

**Cortical and behavioural adaptations induced by
bimanual movement training: an electrophysiological
study in the healthy population**

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

Abstract

Bimanual movement training (BMT) of the upper extremity has been found to improve sensorimotor function of the stroke affected limb for some patients; however, the neurophysiological mechanism underlying behavioural enhancement remains unclear. Determining a measurement tool to gauge within-session cortical excitability modulations in response to training would be advantageous for stroke rehabilitation practitioners not only to understand the mechanism underlying behavioural enhancement, but it would also assess the usefulness of training interventions from an individualistic perspective. The purposes of the current thesis were four fold: 1) to gain a better understanding of the neurophysiological effects of short-term visually cued BMT, of varying types, upon the trained bimanual task and those that generalize to a unimanual task by way of the cue-related movement-related potential (MRP). 2) To determine the generators of the cue-related MRP, an event-related potential (ERP) associated with the preparation and execution of a cued movement versus the Bereitschaftspotential (BP), a similar ERP associated with self-paced movement, 3) to investigate kinematic parameters that may influence the cue-related MRP and 4) to investigate the usefulness of the MRP as a future measurement tool to assess within-session changes of cortical excitability associated with training interventions in the stroke patient population. For the purposes of establishing control data for future stroke related studies, the current thesis was devised to investigate the healthy population.

We hypothesized that inphase (homologous motor movement) BMT more so than antiphase (antagonistic motor movement) BMT would induce cortical excitability modulations within preparatory and executory cortical regions for the trained bimanual

task and a similar unimanual task. Two experiments using EEG and subsequent cue-related MRP revealed that inphase BMT more so than antiphase BMT enhanced the amplitude of the early MRP component denoting preparatory excitability, but not the late MRP component representing executory excitability, and this modulation would also occur despite a simulated flexion contracture. The localization of the cue-related early MRP was found to be predominantly over the lateral premotor cortex, differing from the self-paced early BP determined to predominantly represent SMA excitability. Further confirmation of the localization of the cue-related early MRP versus the self-paced early BP was obtained in another experiment where it was revealed that cued inphase BMT did not affect the amplitude of the early BP (SMA excitability) of a self-paced movement; therefore, cued inphase BMT did not modulate SMA excitability. In a fourth experiment, kinematic parameters such as movement rate, range of motion (ROM) and force production at movement onset or as an inertial load were assessed in relation to modulations of the three cue-related MRP components. The results indicated that the various kinematic parameters had differential modulatory effects upon the cue-related MRP. As a whole, the results of the thesis indicated that 1) the cue-related MRP can be used to assess within-session training-related cortical adaptations in response to inphase BMT. 2) MRP modulations in response to cued inphase BMT remain evident despite a restriction of range of motion and imposed tonic load, indicating the potential to use the MRP in the stroke patient population in future research. 3) The localization of the early MRP component of a cue-related movement originates from the lateral premotor cortex versus the SMA responsible for the early BP component of a self-paced movement, and 4) in order to use the MRP as a measure of cortical excitability, kinematic parameters such as a load placed upon the

musculature must be controlled in an experimental design. The results of the experiments provide insight into the use of the cue-related **MRP** as a measure of cortical excitability modulation in response to cued inphase **BMT**, and will inform future training-related studies using the cued **MRP** as a measure of learning related adaptation in the healthy and stroke patient populations.

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May the fire of intellect
the soul's light to mind
Show us the torchbearer's path
to the height she climbed
And may the material of thought
fuel the flame of insight
On the journey of our souls
quest for right

Ralph Waldo Emerson

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List of Abbreviations

| | |
|-----------|--|
| APBT - | Active-passive bimanual training |
| BEM - | Boundary element model |
| BMT - | Bimanual movement training |
| BOLD - | Blood oxygen level dependent |
| BP - | Self-paced Bereitschaftspotential |
| CDR - | Current density reconstruction |
| CIT - | Constraint induced therapy |
| CNV - | Contingent negative variation |
| ECR - | Extensor carpi radialis |
| ECU - | Extensor carpi ulnaris |
| ED - | Extensor digitorum |
| EEG - | Electroencephalography |
| EMG - | Electromyography |
| ERP - | Event-related potential |
| fMRI - | Functional magnetic resonance imaging |
| FCR - | Flexor carpi radialis |
| FDS - | Flexor digitorum superficialis |
| GABA - | Gamma-aminobutyric-acid |
| GMP - | Generalized motor program |
| LFP - | Local field potential |
| LTP - | Long-term potentiation |
| M1 - | Primary motor cortex |
| MEP - | Motor evoked potential |
| MFP - | Maximum force production |
| MGFP - | Mean global field power |
| MP - | Motor potential |
| MRI - | Magnetic resonance imaging |
| MRP - | Cue-related movement-related potential |
| MT - | Movement time |
| NMDA - | N-methyl-D-aspartic acid |
| NS - | Negative slope |
| P1 - | First positive deflection |
| PM - | Premotor |
| PMd - | Dorsal premotor cortex |
| PPC - | Posterior parietal cortex |
| Pre-SMA - | Pre-supplementary motor area |
| RAP - | Re-afferent potential |
| ROM - | Range of motion |
| rTMS - | Repetitive transcranial magnetic stimulation |
| RT - | Reaction time |
| S1 - | Primary sensory cortex |
| sLORETA - | Standardized low resolution brain electromagnetic tomography |
| SMA - | Supplementary motor area |
| TMS - | Transcranial magnetic stimulation |

Chapter One - Introduction

Overview of thesis

The thesis begins with a statement of the general objectives followed by a review of the relevant literature including such topics as: 1) theories of bimanual movement, 2) cortical regions associated with bimanual movement, 3) bimanual learning and plasticity, 4) bimanual training in the stroke patient population, 5) event-related potentials in response to self-paced versus externally cued movement and 6) cortical mediation of self-paced versus externally cued movement. The last section of Chapter 1 will introduce the specific research objectives that guided the path of this thesis. Subsequent chapters detail the research studies performed to address the research questions, followed by a general and future research discussion.

General objectives of the thesis

The objectives of this thesis were fourfold: 1) to gain a better understanding of the neurophysiological effects of short-term bimanual movement training (**BMT**), of varying types, upon the trained bimanual task and those that generalize to a unimanual task, in the healthy population, 2) to determine the generators of the cue-related movement-related potential (**MRP**), an event-related potential (**ERP**) associated with the preparation and execution of a cued movement versus the **Bereitschaftspotential (BP)**, a similar **ERP** associated with self-paced movement, and 3) to investigate various kinematic parameters that may influence the amplitude of the cue-related **MRP**. 4) Lastly, to investigate the usefulness of the cue-related **MRP** as a future measurement tool to assess within-session changes of cortical excitability associated with training interventions in the stroke patient

population. Despite several studies indicating the behavioural efficacy of BMT as a viable stroke rehabilitation protocol (Cauraugh & Kim, 2002; McCombe Waller & Whittall, 2004; Mudie & Matyas, 2000; Whittall et al., 2000) few studies thus far (Luft et al., 2004; Stinear, Barber, Coxon, Fleming, & Byblow, 2008) have investigated the neurophysiological mechanisms underlying the behavioural enhancements observed in response to bimanual training.

