would be hypothesized that the same effect would not occur for the non-dominant hand during movement of the dominant hand. In turn, it would be interesting to see if increasing or decreasing contralateral sensory input during both dominant and non-dominant hand movement has differential effects. The results of this thesis would hypothesize that it does and the SMA may be a potential site of regulation.

As previously mentioned, somatosensory input is necessary for motor learning and precise motor performance, and intact somatosensory function is associated with better motor recovery in stroke. Recent research has demonstrated that increased somatosensory input leads to up-regulation of sensory-motor cortex (Wu et al. 2005) and has proven to be an effective rehabilitation strategy for improving function of the impaired limb in stroke (Celnik et al. 2007).

A similar strategy has not been attempted for sensory input contralateral to the impaired limb, or during contralateral movement and such interventions may have potential benefit given the results of this thesis. Post-stroke movement is often difficult

due to impairment of the affected limb, however mental or imagined movements produce similar patterns of activation in motor cortices to actual movement, and are also associated with an increase in N30 amplitude (Cheron et al. 1992, Rossini et al. 1996). If sensory input is paired with motor output (Stefan et al. 2000) LTP-like changes have been reported although this intervention has not been studied contralaterally across the upper-limbs or during stimulation to the SMA. The impact of sensory-motor integration across the upper-limbs and the role of the SMA in these protocols may prove a fruitful avenue for research and for rehabilitative strategies for stroke.

References

Abbruzzese, G., & Berardelli, A. (2003). Sensorimotor integration in movement disorders. *Movement Disorders : Official Journal of the Movement Disorder Society, 18*(3), 231-240.

Akkal, D., Dum, R. P., & Strick, P. L. (2007). Supplementary motor area and presupplementary motor area: Targets of basal ganglia and cerebellar output. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 27*(40), 10659-10673.

Alexander, G. E., & Crutcher, M. D. (1990). Preparation for movement: Neural representations of intended direction in three motor areas of the monkey. *Journal of Neurophysiology, 64*(1), 133-150.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res, 85*, 119-146.

Allison, T., McCarthy, G., Wood, C. C., Darcey, T. M., Spencer, D. D., & Williamson, P. D. (1989). Human cortical potentials evoked by stimulation of the median nerve. I. cytoarchitectonic areas generating short-latency activity. *J Neurophysiol, 62*(3), 694-710.

Allison, T., McCarthy, G., Wood, C. C., & Jones, S. J. (1991a). Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. *Brain : A Journal of Neurology, 114 (Pt 6)*(Pt 6), 2465-2503.

Allison, T., McCarthy, G., Wood, C. C., & Jones, S. J. (1991b). Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. *Brain : A Journal of Neurology, 114 (Pt 6)*(Pt 6), 2465-2503.

Allison, T., McCarthy, G., Wood, C. C., Williamson, P. D., & Spencer, D. D. (1989). Human cortical potentials evoked by stimulation of the median nerve. II. cytoarchitectonic areas generating long-latency activity. *Journal of Neurophysiology, 62*(3), 711-722.

Andre-Obadia, N., Garcia-Larrea, L., Garassus, P., & Mauguiere, F. (1999). Timing and characteristics of perceptual attenuation by transcranial stimulation: A study using magnetic cortical stimulation and somatosensory-evoked potentials. *Psychophysiology, 36*(4), 476-483.

Asanuma, H., Larsen, K., & Yumiya, H. (1980). Peripheral input pathways to the monkey motor cortex. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 38*(3), 349-355.

Avanzino, L., Bove, M., Trompetto, C., Tacchino, A., Ogliastro, C., & Abbruzzese, G. (2008). 1-hz repetitive TMS over ipsilateral motor cortex influences the performance of sequential finger movements of different complexity. *The European Journal of Neuroscience, 27*(5), 1285-1291.

Babiloni, C., Carducci, F., Del Gratta, C., Demartin, M., Romani, G. L., Babiloni, F., et al. (2003). Hemispherical asymmetry in human SMA during voluntary simple unilateral movements. an fMRI study. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 39*(2), 293-305.

Barba, C., & Valeriani, M. (2004). Assessing somatosensory evoked potential (SEP) generators by human intracranial recordings. *Clin Neurophysiol, 115*(2), 488-9; author reply 489.

Barba, C., Valeriani, M., Colicchio, G., & Mauguiere, F. (2005). Short and middle-latency median nerve (MN) SEPs recorded by depth electrodes in human pre-SMA and SMA-proper. *Clin Neurophysiol, 116*(11), 2664-2674.

Barba, C., Valeriani, M., Restuccia, D., Colicchio, G., Faraca, G., Tonali, P., et al. (2003). The human supplementary motor area-proper does not receive direct somatosensory inputs from the periphery: Data from stereotactic depth somatosensory evoked potential recordings. *Neurosci Lett, 344*(3), 161-164.

Bastings, E. P., Gage, H. D., Greenberg, J. P., Hammond, G., Hernandez, L., Santago, P., et al. (1998). Co-registration of cortical magnetic stimulation and functional magnetic resonance imaging. *Neuroreport, 9*(9), 1941-1946.

Bestmann, S. (2008). The physiological basis of transcranial magnetic stimulation. *Trends in Cognitive Sciences, 12*(3), 81-83.

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. (2003). Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. *NeuroImage, 20*(3), 1685-1696.

Bestmann, S., Ruff, C. C., Blankenburg, F., Weiskopf, N., Driver, J., & Rothwell, J. C. (2008). Mapping causal interregional influences with concurrent TMS-fMRI. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 191*(4), 383-402.

Brinkman, C. (1984). Supplementary motor area of the monkey's cerebral cortex: Short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *J Neurosci, 4*(4), 918-929.

Brinkman, C., & Porter, R. (1979). Supplementary motor area in the monkey: Activity of neurons during performance of a learned motor task. *Journal of Neurophysiology, 42*(3), 681-709.

Britton, T. C., Meyer, B. U., & Benecke, R. (1991). Central motor pathways in patients with mirror movements. *Journal of Neurology, Neurosurgery, and Psychiatry, 54*(6), 505-510.

Bryden, MP. (1977). Measuring handedness with questionnaires. Neuropsychologia 15(4), 617-624.

Burton, H., Fabri, M., & Alloway, K. (1995). Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: A revised interpretation of the second somatosensory area in macaque monkeys. *The Journal of Comparative Neurology, 355*(4), 539-562.

Calford, M. B. (2002). Dynamic representational plasticity in sensory cortex. *Neuroscience, 111*(4), 709-738.

Canavan, A. G., Nixon, P. D., & Passingham, R. E. (1989). Motor learning in monkeys (macaca fascicularis) with lesions in motor thalamus. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 77*(1), 113-126.

Canedo, A. (1997). Primary motor cortex influences on the descending and ascending systems. *Prog Neurobiol, 51*(3), 287-335.

Carson, R. G., Smethurst, C. J., Oytam, Y., & de Rugy, A. (2007). Postural context alters the stability of bimanual coordination by modulating the crossed excitability of corticospinal pathways. *Journal of Neurophysiology, 97*(3), 2016-2023.

Cavada, C., & Goldman-Rakic, P. S. (1989). Posterior parietal cortex in rhesus monkey: I. parcellation of areas based on distinctive limbic and sensory corticocortical connections. *The Journal of Comparative Neurology, 287*(4), 393-421.