Due to the lack of knowledge regarding cortical and behavioural effects following BMT in the stroke patient population, understanding how varying types of BMT modulate cortical excitability and behaviour in the healthy population is an imperative initial step for future stroke related studies that could inform the development of rehabilitative methods for the stroke patient population. Additionally, establishing a measurement tool (i.e. the cue-related MRP) to gauge cortical changes during and following BMT would be very beneficial in order to quantify: 1) cortical excitability modulations in response to training strategies in the stroke population and 2) the patient's responsiveness to the type of BMT imposed during rehabilitation.

Background research

Theories of bimanual movement

The ability to execute a complex bimanual movement, one that requires skilled independent movements of each hand, demands the suppression of the propensity to couple limb movements spatially and temporally. Investigations of rhythmic coordination highlight the innate desire to meld a bimanual movement into activation of homologous muscles so that both limbs perform the same movements simultaneously; such movement is termed inphase bimanual movement (Franz, 1997; Kelso, Southard, & Goodman,

1979a; Kelso, Southard, & Goodman, 1979b; Kelso, 1984). Conversely, antiphase bimanual movement is the activation of antagonistic muscles; this mode of coordination is highly complex and is not fully understood in terms of the cortical mechanisms that underlie such movement capability. There are three main theories as to how the brain allows bimanual movement to occur: 1) the generalized motor program (GMP) theory, 2) the intermanual crosstalk model and 3) the dynamic systems approach (for review see Cardoso de Oliveira, 2002).

Described by Schmidt et al. (1979) the generalized motor program (GMP) theory asserts that movement patterns are stored within the central nervous system (CNS) as a motor program. The motor program is thought to contain the required “shape” for a movement (Cardoso de Oliveira, 2002); the movement parameters (amplitude, temporal or force characteristics) just need be specified. Schmidt et al. (1979) suggested that this theory could apply to bimanual movements in that one motor program could represent movement of bilateral wrists, for example stable inphase bimanual movement (Schmidt, 1975).

The intermanual crosstalk model (Marteniuk & MacKenzie, 1980) assumes that bimanual coordination is mediated by interhemispheric interaction via cortico-cortical connections through the corpus callosum (Cardoso de Oliveira, 2002). There are two levels of crosstalk: low and high. Low-level crosstalk pertains to the ipsilateral cortical activation of muscles by uncrossed corticospinal neurons leading to the assimilation of movements that are inphase in nature. High-level crosstalk is thought to occur between M1 and premotor regions via callosal connections that link the two hemispheres (Cardoso de Oliveira, 2002).

Lastly, the dynamic systems model theorizes that bimanual movement is controlled by cooperative interaction or oscillation (Swinnen, 2002) between cortical regions (Cardoso de Oliveira, 2002). Therefore, movement occurs due to a distributed network with no one part responsible for an action (Cardoso de Oliveira, 2002).

Cortical regions associated with bimanual movement

The primary motor cortex (M1) is a prominent cortical region implicated in bimanual movement mediation (Cardoso de Oliveira, 2002). Although some studies have indicated the important role of the M1 of the left hemisphere for bimanual performance (Jancke, Shah, & Peters, 2000; Oda & Moritani, 1996; Ullen, Forssberg, & Ehrsson, 2003; Urbano et al., 1998), other authors have contributed evidence to support the idea that both M1 regions act as a functional syncytium (Cardoso de Oliveira, 2002). Therefore, how the M1 mediates bimanual movement is not fully understood.

Another region primarily implicated in bimanual movement mediation is the SMA. Bilateral SMA regions receive thalamocortical input from the globus pallidus (GP) of the basal ganglia (BG) (Hoover & Strick, 1993) and just as the M1; each SMA region is interconnected through the corpus callosum (CC) with its contralateral homologue (Rouiller, Babalian, Kazennikov, Moret, Yu, & Wiesendanger, 1994a). The SMA projects to the ipsilateral and contralateral M1, in addition to a direct connection to the spinal cord; therefore, electrical stimulation of the SMA unilaterally can create a bimanual movement (Fried et al., 1991; Penfield & Welch, 1951). The SMA participates in planning (Gerloff, Corwell, Chen, Hallett, & Cohen, 1997; Tanji & Shima, 1994) and execution of unimanual and bimanual movement (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Rouiller, Babalian, Kazennikov, Moret, Yu, & Wiesendanger, 1994b; Sadato, Yonekura,

Waki, Yamada, & Ishii, 1997; Shibasaki et al., 1993; Toyokura et al., 1999; Wiesendanger, Rouiller, Kazennikov, & Perrig, 1996) and it is one of the primary regions thought to contain the GMP for bimanual movement. A myriad of evidence exists attesting to the role of the SMA in bimanual coordination. However, it is reported to have greatest activation during antiphase bimanual movements compared to inphase bimanual movement (Goerres, Samuel, Jenkins, & Brooks, 1998; Sadato et al., 1997; Toyokura et al., 1999).

Even though the SMA is the region most implicated as coordinating bimanual movement, studies show that there are differentially activated cortical regions during inphase versus antiphase bimanual movement (Immisch, Waldvogel, van Gelderen, & Hallett, 2001; Sadato et al., 1997; Steyvers et al., 2003). Studies of Parkinson's disease patients (Johnson et al., 1998) have revealed that the SMA is crucial for the execution of self-paced antiphase or inphase bimanual movement; however, it is not predominantly required for externally cued inphase bimanual movement. Difficulty in executing self-paced bimanual movement versus externally triggered inphase movement is also found in SMA lesioned patients (Brinkman, 1981).

The cingulate motor area is immediately ventral to the SMA. The cingulate cortex is not a primary region implicated in bimanual movement however it has been found to increase in activity more so during antiphase bimanual movement versus inphase movement (Goerres et al., 1998; Jancke et al., 2000; Sadato et al., 1997; Stephan et al., 1999; Swinnen, 2002) and when lesioned, spatial and temporal bimanual coordination deteriorates (Stephan et al., 1999).

The posterior parietal cortex (PPC) is an area most likely the site of visuomotor integration and lesion studies have found that injury to the PPC results in impaired

bimanual coordination (Serrien, Nirkko, Lovblad, & Wiesendanger, 2001). Specifically, injury to the PPC results in disruption of antiphase bimanual movement rather than inphase bimanual movement. Other investigations of parietal lesions have reported similar results that antiphase pantomime movements (Halsband et al., 2001) and antiphase prehension movements (Jackson et al., 2000) are disrupted but inphase bimanual movements remain intact.

The cerebellum is a region linked to the temporal coupling of a bimanual movement (Ivry & Richardson, 2002), particularly the lateral portion (Ivry, Keele, & Diener, 1988). Investigations of patients with cerebellar lesions present with heightened temporal variability of the ipsilesional hand (Franz, Eliassen, Ivry, & Gazzaniga, 1996; Ivry et al., 1988), which is improved with inphase bimanual movement (Franz et al., 1996), this is termed the “bimanual advantage”. Pollok et al. (2005) links the “bimanual advantage” to functional connectivity between the cerebellar hemispheres, and it is not observed when subjects execute a unimanual movement or antiphase bimanual movement (Pollok, Butz, Gross, & Schnitzler, 2007). Therefore, the cerebellum has particular mediation in the temporal control of inphase bimanual movement.

Lastly, the basal ganglia is implicated in bimanual movement mediation. Studies of Parkinson’s disease patients reveal difficulty performing externally cued antiphase bimanual movement and self-generated antiphase or inphase bimanual movement; however, performance of a cued inphase bimanual movement remains intact.

The cerebral structure most important to the crosstalk theory is the corpus callosum. The corpus callosum represents the major cerebral commissure connecting both hemispheres (Stancak, Cohen, Seidler, Duong, & Kim, 2003) and is thought to be

required to shape the interactions between the movements of the two limbs (Cardoso de Oliveira, 2002). Lesion studies in acallosal patients show a deficit in temporal and spatial coordination of novel antiphase bimanual movement (Eliassen, Baynes, & Gazzaniga, 1999; Franz et al., 2000; Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002; Preilowski, 1972; Sperry, 1968) and show that an intact corpus callosum is necessary to learn novel antiphase bimanual movements (Franz et al., 2000). However, old bimanual patterns remain intact (Preilowski, 1972; Sperry, 1968).

Bimanual learning & plasticity

It is not known which cortical areas undergo plasticity in response to bimanual training and the temporal evolution of this change (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2004). Doyon et al. (2003) and Hikosaka et al (1999) argue that the association cortices namely the prefrontal-parietal network is primarily involved in early learning and the motor cortices (M1 and SMA) are involved when the task is well learned. This information however pertains to unimanual learning. It is unclear if it applies to bimanual learning as well.

A phenomenal feature of the M1 is the ability to change and mediate recovery following an injury. The primary motor cortex, among other cortical regions, is constantly changing in terms of cortical connection and representation. Huntley (1997) explained that representational maps of limb segments in the motor cortex are dynamic, and are able to reorganize due to afferent input, for example, peripheral nerve block (Donoghue, Suner, & Sanes, 1990; Sanes, Suner, Lando, & Donoghue, 1988) amputation (Cohen, Bandinelli, Findley, & Hallett, 1991), electrical stimulation (Nudo, Jenkins, & Merzenich, 1990), ischemic infarct (Nudo & Milliken, 1996), injection of bicuculline (a GABA-A receptor

block) (Jacobs & Donoghue, 1991) and motor learning (Karni et al., 1995; Nudo, Milliken, Jenkins, & Merzenich, 1996). With varying levels of afferent input, the map begins to recede or expand into or away from neighbouring regions via horizontal connections (Huntley, 1997). This theory was confirmed in studies that found reorganization is indeed mediated by pre-existing horizontal connections of intrinsic pyramidal cells in layers II, III and V that traverse representational borders. A depression of GABAergic activity is required to unmask these latent connections (Jacobs & Donoghue, 1991; Kaas, Merzenich, & Killackey, 1983). However, it is only certain parts of the representational map, which contain horizontal connections that undergo plasticity. In studies of the macaque monkey it was found that there were extensive horizontal connections between the digits, wrist, elbow and shoulders; however, very little if any connection between the forelimb and face. The areas with connectivity exhibited activity dependent plasticity. Also in a study by Nudo et al. (1990) it was found that finger and wrist movement training in the monkey model induced motor map reorganization with subsequent performance enhancement; however, the representation of the hand did not enlarge significantly. Instead the representation of the particular movement or movement sequence of the digits and wrist expanded into neighbouring regions; therefore, decreasing the representation of areas that were utilized less.

These data suggest that horizontal connection topography imposes limitations on the path of reorganization (Darian-Smith & Gilbert, 1995). Therefore, it seems that horizontal connections are a major anatomical substrate for motor map modulation during the early phases of motor learning. This, however, does not imply that horizontal connections are the exclusive mediator of short-term plasticity. There is evidence that synapse efficacy can

change under proper conditions (Meftah & Rispal-Padel, 1994). Despite this, it seems the first step to reorganization is unmasking of horizontal connections, in layers II, III and V (Huntley, 1997; Jacobs & Donoghue, 1991).

The initial stages in activating latent horizontal connections in layers II and III of M1 involve increased or decreased cortical excitability. However, note that it is an increase in excitatory activity that eventually leads to representational modulation or plasticity. The underlying mechanism of cortical plasticity and reorganization in the M1 is long-term potentiation (LTP). Long-term potentiation begins with inhibition of GABAergic activity, enabling designated neurons to secrete glutamate; therefore, initiating depolarization that stimulates, postsynaptically, the N-methyl-D-aspartate (NMDA) receptors, allowing an influx of calcium (Buonomano & Merzenich, 1998). The increased excitation induces reorganization of specified cortical areas. Butefisch et al. (2000) found that inhibition of GABAergic activity and NMDA receptors was crucial for LTP because the process of LTP could be prevented if the above two factors were blocked pharmacologically. For example, lorazepam, a drug that increased GABAergic function inhibited LTP and dextromethorphan, a drug that blocked NMDA receptors also blocked LTP. Following LTP, or increased cortical excitation, synaptogenesis (or the sprouting of new axonal connections in the M1) occurs, solidifying the new cortical representation of the novel movement skill. Kleim et al. (2004) shows synapse number significantly increasing after 7-10 days.

According to Classen and colleagues (1998) motor skill learning, also termed learning-related plasticity, can occur within a short time frame within the M1. Using transcranial magnetic stimulation (TMS), Classen et al. (1998) evoked a series of right

thumb flexion movements. Subjects then practiced right thumb extension for 30 minutes. It was found that TMS of the original motor cortical area produced the new trained thumb extension movement. This effect indicated that motor learning in addition to occurring quickly, represented kinematic details of the practiced movement within the M1.

Kinematic details defined as direction. Classen et al. (1998) believed the most important factor influencing the early stage of plasticity in the M1 was the initial movement direction or force. This is logical since these factors are most represented within the M1. However, it must be noted that neither repetition of unskilled movement, strength training, or exercise training is sufficient to induce plasticity (Kleim et al., 2004). The task must be novel and progress to a skilled movement.

Bimanual training - Stroke patient population

Is bimanual movement training (BMT) an effective rehabilitation strategy for stroke survivors with hemiparesis? And if so, what mechanisms could mediate a behavioural change in response to this type of training? A theoretical model has been developed by Mudie and Matyas (2000) that implicates the unaffected hemisphere as an aid to the affected hemisphere leading to reorganization of corticomotoneuronal cells and therefore motor output. Mudie and Matyas (2000) observed that stroke patients improved their ability to produce coordinated movements when executing a task bimanually. Specifically, when both the affected and unaffected limbs were trained in an inphase reach to target task, movements of the affected limb became more coordinated versus moving the affected limb alone or following antiphase bimanual training.

How does BMT utilize both hemispheres? It has been shown that inphase bimanual movement in the healthy population leads to disinhibition of the contralateral hemisphere

(Stinear & Byblow, 2004a). Traditionally, stroke rehabilitation protocols have focused upon unimanual movement tasks for the affected upper limb (Kunkel et al., 1999; Ostendorf & Wolf, 1981; Taub & Morris, 2001). Passive movement is another common rehabilitative method (Nakayama, Jorgensen, Raaschou, & Olsen, 1994) or compensatory training of the unaffected limb (Olsen, 1989). More recently constraint-induced therapy has been added to treatment protocols (Liepert et al., 1998). According to Whitall et al. (2000) stroke rehabilitation has also traditionally focused upon the first three months following a stroke since it was found that recovery plateaus after 3-5 months (Jorgensen, Nakayama, Raaschou, Vive-Larsen, Stoier, & Olsen, 1995a; Jorgensen, Nakayama, Raaschou, Vive-Larsen, Stoier, & Olsen, 1995b). But in recent years, the time line of motor recovery has been challenged. Several animal studies have shown use-dependent plasticity leading to improved functional recovery long after the three month period has lapsed (Nudo & Milliken, 1996; Nudo et al., 1996; Nudo, Wise, SiFuentes, & Milliken, 1996).