Cebolla, A. M., De Saedeleer, C., Bengoetxea, A., Leurs, F., Balestra, C., d'Alcantara, P., et al. (2009). Movement gating of beta/gamma oscillations involved in the N30 somatosensory evoked potential. *Human Brain Mapping, 30*(5), 1568-1579.

Chapman, C. E. (1994). Active versus passive touch: Factors influencing the transmission of somatosensory signals to primary somatosensory cortex. *Can J Physiol Pharmacol, 72*(5), 558-570.

Chapman, C. E., Bushnell, M. C., Miron, D., Duncan, G. H., & Lund, J. P. (1987). Sensory perception during movement in man. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 68*(3), 516-524.

Chen, R., Cohen, L. G., & Hallett, M. (1997). Role of the ipsilateral motor cortex in voluntary movement. *The Canadian Journal of Neurological Sciences.Le Journal Canadien Des Sciences Neurologiques, 24*(4), 284-291.

Chen, R., Gerloff, C., Hallett, M., & Cohen, L. G. (1997). Involvement of the ipsilateral motor cortex in finger movements of different complexities. *Annals of Neurology, 41*(2), 247-254.

Chen, Y. C., Thaler, D., Nixon, P. D., Stern, C. E., & Passingham, R. E. (1995). The functions of the medial premotor cortex. II. the timing and selection of learned movements. *Exp Brain Res, 102*(3), 461-473.

Cheron, G. (1999). Is the frontal N30 component of the somatosensory evoked potentials a reliable physiological index of the dopaminergic motor pathways? *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 110*(10), 1698-1699.

Cheron, G., & Borenstein, S. (1991). Gating of the early components of the frontal and parietal somatosensory evoked potentials in different sensory-motor interference modalities. *Electroencephalogr Clin Neurophysiol, 80*(6), 522-530.

Cheron, G., & Borenstein, S. (1992). Mental movement simulation affects the N30 frontal component of the somatosensory evoked potential. *Electroencephalography and Clinical Neurophysiology, 84*(3), 288-292.

Cheron, G., Cebolla, A. M., De Saedeleer, C., Bengoetxea, A., Leurs, F., Leroy, A., et al. (2007). Pure phase-locking of beta/gamma oscillation contributes to the N30 frontal component of somatosensory evoked potentials. *BMC Neuroscience, 8*, 75.

Cheron, G., Dan, B., & Borenstein, S. (2000). Sensory and motor interfering influences on somatosensory evoked potentials. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society, 17*(3), 280-294.

Cheron, G., Piette, T., Thiriaux, A., Jacquy, J., & Godaux, E. (1994). Somatosensory evoked potentials at rest and during movement in parkinson's disease: Evidence for a specific apomorphine effect on the frontal N30 wave. *Electroencephalogr Clin Neurophysiol, 92*(6), 491-501.

Celnik P., Hummel F., Harris-Love M., Wolk R., & Cohen L.G. (2007). Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. *Arch Phys Med Rehabil. 88(11), 1369-76.*

Civardi, C., Cantello, R., Asselman, P., & Rothwell, J. C. (2001). Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. *NeuroImage, 14*(6), 1444-1453.

Cohen, L. G., Bandinelli, S., Sato, S., Kufta, C., & Hallett, M. (1991). Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation. *Electroencephalography and Clinical Neurophysiology, 81*(5), 366-376.

Cohen, L. G., & Starr, A. (1987). Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. *Brain, 110 (Pt 2)*, 451-467.

Cracco, R. Q., Amassian, V. E., Maccabee, P. J., & Cracco, J. B. (1989). Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroencephalography and Clinical Neurophysiology, 74*(6), 417-424.

Cramer, S. C., Finklestein, S. P., Schaechter, J. D., Bush, G., & Rosen, B. R. (1999). Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *Journal of Neurophysiology, 81*(1), 383-387.

Cunnington, R., Iansek, R., Thickbroom, G. W., Laing, B. A., Mastaglia, F. L., Bradshaw, J. L., et al. (1996). Effects of magnetic stimulation over supplementary motor area on movement in parkinson's disease. *Brain : A Journal of Neurology, 119 (Pt 3)*(Pt 3), 815-822.

Cusick, C. G., Wall, J. T., Felleman, D. J., & Kaas, J. H. (1989). Somatotopic organization of the lateral sulcus of owl monkeys: Area 3b, S-II, and a ventral somatosensory area. *The Journal of Comparative Neurology, 282*(2), 169-190.

Darian-Smith, C., & Darian-Smith, I. (1993). Thalamic projections to areas 3a, 3b, and 4 in the sensorimotor cortex of the mature and infant macaque monkey. *J Comp Neurol, 335*(2), 173-199.

Dassonville, P., Zhu, X. H., Uurbil, K., Kim, S. G., & Ashe, J. (1997). Functional activation in motor cortex reflects the direction and the degree of handedness. *Proceedings of the National Academy of Sciences of the United States of America, 94*(25), 14015-14018.

Deiber, M. P., Passingham, R. E., Colebatch, J. G., Friston, K. J., Nixon, P. D., & Frackowiak, R. S. (1991). Cortical areas and the selection of movement: A study with positron emission tomography. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 84*(2), 393-402.

DeLong, M. R. (1983). The neurophysiologic basis of abnormal movements in basal ganglia disorders. *Neurobehavioral Toxicology and Teratology, 5*(6), 611-616.

Desmedt, J. E., & Bourguet, M. (1985). Color imaging of parietal and frontal somatosensory potential fields evoked by stimulation of median or posterior tibial nerve in man. *Electroencephalography and Clinical Neurophysiology, 62*(1), 1-17.

Desmedt, J. E., & Cheron, G. (1980). Central somatosensory conduction in man: Neural generators and interpeak latencies of the far-field components recorded from neck and right or left scalp and earlobes. *Electroencephalogr Clin Neurophysiol, 50*(5), 382-403.

Desmedt, J. E., & Cheron, G. (1981). Non-cephalic reference recording of early somatosensory potentials to finger stimulation in adult or aging normal man: Differentiation of widespread N18 and contralateral N20 from the prerolandic P22 and N30 components. *Electroencephalography and Clinical Neurophysiology, 52*(6), 553-570.

Desmedt, J. E., Nguyen, T. H., & Bourguet, M. (1987). Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses. *Electroencephalography and Clinical Neurophysiology, 68*(1), 1-19.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., et al. (2008). The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *The Journal of Physiology, 586*(16), 3871-3879.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., et al. (2008). Low-frequency repetitive transcranial magnetic stimulation suppresses

specific excitatory circuits in the human motor cortex. *The Journal of Physiology, 586*(Pt 18), 4481-4487.

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P., et al. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *The Journal of Physiology, 565*(Pt 3), 945-950.

Di Lazzaro, V., Thickbroom, G. W., Pilato, F., Profice, P., Dileone, M., Mazzone, P., et al. (2007). Direct demonstration of the effects of repetitive paired-pulse transcranial magnetic stimulation at I-wave periodicity. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 118*(6), 1193-1197.

Dick, J. P., Benecke, R., Rothwell, J. C., Day, B. L., & Marsden, C. D. (1986). Simple and complex movements in a patient with infarction of the right supplementary motor area. *Movement Disorders : Official Journal of the Movement Disorder Society, 1*(4), 255-266.