Whitall et al. (2000) contend that the forced use strategy with task specificity used in the constraint-induced protocol and in the Nudo et al. (1996a; 1996b & 1996c) experiments were the key to drive enhanced motor recovery in the stroke population. Therefore, Whitall et al. (2000) in addition to McCombe-Waller and Whitall (2004) extend the forced-use paradigm in the form of a repetitive bimanual arm-training task with rhythmic auditory cueing (BATRAC) to assess the behavioural outcomes from such a task. These studies showed that all behavioural tests significantly improved following BATRAC (Whitall et al., 2000) in addition to fine motor control of the hand (McCombe Waller and Whitall, 2004). Cauraugh and Kim (2002) have found similar results with a coupled

protocol utilizing both EMG triggered neuromuscular stimulation in conjunction with bimanual movement training (BMT) in chronic hemiparetic stroke patients.

Few studies have investigated the neurophysiological mechanisms underlying the effects of bimanual training on cortical activity and corresponding behaviour in the healthy or stroke patient populations. In an EEG study, using healthy subjects, by Smith and Staines (2006), BMT caused a cortical excitability change in half the subjects for a unimanual task. The cortical excitability change was also associated with a behavioural improvement of the unimanual wrist flexion task. By measuring the cue-related movement-related potential (MRP) Smith and Staines (2006) found that the early component (preparatory excitability) of the MRP significantly increased in negativity for half of the subjects following BMT and this was associated with a significant decrease in reaction time.

Two studies, one using fMRI and one using TMS, have been published assessing mechanisms of cortical excitability changes following a BMT protocol in the stroke patient population. Luft et al. (2004) used fMRI to measure cortical activity change in response to the same BATRAC protocol as Whitall (2000) and McCombe-Waller and Whitall (2004) versus a dose matched therapeutic exercise protocol. Areas that showed a significant increase in activation following BATRAC included: the contralesional cerebellum, M1 and PM cortex. Therefore, Luft et al. (2004) demonstrated cortical reorganization of contralesional motor-related areas following BATRAC compared to the control group.

In a study by Stinear and Byblow (2008a) TMS was used to assess the role of active-passive bimanual movement training (APBT) on corticomotor function and excitability of wrist muscle representations. Active-passive bimanual movement training was defined as

moving the affected wrist through flexion and extension passively by active wrist flexion and extension of the unaffected hand via a manipulandum. Movement patterns were executed in an inphase manner. Stinear and Byblow (2008a) found that motricity significantly increased following APBT and it was not dependent upon chronicity or impairment level; however, it seemed more useful for subcortical patients. Measurement of cortical map size revealed that APBT significantly decreased representational size in the unaffected M1 and patients with this map change also had a behavioural enhancement. The patients who did not have a map change in the unaffected hemisphere also did not exhibit a behavioural change following training.

Event-related potentials associated with self-paced versus cued movement

The self-paced Bereitschaftspotential

The Bereitschaftspotential (BP; Figure 1-1A) was first described by Kornhuber and Deecke (1965). It is a slow negative event-related potential (ERP) that is extracted from an EEG recording prior to and following self-paced movement onset. The BP can have an amplitude between 1 to 10 μ V and is generated by averaging 60 – 80 artifact free epochs time-locked to the onset of muscle activity (Colebatch, 2007). Traditionally, the BP has been recorded from discrete finger movements; however, this slow negative potential can also be recorded from the movement of the wrist, foot or tongue and ocular saccades (Jankelowitz & Colebatch, 2002; Milliken, Stokic, & Tarkka, 1999; Shibasaki, Barrett, Halliday, & Halliday, 1981; Smith & Staines, 2006; Thickbroom & Mastaglia, 1985).

The BP has several components (Fig. 1-1A): 1) the early BP component is a slow rising negative potential occurring between -2 s to -500 ms relative to movement onset (indicated at time zero) and is maximal in frontal midline electrode sites (FCZ, CZ). 2) The

later portion of the early BP has been further divided into another segment called the negative slope (NS), which occurs between -500 ms up to -50 ms prior to movement onset, 3) the late component is a peak negativity occurring between 70 - 160 ms after movement onset and it is lateralized over the M1 and 4) the re-afferent potential (RAP) with latency between 200-350 ms after movement onset. The early BP component is thought to be generated by the SMA (Cui et al., 1999; Deecke & Kornhuber, 1978), the NS within the SMA and contralateral M1, the late BP component within the contralateral M1 (Shibasaki & Hallett, 2006), and RAP within the contralateral S1. Even though subcortical activity occurs at the same time within the cerebellum, basal ganglia and thalamus, these structures do not contribute directly to the scalp recordings (Birbaumer et al., 1990; Rektor, 2002). There is great intersubject variability regarding the BP; some subjects may not exhibit all components (Colebatch, 2007; Deecke, Grozinger, & Kornhuber, 1976).

Factors that may affect the presentation of the BP include: 1) cortical anatomy; the orientation of neuronal populations may hinder the presentation of the BP. 2) How force production affects the BP is debatable. Siemionow et al. (2000) has shown that force increases the amplitude of the late BP component (M1 excitability), but Slobounov et al. (1998) argue that the late BP component is not affected, but the RAP is. 3) The effects of fatigue are variable. Johnston et al. (2001) and Dimberger et al. (2004) show that fatigue (defined as a decrease in maximum voluntary contraction) increases the amplitude of the late BP component (M1 excitability), while Schillings et al. (2006) reported that fatigue affects only the early BP component (SMA excitability). On the other hand, factors that do not seem to affect the components of the BP include: 1) age (Singh, Knight, Woods,

Beckley, & Clayworth, 1990), 2) movement amplitude and speed (Dick et al., 1987), 3) or muscle weakness caused by muscle paralysis (Jankelowitz & Colebatch, 2005).

Cue-related movement-related potential

The **Bereitschaftspotential** is a useful **ERP** in that it allows us to measure the amount of cortical excitability during motor preparation, execution and pertaining to the feedback of a self-paced movement. The cue-related movement-related potential (**MRP**) is a similar **ERP** to the self-paced **BP**; however, it is likely generated by differing cortical regions. The term **MRP** has been used previously in the literature to describe self-paced and cued **ERPs** (Cui & Mackinnon, 2009; Jahanshahi et al., 1995; Jankelowitz & Colebatch, 2002; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). In an EEG study by Jankelowitz and Colebatch (2002) it was reported that the **BP** and the cued **MRP** presented as similar, but the cued **MRP** did not have a distinction between the early component and negative slope (**NS**). The authors argued that the cued **MRP** was probably generated by the same structures as the **BP** (**SMA** and **M1**), but the cued **MRP** recruited these areas sooner; therefore, blurring the onset of the **NS**. Jahanshahi et al. (1995), on the other hand, did not agree that a similar network generated the **BP** and cued **MRP**. Jahanshahi et al. (1995) observed that the early **BP** component was not present in Parkinson's disease patients, but the cued early **MRP** component remained intact. Therefore, the two **ERPs** could not be generated by the same cortical structures.