Donchin, O., Gribova, A., Steinberg, O., Mitz, A. R., Bergman, H., & Vaadia, E. (2002). Single-unit activity related to bimanual arm movements in the primary and supplementary motor cortices. *Journal of Neurophysiology, 88*(6), 3498-3517.

Duque, J., Murase, N., Celnik, P., Hummel, F., Harris-Love, M., Mazzocchio, R., et al. (2007). Intermanual differences in movement-related interhemispheric inhibition. *Journal of Cognitive Neuroscience, 19*(2), 204-213

.

Ebner, A., & Deuschl, G. (1988). Frontal and parietal components of enhanced somatosensory evoked potentials: A comparison between pathological and pharmacologically induced conditions. *Electroencephalography and Clinical Neurophysiology, 71*(3), 170-179.

Ebner, T. J., & Bloedel, J. R. (1981). Correlation between activity of purkinje cells and its modification by natural peripheral stimuli. *Journal of Neurophysiology, 45*(5), 948-961.

Enomoto, H., Ugawa, Y., Hanajima, R., Yuasa, K., Mochizuki, H., Terao, Y., et al. (2001). Decreased sensory cortical excitability after 1 hz rTMS over the ipsilateral primary motor cortex. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 112*(11), 2154-2158.

Evarts, E. V. (1973). Motor cortex reflexes associated with learned movement. *Science (New York, N.Y.), 179*(72), 501-503.

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *The Journal of Physiology, 453*, 525-546.

Floel, A., Nagorsen, U., Werhahn, K. J., Ravindran, S., Birbaumer, N., Knecht, S., et al. (2004). Influence of somatosensory input on motor function in patients with chronic stroke. *Annals of Neurology, 56*(2), 206-212.

Francois-Brosseau, FE., Martinu, K., Strafella, A.P., Petrides, M., et al. (2009). Basal ganglia and frontal involvement in self-generated and externally-triggered finger movements in the dominant and non-dominant hand. *Eur. J. Neurosci*., 29(6), 1277-1286.

Friedman, D. P., & Murray, E. A. (1986). Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *The Journal of Comparative Neurology, 252*(3), 348-373.

Garraghty, P. E., Pons, T. P., & Kaas, J. H. (1990). Ablations of areas 3b (SI proper) and 3a of somatosensory cortex in marmosets deactivate the second and parietal ventral somatosensory areas. *Somatosens Mot Res, 7*(2), 125-135.

Garry, M. I., Kamen, G., & Nordstrom, M. A. (2004). Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. *Journal of Neurophysiology, 91*(4), 1570-1578.

Gaymard, B., Pierrot-Deseilligny, C., & Rivaud, S. (1990). Impairment of sequences of memory-guided saccades after supplementary motor area lesions. *Annals of Neurology, 28*(5), 622-626.

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., & Classen, J. (2008). Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: Evidence of rapid polarity-reversing metaplasticity. *Cerebral Cortex (New York, N.Y.: 1991), 18*(9), 2046-2053.

Gerloff, C., Corwell, B., Chen, R., Hallett, M., & Cohen, L. G. (1997). Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain : A Journal of Neurology, 120 (Pt 9)*(Pt 9), 1587-1602.

Geyer, S., Matelli, M., Luppino, G., & Zilles, K. (2000). Functional neuroanatomy of the primate isocortical motor system. *Anatomy and Embryology, 202*(6), 443-474.

Ghacibeh, G. A., Mirpuri, R., Drago, V., Jeong, Y., Heilman, K. M., & Triggs, W. J. (2007). Ipsilateral motor activation during unimanual and bimanual motor tasks. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 118*(2), 325-332.

Ghez, C., & Lenzi, G. L. (1971). Modulation of sensory transmission in cat lemniscal system during voluntary movement. *Pflugers Archiv : European Journal of Physiology, 323*(3), 273-278.

Ghosh, S., Brinkman, C., & Porter, R. (1987). A quantitative study of the distribution of neurons projecting to the precentral motor cortex in the monkey (M. fascicularis). *The Journal of Comparative Neurology, 259*(3), 424-444.

Ghosh, S., & Porter, R. (1988). Corticocortical synaptic influences on morphologically identified pyramidal neurones in the motor cortex of the monkey. *The Journal of Physiology, 400*, 617-629.

Gironell, A., Rodriguez-Fornells, A., Kulisevsky, J., Pascual, B., Barbanoj, M., & Otermin, P. (2002). Motor circuitry re-organization after pallidotomy in parkinson disease: A neurophysiological study of the bereitschaftspotential, contingent negative variation, and N30. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society, 19*(6), 553-561.

Goble, D. J., & Brown, S. H. (2008). The biological and behavioral basis of upper limb asymmetries in sensorimotor performance. *Neuroscience and Biobehavioral Reviews, 32*(3), 598-610.

Haaland, K. Y., & Harrington, D. (1989a). The role of the hemispheres in closed loop movements. *Brain and Cognition, 9*(2), 158-180.

Haaland, K. Y., & Harrington, D. L. (1989b). Hemispheric control of the initial and corrective components of aiming movements. *Neuropsychologia, 27*(7), 961-969.

Halsband, U., Ito, N., Tanji, J., & Freund, H. J. (1993). The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain : A Journal of Neurology, 116 (Pt 1)*(Pt 1), 243-266.

Halsband, U., Matsuzaka, Y., & Tanji, J. (1994). Neuronal activity in the primate supplementary, pre-supplementary and premotor cortex during externally and internally instructed sequential movements. *Neuroscience Research, 20*(2), 149-155.

Halsband, U., & Passingham, R. (1982). The role of premotor and parietal cortex in the direction of action. *Brain Research, 240*(2), 368-372.

Halsband, U., & Passingham, R. E. (1985). Premotor cortex and the conditions for movement in monkeys (macaca fascicularis). *Behavioural Brain Research, 18*(3), 269-277.

Hamada, M., Ugawa, Y., Tsuji, S., & Effectiveness of rTMS on Parkinson's Disease Study Group, Japan. (2008). High-frequency rTMS over the supplementary motor area for treatment of parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society, 23*(11), 1524-1531.

Hanakawa, T., Parikh, S., Bruno, M. K., & Hallett, M. (2005). Finger and face representations in the ipsilateral precentral motor areas in humans. *Journal of Neurophysiology, 93*(5), 2950-2958.

Hannula, H., Ylioja, S., Pertovaara, A., Korvenoja, A., Ruohonen, J., Ilmoniemi, R. J., et al. (2005). Somatotopic blocking of sensation with navigated transcranial magnetic stimulation of the primary somatosensory cortex. *Human Brain Mapping, 26*(2), 100-109.

Hari, R., Hamalainen, M., Kaukoranta, E., Reinikainen, K., & Teszner, D. (1983). Neuromagnetic responses from the second somatosensory cortex in man. *Acta Neurologica Scandinavica, 68*(4), 207-212.

Harris, J. A., Miniussi, C., Harris, I. M., & Diamond, M. E. (2002). Transient storage of a tactile memory trace in primary somatosensory cortex. *J Neurosci, 22*(19), 8720-8725.

Hernandez, A., Zainos, A., & Romo, R. (2002). Temporal evolution of a decision-making process in medial premotor cortex. *Neuron, 33*(6), 959-972.