Therefore, we are not the first to use a cued paradigm and subsequent cue-related **MRP** as a measurement tool. We are; however, the first to investigate the usefulness of the cue-related **MRP** as a measure of cortical excitability following a motor learning task. The only question is, which network governs the self-paced **BP** versus the cued **MRP**?

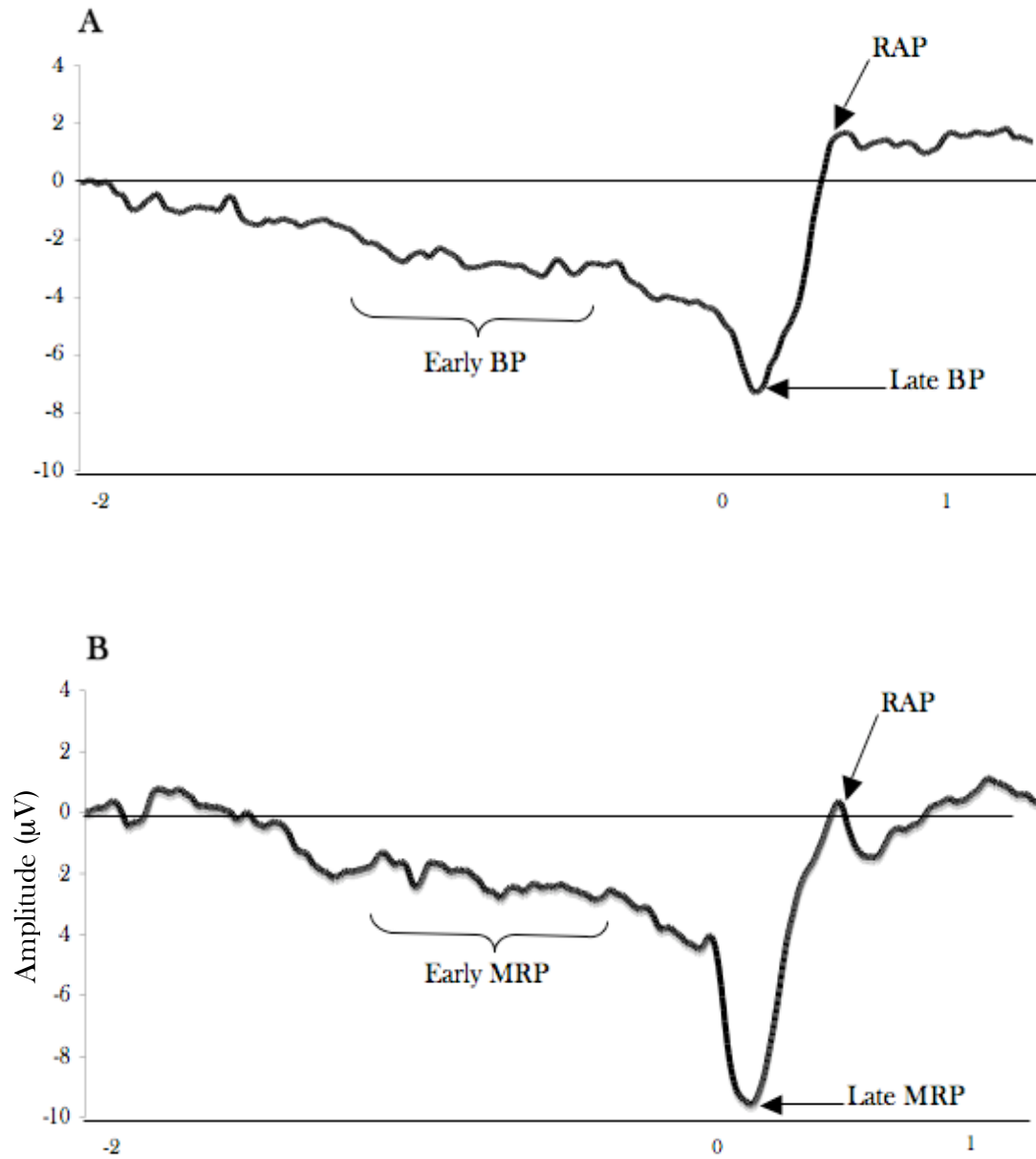


Figure 1-1 - (A) The self-paced Bereitschaftspotential (BP). (B) The cue-related movement-related potential (MRP). Data is shown for electrode site FCZ

Cued versus self-paced movement

Differing cortical networks generate cued and self-paced movements (Mushiake et al., 1991). More specifically, the SMA in addition to the BG, M1 and specific thalamic locations are predominantly active during self-paced movement (Crawford, Henderson, & Kennard, 1989; Halsband, Matsuzaka, & Tanji, 1994; Jenkins et al., 2000; Jueptner & Weiller, 1998; Kawashima et al., 2000; Kurata & Wise, 1988; Larsson, Gulyas, & Roland, 1996; MacMillan, Dostrovsky, Lozano, & Hutchison, 2004; Mushiake & Strick, 1995; Rao et al., 1997; Schultz & Romo, 1987; Van Donkelaar, Stein, Passingham, & Miall, 1999; Wessel, Zeffiro, Toro, & Hallett, 1997). On the other hand, externally triggered movements have been found to be mediated by parietal regions, areas of the cerebellum, specific areas of the thalamus, lateral premotor cortex and M1 (Jueptner, Jenkins, Brooks, Frackowiak, & Passingham, 1996; Jueptner & Weiller, 1998). Other studies have found conflicting results regarding the locus of internal or external movement generation. Deiber et al. (1991) found that the lateral premotor cortex was not activated more during externally triggered movement versus self-paced, and Remy et al. (1994) found more activation of the SMA during externally triggered movement opposed to self-paced movement.

Specific research objectives

Objective 1:

To gain a better understanding of the neurophysiological effects of short-term bimanual movement training (BMT), of varying types, upon the trained bimanual task and those that generalize to a unimanual task, in the healthy population.

In a previous study from our laboratory (Smith & Staines, 2006) we reported an increase in preparatory excitability for a one-handed task following a cued BMT paradigm comprised of inphase and antiphase bimanual movements. We also observed an increase of preparatory excitability in the later stage of the BMT paradigm. We could not discern if the observed modulations were primarily in response to the inphase or antiphase nature of the bimanual task. Dissociation of these two types of bimanual training is important to further understand training-related adaptation of the MRP and behaviour.

Hypotheses - 1) Bimanual movement training that emphasizes inphase, synchronous wrist movements, rather than antiphase asynchronous movements, will induce larger cortical adaptations within regions subserving motor preparation and execution. 2) Repetitive unimanual training would induce cortical activity modulations only associated with motor execution, and 3) training-induced cortical adaptations would be associated with enhanced behavioural performance.

Objective 2:

To determine the generators of the cue-related movement related potential (MRP), an ERP associated with the preparation and execution of a cued movement versus the Bereitschaftspotential (BP), a similar ERP associated with self-paced movement

The topography of the cue-related MRP (Fig. 1-1B) is similar to the self-paced BP in terms of exhibiting an initial slow negative slope called the early MRP component; a peak negativity termed the late MRP component and a re-afferent (RAP) potential. Cortical

localization of the self-paced BP reveals that the early BP component is primarily generated by the SMA, whilst the late BP component and RAP are generated by the M1 and S1 respectively. We hypothesize that the cue-related MRP, specifically the early MRP is generated predominantly by the lateral premotor cortex, in addition to the M1 (late MRP) and S1 (RAP).