Hikosaka, O., Sakai, K., Miyauchi, S., Takino, R., Sasaki, Y., & Putz, B. (1996). Activation of human presupplementary motor area in learning of sequential procedures: A functional MRI study. *Journal of Neurophysiology, 76*(1), 617-621.

Horenstein, C., Lowe, M. J., Koenig, K. A., & Phillips, M. D. (2009). Comparison of unilateral and bilateral complex finger tapping-related activation in premotor and primary motor cortex. *Human Brain Mapping, 30*(4), 1397-1412.

Hoshi, E., & Tanji, J. (2004). Differential roles of neuronal activity in the supplementary and presupplementary motor areas: From information retrieval to motor planning and execution. *Journal of Neurophysiology, 92*(6), 3482-3499.

Hoshiyama, M., & Kakigi, R. (1999). Changes of somatosensory evoked potentials during writing with the dominant and non-dominant hands. *Brain Res, 833*(1), 10-19.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206.

Huang, Y. Z., Rothwell, J. C., Edwards, M. J., & Chen, R. S. (2008). Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. *Cerebral Cortex (New York, N.Y.: 1991), 18*(3), 563-570.

Huang, Y. Z., Rothwell, J. C., Lu, C. S., Wang, J., Weng, Y. H., Lai, S. C., et al. (2009). The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 120*(4), 796-801.

Huerta, M. F., & Pons, T. P. (1990). Primary motor cortex receives input from area 3a in macaques. *Brain Res, 537*(1), 367-371.

Hummelsheim, H., Bianchetti, M., Wiesendanger, M., & Wiesendanger, R. (1988). Sensory inputs to the agranular motor fields: A comparison between precentral, supplementary-motor and premotor areas in the monkey. *Exp Brain Res, 69*(2), 289-298.

Huttunen, J., Wikstrom, H., Korvenoja, A., Seppalainen, A. M., Aronen, H., & Ilmoniemi, R. J. (1996). Significance of the second somatosensory cortex in sensorimotor integration: Enhancement of sensory responses during finger movements. *Neuroreport, 7*(5), 1009-1012.

Ishikawa, S., Matsunaga, K., Nakanishi, R., Kawahira, K., Murayama, N., Tsuji, S., et al. (2007). Effect of theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 118*(5), 1033-1043.

Johnson, D., Jurgens, R., Kongehl, G., & Kornhuber, H. H. (1975). Somatosensory evoked potentials and magnitude of perception. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 22*(3), 331-334.

Jones, E. G., Coulter, J. D., & Hendry, S. H. (1978). Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *J Comp Neurol, 181*(2), 291-347.

Jones, E. G., & Powell, T. P. (1969a). Connexions of the somatic sensory cortex of the rhesus monkey. I. ipsilateral cortical connexions. *Brain : A Journal of Neurology, 92*(3), 477-502.

Jones, E. G., & Powell, T. P. (1969b). Connexions of the somatic sensory cortex of the rhesus monkey. II. contralateral cortical connexions. *Brain : A Journal of Neurology, 92*(4), 717-730.

Jones, E. G., & Powell, T. P. (1969c). The cortical projection of the ventroposterior nucleus of the thalamus in the cat. *Brain Res, 13*(2), 298-318.

Jurgens, U. (1984). The efferent and afferent connections of the supplementary motor area. *Brain Research, 300*(1), 63-81.

Kakigi, R. (1986). Ipsilateral and contralateral SEP components following median nerve stimulation: Effects of interfering stimuli applied to the contralateral hand. *Electroencephalography and Clinical Neurophysiology, 64*(3), 246-259.

Kakigi, R. (1994). Somatosensory evoked magnetic fields following median nerve stimulation. *Neuroscience Research, 20*(2), 165-174.

Kanda, M., Mima, T., Oga, T., Matsuhashi, M., Toma, K., Hara, H., et al. (2003). Transcranial magnetic stimulation (TMS) of the sensorimotor cortex and medial frontal cortex modifies human pain perception. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 114*(5), 860-866.

Kanovsky, P., Bares, M., & Rektor, I. (2003). The selective gating of the N30 cortical component of the somatosensory evoked potentials of median nerve is different in the mesial and dorsolateral frontal cortex: Evidence from intracerebral recordings. *Clin Neurophysiol, 114*(6), 981-991.

Kansaku, K., Muraki, S., Umeyama, S., Nishimori, Y., Kochiyama, T., Yamane, S., et al. (2005). Cortical activity in multiple motor areas during sequential finger movements: An application of independent component analysis. *NeuroImage, 28*(3), 669-681.

Katayama, T., & Rothwell, J. C. (2007). Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 118*(11), 2506-2511.

Kawashima, R., Inoue, K., Sato, K., & Fukuda, H. (1997). Functional asymmetry of cortical motor control in left-handed subjects. *Neuroreport, 8*(7), 1729-1732.

Kawashima, R., Yamada, K., Kinomura, S., Yamaguchi, T., Matsui, H., Yoshioka, S., et al. (1993). Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. *Brain Research, 623*(1), 33-40.

Kazennikov, O., Hyland, B., Wicki, U., Perrig, S., Rouiller, E. M., & Wiesendanger, M. (1998). Effects of lesions in the mesial frontal cortex on bimanual co-ordination in monkeys. *Neuroscience, 85*(3), 703-716.

Kermadi, I., Liu, Y., Tempini, A., & Rouiller, E. M. (1997). Effects of reversible inactivation of the supplementary motor area (SMA) on unimanual grasp and bimanual pull and grasp performance in monkeys. *Somatosensory & Motor Research, 14*(4), 268-280.

Kida, T., Wasaka, T., Nakata, H., Akatsuka, K., & Kakigi, R. (2006). Centrifugal regulation of a task-relevant somatosensory signal triggering voluntary movement without a preceding warning signal. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 173*(4), 733-741.

Kim, S. G., Ashe, J., Hendrich, K., Ellermann, J. M., Merkle, H., Ugurbil, K., et al. (1993). Functional magnetic resonance imaging of motor cortex: Hemispheric asymmetry and handedness. *Science (New York, N.Y.), 261*(5121), 615-617.

Knecht, S., Ellger, T., Breitenstein, C., Bernd Ringelstein, E., & Henningsen, H. (2003). Changing cortical excitability with low-frequency transcranial magnetic stimulation can induce sustained disruption of tactile perception. *Biological Psychiatry, 53*(2), 175-179.

Kobayashi, M., Hutchinson, S., Schlaug, G., & Pascual-Leone, A. (2003). Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *NeuroImage, 20*(4), 2259-2270.

Koch, G., Brusa, L., Caltagirone, C., Peppe, A., Oliveri, M., Stanzione, P., et al. (2005). rTMS of supplementary motor area modulates therapy-induced dyskinesias in parkinson disease. *Neurology, 65*(4), 623-625.

Koch, G., Franca, M., Albrecht, U. V., Caltagirone, C., & Rothwell, J. C. (2006). Effects of paired pulse TMS of primary somatosensory cortex on perception of a peripheral electrical stimulus. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 172*(3), 416-424.

Krainik, A., Lehericy, S., Duffau, H., Vlaicu, M., Poupon, F., Capelle, L., et al. (2001). Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. *Neurology, 57*(5), 871-878.

Kujirai, T., Sato, M., Rothwell, J. C., & Cohen, L. G. (1993). The effect of transcranial magnetic stimulation on median nerve somatosensory evoked potentials. *Electroencephalography and Clinical Neurophysiology, 89*(4), 227-234.

Lacruz, F., Artieda, J., Pastor, M. A., & Obeso, J. A. (1991). The anatomical basis of somaesthetic temporal discrimination in humans. *Journal of Neurology, Neurosurgery, and Psychiatry, 54*(12), 1077-1081.

Laplane, D., Talairach, J., Meininger, V., Bancaud, J., & Orgogozo, J. M. (1977). Clinical consequences of corticectomies involving the supplementary motor area in man. *Journal of the Neurological Sciences, 34*(3), 301-314.

Lee, K. M., Chang, K. H., & Roh, J. K. (1999). Subregions within the supplementary motor area activated at different stages of movement preparation and execution. *NeuroImage, 9*(1), 117-123.

Legon, W., Meehan, S. K., & Staines, W. R. (2008). The relationship between frontal somatosensory-evoked potentials and motor planning. *Neuroreport, 19*(1), 87-91.

Lemon, R. N., & Porter, R. (1976). Afferent input to movement-related precentral neurones in conscious monkeys. *Proceedings of the Royal Society of London.Series B, Containing Papers of a Biological Character.Royal Society (Great Britain), 194*(1116), 313-339.

Luders, H., Lesser, R. P., Dinner, D. S., Hahn, J. F., Salanga, V., & Morris, H. H. (1985). The second sensory area in humans: Evoked potential and electrical stimulation studies. *Annals of Neurology, 17*(2), 177-184.

Luppino, G., Matelli, M., Camarda, R., & Rizzolatti, G. (1993). Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J Comp Neurol, 338*(1), 114-140.

Mackel, R., & Miyashita, E. (1992). Dorsal column input to thalamic VL neurons: An intracellular study in the cat. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 88*(3), 551-559.

Manganotti, P., Zanette, G., Bonato, C., Tinazzi, M., Polo, A., & Fiaschi, A. (1997). Crossed and direct effects of digital nerves stimulation on motor evoked potential: A study with magnetic brain stimulation. *Electroencephalography and Clinical Neurophysiology, 105*(4), 280-289.

Manzoni, T., Barbaresi, P., & Conti, F. (1984). Callosal mechanism for the interhemispheric transfer of hand somatosensory information in the monkey. *Behav Brain Res, 11*(2), 155-170.

Matelli, M., & Luppino, G. (1996). Thalamic input to mesial and superior area 6 in the macaque monkey. *The Journal of Comparative Neurology, 372*(1), 59-87.

Matsunaga, K., Maruyama, A., Fujiwara, T., Nakanishi, R., Tsuji, S., & Rothwell, J. C. (2005). Increased corticospinal excitability after 5 hz rTMS over the human supplementary motor area. *The Journal of Physiology, 562*(Pt 1), 295-306.

Matsunaga, K., Nitsche, M. A., Tsuji, S., & Rothwell, J. C. (2004). Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 115*(2), 456-460.

Matsuzaka, Y., Aizawa, H., & Tanji, J. (1992). A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: Neuronal activity during a learned motor task. *Journal of Neurophysiology, 68*(3), 653-662.

Matsuzaka, Y., & Tanji, J. (1996). Changing directions of forthcoming arm movements: Neuronal activity in the presupplementary and supplementary motor area of monkey cerebral cortex. *Journal of Neurophysiology, 76*(4), 2327-2342.

Mauguiere, F., & Desmedt, J. E. (1991). Focal capsular vascular lesions can selectively deafferent the prerolandic or the parietal cortex: Somatosensory evoked potentials evidence. *Ann Neurol, 30*(1), 71-75.

Mauguiere, F., Desmedt, J. E., & Courjon, J. (1983). Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions. detailed correlations with clinical signs and computerized tomographic scanning. *Brain, 106 (Pt 2)*, 271-311.

Mauguiere, F., Merlet, I., Forss, N., Vanni, S., Jousmaki, V., Adeleine, P., et al. (1997). Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. part I: Location and activation timing of SEF sources. *Electroencephalography and Clinical Neurophysiology, 104*(4), 281-289.

McKay, D. R., Ridding, M. C., & Miles, T. S. (2003a). Magnetic stimulation of motor and somatosensory cortices suppresses perception of ulnar nerve stimuli. *Int J Psychophysiol, 48*(1), 25-33.

McKay, D. R., Ridding, M. C., & Miles, T. S. (2003b). Magnetic stimulation of motor and somatosensory cortices suppresses perception of ulnar nerve stimuli. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology, 48*(1), 25-33.

Meehan, S. K., Legon, W., & Staines, W. R. (2008). Paired-pulse transcranial magnetic stimulation of primary somatosensory cortex differentially modulates perception and sensorimotor transformations. *Neuroscience, 157*(2), 424-431.

Middleton, F. A., & Strick, P. L. (2000). Basal ganglia and cerebellar loops: Motor and cognitive circuits. *Brain Res Brain Res Rev, 31*(2), 236-250.

Milne, R. J., Aniss, A. M., Kay, N. E., & Gandevia, S. C. (1988). Reduction in perceived intensity of cutaneous stimuli during movement: A quantitative study. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 70*(3), 569-576.

Mima, T., Ikeda, A., Nagamine, T., Yazawa, S., Kunieda, T., Mikuni, N., et al. (1997). Human second somatosensory area: Subdural and magnetoencephalographic recording of somatosensory evoked responses. *Journal of Neurology, Neurosurgery, and Psychiatry, 63*(4), 501-505.

Mochizuki, H., Terao, Y., Okabe, S., Furubayashi, T., Arai, N., Iwata, N. K., et al. (2004). Effects of motor cortical stimulation on the excitability of contralateral motor and sensory cortices. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 158*(4), 519-526.

Morel, A., Liu, J., Wannier, T., Jeanmonod, D., & Rouiller, E. M. (2005). Divergence and convergence of thalamocortical projections to premotor and supplementary motor cortex: A multiple tracing study in the macaque monkey. *Eur J Neurosci, 21*(4), 1007-1029.

Morley, J. W., Vickery, R. M., Stuart, M., & Turman, A. B. (2007). Suppression of vibrotactile discrimination by transcranial magnetic stimulation of primary somatosensory cortex. *The European Journal of Neuroscience, 26*(4), 1007-1010.

Mountcastle, V. B., LaMotte, R. H., & Carli, G. (1972). Detection thresholds for stimuli in humans and monkeys: Comparison with threshold events in mechanoreceptive afferent nerve fibers innervating the monkey hand. *Journal of Neurophysiology, 35*(1), 122-136.

Mushiake, H., Inase, M., & Tanji, J. (1991). Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. *Journal of Neurophysiology, 66*(3), 705-718.

Nager, W., Wolters, C., Munte, T. F., & Johannes, S. (2004). Transcranial magnetic stimulation to the parietal lobes reduces detection of contralateral somatosensory stimuli. *Acta Neurologica Scandinavica, 109*(2), 146-150.

Nambu, A., Yoshida, S., & Jinnai, K. (1991). Movement-related activity of thalamic neurons with input from the globus pallidus and projection to the motor cortex in the monkey. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 84*(2), 279-284.

Nelson, R. J. (1996a). Interactions between motor commands and somatic perception in sensorimotor cortex. *Curr Opin Neurobiol, 6*(6), 801-810.