Hypotheses – Cued inphase BMT has been reported to increase preparatory excitability of the cue-related MRP. We hypothesize that the lateral premotor cortex primarily underlies the observed preparatory activity. Conversely, the SMA primarily generates the preparatory excitability of the self-paced BP. Due to the differential cortical localization of the preparatory excitability of the two ERPs we hypothesize that specific training types can differentially modulate the preparatory activity of the two ERPs

Objective 3:

To investigate kinematic parameters that influence the cue-related MRP

Investigations of the self-paced BP have determined that range of motion, rate of movement and force modulate the amplitude of various components. It is possible that different cortical regions generate the cue-related MRP and therefore may be a different event-related potential compared to the self-paced BP. Therefore, understanding how various kinematic parameters affect the components of the cue-related MRP would inform experimental design utilizing the cue-related MRP in future research projects.

Hypothesis – Kinematic parameters such as movement rate, force production at movement onset or as an inertial load and range of motion will influence the amplitude of the cue-related MRP components.

Objective 4:

To investigate the usefulness of the cue-related MRP as a measure of cortical excitability modulation in response to cued inphase BMT with an imposed movement restriction and tonic load placed upon the musculature. This study was designed to assess the likelihood of using the cue-related MRP in the stroke patient population.

The cue-related MRP may be an effective measurement tool for cortical excitability modulations in response to bimanual movement training in future stroke-related studies.

However, most stroke patients present with a range of motion restriction and tonic muscle contraction due to spasticity. The typical posture imposed by a flexion contracture is flexion of the wrist and digits, which in turn causes a perpetual tonic contraction of the forearm flexors. It is unclear whether the cue-related MRP can be elicited during such a state or if learning effects measured by the MRP will still be evident. Healthy subjects were recruited as a first step before assessing the cue-related MRP in the stroke patient population.

Hypothesis - Despite an imposed range of motion restriction and tonic load placed upon the musculature, preparatory excitability will exhibit modulation in response to cued inphase BMT.

Chapter Two - Cortical and behavioural adaptations in response to short-term inphase versus antiphase bimanual movement training

Smith, A.L. & Staines, W.R.

Overview

Bimanual movement training (BMT) may be an effective rehabilitative protocol for movement related deficits following a stroke; however, it is unclear how varying types of BMT induce cortical adaptations and influence behaviour in the healthy population.

Therefore, the present study investigated the cortical and behavioural adaptations induced by cued inphase versus antiphase BMT upon a similar cued unimanual task in the healthy population ($n = 10$). Inphase BMT is defined as simultaneous activation of homologous muscle representations; therefore, two flexion or extension movements of the wrists.

Conversely, antiphase BMT is defined as activation of non-homologous (antagonist/agonist) muscle representations; therefore, one flexion with one extension movement of the wrists. Three specific hypotheses were investigated: 1) cued inphase BMT would induce cortical adaptations within regions subserving motor preparation and movement execution, 2) repetitive cued unimanual training would induce cortical activity modulations associated with motor execution, and 3) increased cortical activity would be associated with enhanced performance. All subjects participated on three separate days, EEG was recorded from 22 electrodes during three types of cued movement training: inphase BMT, antiphase BMT and repetitive unimanual movement, in addition to pre- and post-training unimanual movement trials that involved cued right wrist flexion.

Movement-related potentials (MRPs) related to motor preparation (early MRP), execution (late MRP) and sensory feedback (RAP) were quantified in each of these conditions.

There was a significant training-related increase in early MRP amplitude that correlated

with a decrease in reaction time following cued inphase BMT. During the cued inphase BMT intervention, early MRP amplitude increased during the later compared to the initial trials. No significant MRP modulation occurred in response to cued antiphase BMT or repetitive unimanual movement training either during or following the training intervention. These results suggest that simultaneous activation of homologous motor representations is important in inducing short-term training-related cortical motor adaptations.

Introduction

Of a variety of treatment strategies, bimanual movement training (BMT) of the upper limbs is one that has specifically shown some potential to lead to behavioural and functional improvement in both the subacute and chronic phases of stroke recovery (Cauraugh & Kim, 2002; Cuadrado & Arias, 2001; Luft et al., 2004; McCombe Waller & Whitall, 2008; Mudie & Matyas, 2000; Stewart, Cauraugh, & Summers, 2006; Whitall et al., 2000). Although there is some evidence that bimanual movement, involving both the damaged and intact hemispheres, may enhance motor-related brain activity in the stroke-hemisphere in some patients (Silvestrini, Cupini, Placidi, Diomedi, & Bernardi, 1998; Staines, Padilla, & Knight, 2002), the neurophysiological mechanisms that contribute to the benefits of BMT are not yet clear. More specifically, few studies to date (Luft et al., 2004; Stinear, Barber, Coxon, Fleming, & Byblow, 2008a) have reported on the underlying cortical excitability modulations that underlie observed behavioural improvements following BMT in stroke patients. Therefore, in this study we chose to take one step back from the stroke patient population and focus upon the healthy population to explore the possibility of using the cue-related movement-related potential (MRP), an event-related

potential (ERP) extracted from an EEG recording around cued movement onset, to assess cortical excitability transfer effects to a cued one-handed task following varying types of cued BMT. In this instance we were most interested in cortical excitability modulations in response to visually cued inphase versus antiphase BMT. The strategy of focusing in upon the healthy population allowed us to observe the effects of BMT upon cortical excitability and observe the use of the MRP to assess such effects without the added complication of cortical injury, and it allowed us to establish control data that can be used for future stroke related studies.

Previous authors have reported using ERPs to measure visuomotor learning in the healthy population. Staines et al. (2002) reported that the MRP, in response to a cue, in addition to an ERP extracted around the presentation of a cue, modulated in response to learning a novel unimanual visuomotor task using wrist extension. Subjects were asked to move a cursor on a computer screen using a joystick to a target in response to a visual cue. After a short duration, of approximately 30 minutes of practice, the components of the cue-related MRP and cue-related ERP were shown to change in amplitude. More specifically, the early and late components of the MRP were shown to increase in negativity, denoting an increase in cortical excitability, and the P1 component of the cue-related ERP decreased in amplitude. In another study by Hill (2009) an ERP comprising similar components to the MRP was extracted from an EEG recording in response to target trajectory change and movement error correction during a continuous unimanual target tracking task involving the use of a computer mouse, joystick or a combination of both. This study (Hill, 2009) showed that the prominent positive component of the measured ERP was enhanced in response to visuomotor learning. Therefore, these studies (Hill, 2009; Staines et al., 2002)

demonstrated that the **MRP** or other similar types of **ERPs** can measure cortical modulations during short duration novel visuomotor learning in healthy participants.