Nelson, R. J. (1996b). Interactions between motor commands and somatic perception in sensorimotor cortex. *Current Opinion in Neurobiology, 6*(6), 801-810.

Netz, J., Ziemann, U., & Homberg, V. (1995). Hemispheric asymmetry of transcallosal inhibition in man. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 104*(3), 527-533.

Nguyen, J. P., Lefaucheur, J. P., Decq, P., Uchiyama, T., Carpentier, A., Fontaine, D., et al. (1999). Chronic motor cortex stimulation in the treatment of central and neuropathic pain. correlations between clinical, electrophysiological and anatomical data. *Pain, 82*(3), 245-251.

Nudo, R. J. (1999). Recovery after damage to motor cortical areas. *Current Opinion in Neurobiology, 9*(6), 740-747.

Obhi, S. S., Haggard, P., Taylor, J., & Pascual-Leone, A. (2002). rTMS to the supplementary motor area disrupts bimanual coordination. *Motor Control, 6*(4), 319-332.

Oliveri, M., Babiloni, C., Filippi, M. M., Caltagirone, C., Babiloni, F., Cicinelli, P., et al. (2003). Influence of the supplementary motor area on primary motor cortex excitability during movements triggered by neutral or emotionally unpleasant visual cues. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 149*(2), 214-221.

Oliveri, M., Caltagirone, C., Filippi, M. M., Traversa, R., Cicinelli, P., Pasqualetti, P., et al. (2000). Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. *The Journal of Physiology, 529 Pt 2*, 461-468.

Oliveri, M., Rossini, P. M., Pasqualetti, P., Traversa, R., Cicinelli, P., Palmieri, M. G., et al. (1999). Interhemispheric asymmetries in the perception of unimanual and bimanual cutaneous stimuli. A study using transcranial magnetic stimulation. *Brain : A Journal of Neurology, 122 (Pt 9)*(Pt 9), 1721-1729.

Paul, D. D., & Sutton, S. (1973). Evoked potential correlates of psychophysical judgments: The threshold problem. A new reply to clark, butler, and rosner. *Behavioral Biology, 9*(4), 421-433.

Pavlides, C., Miyashita, E., & Asanuma, H. (1993). Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. *Journal of Neurophysiology, 70*(2), 733-741.

Pearson, K. (2000). Motor systems. *Current Opinion in Neurobiology, 10*(5), 649-654.

Pierantozzi, M., Mazzone, P., Bassi, A., Rossini, P. M., Peppe, A., Altibrandi, M. G., et al. (1999). The effect of deep brain stimulation on the frontal N30 component of somatosensory evoked potentials in advanced parkinson's disease patients. *Clin Neurophysiol, 110*(10), 1700-1707.

Pons, T. P., Garraghty, P. E., Friedman, D. P., & Mishkin, M. (1987). Physiological evidence for serial processing in somatosensory cortex. *Science, 237*(4813), 417-420.

Pons, T. P., Garraghty, P. E., & Mishkin, M. (1992). Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. *J Neurophysiol, 68*(2), 518-527.

Pons, T. P., & Kaas, J. H. (1986). Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: A correlative anatomical and electrophysiological study. *J Comp Neurol, 248*(3), 313-335.

Porter, L. L. (1991). Patterns of connectivity in the cat sensory-motor cortex: A light and electron microscope analysis of the projection arising from area 3a. *The Journal of Comparative Neurology, 312*(3), 404-414.

Porter, L. L. (1992). Patterns of projections from area 2 of the sensory cortex to area 3a and to the motor cortex in cats. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 91*(1), 85-93.

Rabin, E., & Gordon, A. M. (2004). Tactile feedback contributes to consistency of finger movements during typing. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 155*(3), 362-369.

Ragert, P., Dinse, H. R., Pleger, B., Wilimzig, C., Frombach, E., Schwenkreis, P., et al. (2003). Combination of 5 hz repetitive transcranial magnetic stimulation (rTMS) and tactile coactivation boosts tactile discrimination in humans. *Neuroscience Letters, 348*(2), 105-108.

Reding, M. J., & Potes, E. (1988). Rehabilitation outcome following initial unilateral hemispheric stroke. life table analysis approach. *Stroke; a Journal of Cerebral Circulation, 19*(11), 1354-1358.

Reilly, J. A., Hallett, M., Cohen, L. G., Tarkka, I. M., & Dang, N. (1992). The N30 component of somatosensory evoked potentials in patients with dystonia. *Electroencephalogr Clin Neurophysiol, 84*(3), 243-247.

Restuccia, D., Valeriani, M., Barba, C., Le Pera, D., Tonali, P., & Mauguiere, F. (1999). Different contribution of joint and cutaneous inputs to early scalp somatosensory evoked potentials. *Muscle & Nerve, 22*(7), 910-919.

Restuccia, D., Valeriani, M., Insola, A., Lo Monaco, M., Grassi, E., Barba, C., et al. (2002). Modality-related scalp responses after electrical stimulation of cutaneous and muscular upper limb afferents in humans. *Muscle & Nerve, 26*(1), 44-54.

Ridding, M. C., Inzelberg, R., & Rothwell, J. C. (1995). Changes in excitability of motor cortical circuitry in patients with parkinson's disease. *Annals of Neurology, 37*(2), 181-188.

Rizzolatti, G., Gentilucci, M., Camarda, R. M., Gallese, V., Luppino, G., Matelli, M., et al. (1990). Neurons related to reaching-grasping arm movements in the rostral part of area 6 (area 6a beta). *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 82*(2), 337-350.

Roland, P. E., Larsen, B., Lassen, N. A., & Skinhoj, E. (1980). Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J Neurophysiol, 43*(1), 118-136.

Romo, R., Merchant, H., Zainos, A., & Hernandez, A. (1997). Categorical perception of somesthetic stimuli: Psychophysical measurements correlated with neuronal events in primate medial premotor cortex. *Cerebral Cortex (New York, N.Y.: 1991), 7*(4), 317-326.

Romo, R., Ruiz, S., Crespo, P., Zainos, A., & Merchant, H. (1993). Representation of tactile signals in primate supplementary motor area. *J Neurophysiol, 70*(6), 2690-2694.

Romo, R., & Salinas, E. (2001). Touch and go: Decision-making mechanisms in somatosensation. *Annual Review of Neuroscience, 24*, 107-137.

Romo, R., & Salinas, E. (2003). Flutter discrimination: Neural codes, perception, memory and decision making. *Nature Reviews.Neuroscience, 4*(3), 203-218.

Rosen, I., & Asanuma, H. (1972). Peripheral afferent inputs to the forelimb area of the monkey motor cortex: Input-output relations. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 14*(3), 257-273.

Rossini, P. M. (1996). N30 in PD. *Neurology, 47*(1), 303-4; author reply 304-6.

Rossini, P. M., Babiloni, C., Babiloni, F., Ambrosini, A., Onorati, P., Carducci, F., et al. (1999a). "Gating" of human short-latency somatosensory evoked cortical responses during execution of movement. A high resolution electroencephalography study. *Brain Res, 843*(1), 161-170.

Rossini, P. M., Babiloni, F., Bernardi, G., Cecchi, L., Johnson, P. B., Malentacca, A., et al. (1989). Abnormalities of short-latency somatosensory evoked potentials in parkinsonian patients. *Electroencephalogr Clin Neurophysiol, 74*(4), 277-289.

Rossini, P. M., Bassetti, M. A., & Pasqualetti, P. (1995). Median nerve somatosensory evoked potentials. apomorphine-induced transient potentiation of frontal components in parkinson's disease and in parkinsonism. *Electroencephalogr Clin Neurophysiol, 96*(3), 236-247.

Rossini, P. M., Caramia, D., Bassetti, M. A., Pasqualetti, P., Tecchio, F., & Bernardi, G. (1996). Somatosensory evoked potentials during the ideation and execution of individual finger movements. *Muscle Nerve, 19*(2), 191-202.

Rossini, P. M., Paradiso, C., Zarola, F., Bernardi, G., Caramia, M. D., Margari, L., et al. (1991). Brain excitability and long latency muscular arm responses: Non-invasive evaluation in healthy and parkinsonian subjects. *Electroencephalogr Clin Neurophysiol, 81*(6), 454-465.

Rossini, P. M., Paradiso, C., Zarola, F., Mariorenzi, R., Traversa, R., Martino, G., et al. (1990). Bit-mapped somatosensory evoked potentials and muscular reflex responses in man: Comparative analysis in different experimental protocols. *Electroencephalogr Clin Neurophysiol, 77*(4), 266-275.

Rossini, P. M., Zarola, F., Stalberg, E., & Caramia, M. (1988). Pre-movement facilitation of motor-evoked potentials in man during transcranial stimulation of the central motor pathways. *Brain Research, 458*(1), 20-30.

Rothwell, J. C., Traub, M. M., Day, B. L., Obeso, J. A., Thomas, P. K., & Marsden, C. D. (1982). Manual motor performance in a deafferented man. *Brain : A Journal of Neurology, 105 (Pt 3)*(Pt 3), 515-542.

Rothwell, J.C., Colebatch, J., & Britton, T.C. (1991) Physiological studies in a patient with mirror movements and agenesis of the corpus-callosum. Journal of Physiology – London, 438, P34-P34.

Rouiller, E. M., Babalian, A., Kazennikov, O., Moret, V., Yu, X. H., & Wiesendanger, M. (1994). Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 102*(2), 227-243.

Rushton, D. N., Rothwell, J. C., & Craggs, M. D. (1981). Gating of somatosensory evoked potentials during different kinds of movement in man. *Brain, 104*(3), 465-491.

Sailer, A., Molnar, G. F., Paradiso, G., Gunraj, C. A., Lang, A. E., & Chen, R. (2003). Short and long latency afferent inhibition in parkinson's disease. *Brain : A Journal of Neurology, 126*(Pt 8), 1883-1894.

Salinas, E., & Romo, R. (1998). Conversion of sensory signals into motor commands in primary motor cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 18*(1), 499-511.

Satow, T., Mima, T., Yamamoto, J., Oga, T., Begum, T., Aso, T., et al. (2003). Short-lasting impairment of tactile perception by 0.9Hz-rTMS of the sensorimotor cortex. *Neurology, 60*(6), 1045-1047.

Schell, G. R., & Strick, P. L. (1984). The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *J Neurosci, 4*(2), 539-560.

Schmidt, R. F., Schady, W. J., & Torebjork, H. E. (1990). Gating of tactile input from the hand. I. effects of finger movement. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 79*(1), 97-102.

Schwark, H. D., Esteky, H., & Jones, E. G. (1992). Corticocortical connections of cat primary somatosensory cortex. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 91*(3), 425-434.

Serrien, D. J., Strens, L. H., Oliviero, A., & Brown, P. (2002). Repetitive transcranial magnetic stimulation of the supplementary motor area (SMA) degrades bimanual movement control in humans. *Neuroscience Letters, 328*(2), 89-92.

Seyal, M., Browne, J. K., Masuoka, L. K., & Gabor, A. J. (1993). Enhancement of the amplitude of somatosensory evoked potentials following magnetic pulse stimulation of the human brain. *Electroencephalography and Clinical Neurophysiology, 88*(1), 20-27.

Seyal, M., Masuoka, L. K., & Browne, J. K. (1992). Suppression of cutaneous perception by magnetic pulse stimulation of the human brain. *Electroencephalography and Clinical Neurophysiology, 85*(6), 397-401.

Seyal, M., Shatzel, A. J., & Richardson, S. P. (2005). Crossed inhibition of sensory cortex by 0.3 hz transcranial magnetic stimulation of motor cortex. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society, 22*(6), 418-421.

Shibasaki, H., & Hallett, M. (2006). What is the bereitschaftspotential? *Clin Neurophysiol, 117*(11), 2341-2356.

Shima, K., & Tanji, J. (1998). Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements. *Journal of Neurophysiology, 80*(6), 3247-3260.

Shima, K., & Tanji, J. (2000). Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. *Journal of Neurophysiology, 84*(4), 2148-2160.

Siebner, H. R., Auer, C., Ceballos-Baumann, A., & Conrad, B. (1999). Has repetitive transcranial magnetic stimulation of the primary motor hand area a therapeutic application in writer's cramp? *Electroencephalography and Clinical Neurophysiology.Supplement, 51*, 265-275.

Singh, L. N., Higano, S., Takahashi, S., Abe, Y., Sakamoto, M., Kurihara, N., et al. (1998). Functional MR imaging of cortical activation of the cerebral hemispheres during motor tasks. *AJNR.American Journal of Neuroradiology, 19*(2), 275-280.

Singh, L. N., Higano, S., Takahashi, S., Kurihara, N., Furuta, S., Tamura, H., et al. (1998). Comparison of ipsilateral activation between right and left handers: A functional MR imaging study. *Neuroreport, 9*(8), 1861-1866.

Slimp, J. C., Tamas, L. B., Stolov, W. C., & Wyler, A. R. (1986). Somatosensory evoked potentials after removal of somatosensory cortex in man. *Electroencephalogr Clin Neurophysiol, 65*(2), 111-117.

Smith, A. M. (1979). The activity of supplementary motor area neurons during a maintained precision grip. *Brain Research, 172*(2), 315-327.

Solodkin, A., Hlustik, P., Noll, D. C., & Small, S. L. (2001). Lateralization of motor circuits and handedness during finger movements. *European Journal of Neurology : The Official Journal of the European Federation of Neurological Societies, 8*(5), 425-434.

Staines, W. R., Graham, S. J., Black, S. E., & McIlroy, W. E. (2002). Task-relevant modulation of contralateral and ipsilateral primary somatosensory cortex and the role of a prefrontal-cortical sensory gating system. *NeuroImage, 15*(1), 190-199.

Starr, A., & Cohen, L. G. (1985). 'Gating' of somatosensory evoked potentials begins before the onset of voluntary movement in man. *Brain Res, 348*(1), 183-186.

Stefan K., Kunesch E., Cohen L.G., Benecke R., Classen J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain, 123(3), 572-84.*

Stepniewska, I., Sakai, S. T., Qi, H. X., & Kaas, J. H. (2003). Somatosensory input to the ventrolateral thalamic region in the macaque monkey: Potential substrate for parkinsonian tremor. *The Journal of Comparative Neurology, 455*(3), 378-395.

Steyvers, M., Etoh, S., Sauner, D., Levin, O., Siebner, H. R., Swinnen, S. P., et al. (2003). High-frequency transcranial magnetic stimulation of the supplementary motor area reduces bimanual coupling during anti-phase but not in-phase movements. *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 151*(3), 309-317.