In a previous study from our laboratory (Smith & Staines, 2006) we also showed that the cue-related **MRP** could be used to measure learning related adaptations during a cued unimanual task in response to short duration cued bimanual movement training (**BMT**). In this study we investigated cortical adaptations associated with motor skill learning that required cued bimanual movement of inphase and antiphase nature in healthy individuals. Inphase bimanual movement specifically refers to movements of the homologous effectors in both limbs such as bilateral wrist flexion or extension, whereas antiphase movement refers to movements of the opposite effectors, such as right wrist flexion in conjunction with left wrist extension and vice versa. In our previous study (Smith & Staines, 2006), cortical adaptations were assessed using **MRPs** from scalp **EEG** recordings, time-locked to movement onset of a visually cued task that required flexion of the right wrist to move a cursor to a target, recorded before and after a single-session of cued **BMT**, which lasted approximately 45 minutes (Smith & Staines, 2006). Following novel bimanual training, incorporating both inphase and antiphase bimanual movement patterns, early **MRP** amplitudes were significantly enhanced and significantly associated with a decrease in reaction time (**RT**) during a similar cued unimanual task. This suggested that a single session of cued **BMT**, lasting approximately 45 minutes, produced transfer effects to a unimanual movement task. Therefore, we showed that the cue-related **MRP** had promise to quantify cortical adaptations that are rapidly induced and there was a possibility to use the **MRP** to assess cortical excitability modulations in response to

visuomotor learning and rehabilitative protocols in the healthy and possibly the stroke patient populations.

A question that we could not answer following our previous study (Smith & Staines, 2006) pertained to the specific type of bimanual coordination executed during BMT. We could not discern if there was a differential degree of cortical and behavioural adaptation following cued inphase versus cued antiphase bimanual training. Past stroke related studies have observed that inphase more so than antiphase bimanual paradigms seem to spur behavioural enhancements; however, the mechanism underlying this effect is not known. In several transcranial magnetic stimulation (TMS) studies using healthy participants (Stinear & Byblow, 2002; Stinear & Byblow, 2004a) it has been reported that inphase bimanual movements disinhibit homologous muscle representations within the primary motor cortex (M1) whereas antiphase movement increases inhibition within the same areas. Therefore, it may have been possible that the inphase component of our bimanual paradigm (Smith & Staines, 2006) disinhibited cortical regions leading to the increase in early MRP amplitude and decrease in RT. However, the localization of the early MRP component is not known; therefore, this idea cannot be confirmed, and it is difficult to link observations of TMS studies with EEG studies.

Therefore, in accordance with current literature and our previous findings we tested the following three hypotheses: 1) Cued bimanual movement training that emphasized inphase wrist movements would induce larger cortical adaptations within regions subserving motor preparation and execution, as evidenced by changes in the early and late MRPs respectively, than training that required cued antiphase bimanual wrist movements or repetitive unimanual wrist movements; 2) Repetitive unimanual training would induce

cortical activity modulations only associated with motor execution; and 3) Training-induced cortical adaptations (MRP enhancements) would be associated with enhanced performance (decrease in RT). To investigate the above hypotheses the present study utilized the MRP determined from a unimanual visually cued task in which participants used flexion of the right wrist to move a cursor to a specified target on a computer screen prior to and following training interventions.

Materials & Methods

Subjects

Ten healthy, normal participants (2 male, 8 female; age range 22-35) participated in the study, each providing written informed consent. All were right-handed by self-report and did not report any history of neurological impairments. Participants were paid a nominal fee for their participation. The experimental procedures were approved by the Office of Research Ethics at the University of Waterloo and the research ethics board at the Toronto Rehabilitation Institute.

EMG & EEG Recording Procedure

Electromyography (EMG) was recorded from the right flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles using bipolar electrodes placed longitudinally over the muscle bellies. Scalp electroencephalographs (EEG) were recorded from 22 electrodes using the international 10-20 system guidelines and an electrode cap (Quick-Cap, Neuroscan, Compumedics, NC). These channels were recorded to determine the topography of the MRP; however, not all were included in quantitative analysis. All EEG channels were referenced to linked electrodes placed on the left and right mastoid processes. Vertical and horizontal eye movements were monitored with bipolar recordings

above and below the left eye and at the lateral aspect of the left and right eyes respectively. All channels were amplified (20,000x), low pass filtered (50 Hz), digitized at a rate of 250 Hz (Neuroscan, Compumedics, NC) and impedance was below 5 k Ω . All post-processing of the EEG data was performed using Neuroscan® (Compumedics, NC).

Behavioural Task

All subjects came into the lab on three separate days to perform three blocks of visually cued movement trials as follows: pre-training cued unimanual movement (right wrist flexion - 40 repetitions), cued inphase/antiphase bimanual movement training (combinations of right/left wrist flexion/extension - 160 repetitions) or repetitive unimanual movement training as a control (right wrist flexion - 160 repetitions), and post-training cued unimanual movement (right wrist flexion - 40 repetitions). Therefore, the experiment was a repeated measures design (all 10 subjects performed each of the training interventions on three separate days). The order of training intervention day (inphase, antiphase and repetitive unimanual training) was randomized across subjects.

Subjects were seated in a dimly lit room, in front of a computer monitor with arms and head supported. The medial aspects of bilateral forearms were supported with elbows flexed to 90° and the shoulder in forward flexion ~0-10°. The wrist was oriented in a neutral position so that flexion and extension of the wrist occurred in the horizontal plane. This position was maintained for all trials. Electrogoniometric sensors (Biometrics, Wales) were placed on the posterior surface of the 3rd metacarpal and the distal forearm of each upper limb in order to measure wrist flexion and extension. The sensors, in conjunction with a customized program written in LabVIEW (National Instruments, Austin, TX), allowed the subjects to control a cursor on a computer monitor by flexing and extending

the wrists (Fig. 2-1). Right wrist extension controlled upward movement of the cursor, and right wrist flexion controlled downward movement of the cursor. Left wrist extension controlled leftward movement of the cursor and left wrist flexion controlled rightward movement of the cursor. Simultaneous right/left wrist flexion/extension produced diagonal movement of the cursor on the screen (Fig. 2-2).

Pre- and post-training trials were identical and required subjects to move the cursor (8 mm in diameter) from a starting position to a target (1.5 cm²) displayed in the bottom-centre of the screen (Fig. 2-3A). In order to assess the influence of the three types of training (inphase, antiphase and repetitive unimanual movement) upon the cue-related movement-related potential (MRP) it was important for the pre- and post-training trial movement to be discrete and simple. Movement of the cursor was calibrated for each subject so that maximal flexion or extension of the wrist would not allow cursor movement to over exceed the target location. Calibration prevented the subject from over shooting the target, which would interfere with accuracy of the task and it held movement amplitude (ROM) constant. For the pre- and post-training trials, the target always appeared in the same position and required subjects to make a right wrist flexion movement only of approximately 60°. The bimanual movement training (Fig. 2-3B) involved producing cursor movements to visual targets using combinations of left and right wrist flexion and extension movements. For each of the training tasks subjects performed 160 repetitions. As shown in Fig. 2-3A & B, all trials would begin with the subject bringing the cursor to a center position (X). Subjects were allowed to determine the length of the rest period between trials. Following this, the cursor would disappear, and a visual target would appear after a 100 ms delay. For the pre- and post-training unimanual movement trials (Fig. 2-3A)

the target always appeared for each repetition, with the same distance and the same position at the bottom-centre of the screen as described above. For the inphase bimanual movement-training task (Fig 2-3B – black target), the target appeared randomly, and at varying distances along the black diagonal line shown in the diagram, for 160 repetitions within the top left and bottom right quadrants of the task box. Therefore, inphase bimanual training required movements of equal amplitude to move the cursor to the target. Importantly, these movements involved activation of homologous muscle groups in both the left and right forearms. Targets appeared for 80 repetitions within each of the two quadrants.