Swayne, O., Rothwell, J., & Rosenkranz, K. (2006). Transcallosal sensorimotor integration: Effects of sensory input on cortical projections to the contralateral hand. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 117*(4), 855-863.

Talbot, W. H., Darian-Smith, I., Kornhuber, H. H., & Mountcastle, V. B. (1968). The sense of flutter-vibration: Comparison of the human capacity with response

patterns of mechanoreceptive afferents from the monkey hand. *Journal of Neurophysiology, 31*(2), 301-334.

Tamburin, S., Fiaschi, A., Idone, D., Lochner, P., Manganotti, P., & Zanette, G. (2003). Abnormal sensorimotor integration is related to disease severity in parkinson's disease: A TMS study. *Movement Disorders : Official Journal of the Movement Disorder Society, 18*(11), 1316-1324.

Tanji, J. (1985). Comparison of neuronal activities in the monkey supplementary and precentral motor areas. *Behav Brain Res, 18*(2), 137-142.

Tanji, J. (1994). The supplementary motor area in the cerebral cortex. *Neuroscience Research, 19*(3), 251-268.

Tanji, J. (2001). Sequential organization of multiple movements: Involvement of cortical motor areas. *Annual Review of Neuroscience, 24*, 631-651.

Tanji, J., Okano, K., & Sato, K. C. (1987). Relation of neurons in the nonprimary motor cortex to bilateral hand movement. *Nature, 327*(6123), 618-620.

Tanji, J., Okano, K., & Sato, K. C. (1988). Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. *Journal of Neurophysiology, 60*(1), 325-343.

Tanji, J., & Shima, K. (1994). Role for supplementary motor area cells in planning several movements ahead. *Nature, 371*(6496), 413-416.

Tapia, M. C., Cohen, L. G., & Starr, A. (1987). Selectivity of attenuation (i.e., gating) of somatosensory potentials during voluntary movement in humans. *Electroencephalogr Clin Neurophysiol, 68*(3), 226-230.

Tegenthoff, M., Ragert, P., Pleger, B., Schwenkreis, P., Forster, A. F., Nicolas, V., et al. (2005). Improvement of tactile discrimination performance and enlargement of cortical somatosensory maps after 5 hz rTMS. *PLoS Biology, 3*(11), e362.

Teitti, S., Maatta, S., Saisanen, L., Kononen, M., Vanninen, R., Hannula, H., et al. (2008). Non-primary motor areas in the human frontal lobe are connected directly to hand muscles. *NeuroImage, 40*(3), 1243-1250.

Terao, Y., Furubayashi, T., Okabe, S., Mochizuki, H., Arai, N., Kobayashi, S., et al. (2007). Modifying the cortical processing for motor preparation by repetitive transcranial magnetic stimulation. *Journal of Cognitive Neuroscience, 19*(9), 1556-1573.

Terao, Y., Ugawa, Y., Enomoto, H., Furubayashi, T., Shiio, Y., Machii, K., et al. (2001). Hemispheric lateralization in the cortical motor preparation for human vocalization. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 21*(5), 1600-1609.

Thaler, D., Chen, Y. C., Nixon, P. D., Stern, C. E., & Passingham, R. E. (1995). The functions of the medial premotor cortex. I. simple learned movements. *Exp Brain Res, 102*(3), 445-460.

Tsuji, T., & Rothwell, J. C. (2002). Long lasting effects of rTMS and associated peripheral sensory input on MEPs, SEPs and transcortical reflex excitability in humans. *The Journal of Physiology, 540*(Pt 1), 367-376.

Urushihara, R., Murase, N., Rothwell, J. C., Harada, M., Hosono, Y., Asanuma, K., et al. (2006). Effect of repetitive transcranial magnetic stimulation applied over the premotor cortex on somatosensory-evoked potentials and regional cerebral blood flow. *NeuroImage, 31*(2), 699-709.

Verstynen, T., Diedrichsen, J., Albert, N., Aparicio, P., & Ivry, R. B. (2005). Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *Journal of Neurophysiology, 93*(3), 1209-1222.

Verwey, W. B., Lammens, R., & van Honk, J. (2002). On the role of the SMA in the discrete sequence production task: A TMS study. transcranial magnetic stimulation. *Neuropsychologia, 40*(8), 1268-1276.

Vogt, B. A., & Pandya, D. N. (1978). Cortico-cortical connections of somatic sensory cortex (areas 3, 1 and 2) in the rhesus monkey. *The Journal of Comparative Neurology, 177*(2), 179-191.

Waberski, T. D., Buchner, H., Perkuhn, M., Gobbele, R., Wagner, M., Kucker, W., et al. (1999). N30 and the effect of explorative finger movements: A model of the contribution of the motor cortex to early somatosensory potentials. *Clin Neurophysiol, 110*(9), 1589-1600.

Wasaka, T., Nakata, H., Akatsuka, K., Kida, T., Inui, K., & Kakigi, R. (2005). Differential modulation in human primary and secondary somatosensory cortices during the preparatory period of self-initiated finger movement. *The European Journal of Neuroscience, 22*(5), 1239-1247.

Werhahn, K.J., Mortensen, J., Van Boven, R.W., Zeuner, K.E., Cohen, L.G. (2002) Enhanced tactile spatial acuity and cortical processing during acute hand deafferentation. *Nat. Neurosci, 5(10), 936-938.*

Wiesendanger, M. (1986). Recent developments in studies of the supplementary motor area of primates. *Reviews of Physiology, Biochemistry and Pharmacology, 103*, 1-59.

Wiesendanger, M., Hummelsheim, H., & Bianchetti, M. (1985). Sensory input to the motor fields of the agranular frontal cortex: A comparison of the precentral, supplementary motor and premotor cortex. *Behav Brain Res, 18*(2), 89-94.

Wiesendanger, R., & Wiesendanger, M. (1985). The thalamic connections with medial area 6 (supplementary motor cortex) in the monkey (macaca fascicularis). *Experimental Brain Research.Experimentelle Hirnforschung.Experimentation Cerebrale, 59*(1), 91-104.

Williams, S. R., Shenasa, J., & Chapman, C. E. (1998). Time course and magnitude of movement-related gating of tactile detection in humans. I. importance of stimulus location. *Journal of Neurophysiology, 79*(2), 947-963.

Wu C.W., van Gelderen P., Hanakawa T., Yaseen Z., & Cohen L. G. (2005). Enduring representational plasticity after somatosensory stimulation. *Neuroimage, 27(4), 872-84.*

Yoo, W. K., You, S. H., Ko, M. H., Tae Kim, S., Park, C. H., Park, J. W., et al. (2008). High frequency rTMS modulation of the sensorimotor networks: Behavioral changes and fMRI correlates. *NeuroImage, 39*(4), 1886-1895.

Ziemann, U., & Hallett, M. (2001). Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: Further evidence for motor dominance. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 112*(1), 107-113.

Ziemann, U., Ishii, K., Borgheresi, A., Yaseen, Z., Battaglia, F., Hallett, M., et al. (1999). Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles. *The Journal of Physiology, 518 (Pt 3)*(Pt 3), 895-906.

Ziemann, U., Muellbacher, W., Hallett, M., & Cohen, L. G. (2001). Modulation of practice-dependent plasticity in human motor cortex. *Brain : A Journal of Neurology, 124*(Pt 6), 1171-1181.