For the antiphase bimanual movement training task (Fig 2-3B – grey target), the target appeared randomly, and at varying distances, for 160 repetitions within the top right and bottom left quadrants of the task box, along the grey diagonal line shown in Figure 2-3B. Therefore, the antiphase bimanual training task required movement of antagonistic muscle representations of similar amplitudes in the two limbs. Repetitive unimanual training consisted of 160 repetitions to the bottom-centre target location just as in the pre- and post-training unimanual movement blocks. Two seconds following target appearance (preparation period), the cursor would reappear, and the subject was to move the cursor to the center of the target as quickly and accurately as possible. Following a successful trial, a message would appear on the screen displaying total response time (reaction time + movement time) for that trial. Subjects had a maximum of 2 s to reach the target before the trial ended. An individual trial was deemed successful if the target was reached within 2 s.

Event-related potentials

Event-related potentials were extracted from the EEG by averaging individual, artifact-free epochs, time-locked to the onset of cued movement (movement related potentials or MRPs), determined as the onset of EMG activity. Prior to averaging, individual epochs containing artifacts (i.e. from blinks or muscle contractions), defined as deflections greater than 80 μV , were removed from further analysis. Averaged epochs extended from 2000 ms prior to 1000 ms after cued movement onset. Since a MRP has a frequency less than 1 Hz, the MRP was filtered with a 5 Hz low-pass filter.

The MRP consisted of three sub-components, an early slow negativity with an onset \sim 1300-1600 ms prior to movement (early MRP), a sharper negativity beginning \sim 100-150 ms prior to movement onset and peaking between \sim 0 and 150 ms immediately following the onset of movement (late MRP). Lastly, a positive deflection, resembling the re-afferent potential (RAP) commonly observed following self-paced movement, was evident \sim 200-350 ms after movement onset. The early MRPs in this experiment were distributed over frontocentral electrode sites and maximal at FC3. The late MRP was lateralized and maximal over electrode site FC3.

The latency of the late MRP was determined as the peak negativity between 0 to +150 ms after the onset of movement (onset of movement occurred at time zero). For the early MRP, amplitudes were quantified by calculating the mean amplitude between the range of -1000 ms to -50 ms before movement onset. Late MRP amplitudes were taken as the peak-to-peak value from the mean value calculated for the early MRP component to the peak negativity of the late MRP between 0 to +150 ms after movement onset. The re-afferent potential (RAP) amplitude was taken as the peak-to-peak value from the peak

negativity of the late MRP (0 to +150 ms after movement onset) to the peak of the RAP that occurred between +200 to +350 ms after movement onset. In addition, the contingent negative variation (CNV) was quantified by averaging epochs over the 2 s foreperiod (between target presentation and the reappearance of the cursor that served as the cue to move). CNV amplitude was measured as the mean amplitude between the range of -1000 ms to -50 ms before the presentation of the cue to move, over electrodes CZ and FCZ.

Data analysis

Firstly, a one-way repeated measures ANOVA was used to determine that all MRP component amplitudes (early MRP, late MRP and RAP) were of similar amplitudes in the pre-training task across each training day. To test the first hypothesis that inphase BMT would induce larger cortical adaptations within regions subserving motor preparation and execution than either antiphase BMT or repetitive unimanual training, we used separate one-way repeated measures ANOVAs with training type as the factor (inphase BMT, antiphase BMT, unimanual). The dependent measures were the difference in early and late MRP amplitudes in the post-training compared to the pre-training unimanual movement task. *A priori* contrasts were used to test the specifically hypothesized differences between the training interventions. To limit the number of comparisons, statistical tests were performed over specific electrode positions, identified by visual inspection of the topographical distribution of the MRP. For the pre- versus post-training unimanual movement analysis frontocentral sites CZ, FCZ, C3 and FC3 were analyzed (CZ, FCZ for the early MRP and C3, FC3 for the late MRP). Similar analyses, excluding the *a priori* contrasts, were also conducted with RAP and CNV amplitudes as the dependent measures.

To test the second hypothesis that repetitive unimanual training would induce cortical activity modulations within the contralateral M1 we used one-way repeated measures ANOVAs with time relative to unimanual movement training as the factor (pre-, post-) and late MRP amplitude as the dependent measure. The third hypothesis that training-induced cortical adaptations (MRP enhancements) would be associated with enhanced performance (decrease in RT) was tested by first conducting one-way repeated measures ANOVAs with time relative to unimanual movement training as the factor (pre-, post-) and RT as the dependent measure. Secondly, the Pearson product moment correlation coefficient (r) was calculated between these measures. Specifically, post-training minus pre-training RT was plotted against post-training minus pre-training early MRP amplitudes for the individual inphase BMT, antiphase BMT and repetitive unimanual training blocks. Prior to analysis, reaction times faster than 150 ms or that exceeded 500 ms were eliminated from further analysis. Reaction time that was less than 150 ms meant that the subject moved the cursor toward the target before the visual cue appeared and RT over 500 ms meant that the subject made an error during the task. The instance of a RT less than 150 ms or over 500 ms was rare, occurring approximately once or twice in the pre- or post-training trials. Also, one-way repeated measures ANOVAs with time relative to unimanual movement training as the factor (pre-, post-) and MT as the dependent measure was conducted and a second correlation analysis assessing post-training minus pre-training movement time (MT) plotted against post-training minus pre-training early MRP amplitudes for the individual inphase BMT, antiphase BMT and repetitive unimanual training blocks.

To assess cortical and behavioural adaptation during skill acquisition (trial 2) for all movement training types, early and late MRP amplitudes and RAP amplitudes were quantified from averages of the first 40 and the last 40 repetitions for FCZ, CZ, C3, C4, FC3 and FC4 compared using repeated measures ANOVAs with posthoc comparisons. For all measures, significance was taken as $p < 0.05$.

Results

Pre- versus post-training unimanual movement – group analysis

The early MRP was maximal over frontocentral electrode sites (greatest at FC3: $-2.44 \mu\text{V} \pm 0.93$) and had an onset latency of approximately 1300-1600 ms prior to movement onset (mean \pm SE in ms; FCZ: -1300 ± 90 ; CZ: -1358 ± 73 ; C3: -1428 ± 77 ; FC3: -1569 ± 70). The late MRP peaked after movement onset (mean \pm SE in ms; FCZ: 156 ± 18 ; CZ: 152 ± 13 ; C3: 143 ± 22 ; FC3: 126 ± 13). The scalp distribution of the late MRP was lateralized to the left hemisphere and was maximal over FC3 ($-4.48 \mu\text{V} \pm 0.94$). The re-afferent potential (RAP) was maximal at CZ ($6.78 \mu\text{V} \pm 1.17$) with latency occurring before 350 ms following movement onset (FCZ: 337 ± 34 ; CZ: 322 ± 33 ; C3: 303 ± 35 ; FC3: 259 ± 25).

Firstly, there were no significant main effects of training day on pre-training early MRP amplitudes (FCZ: $F_{2,18} = 1.58$, $p = 0.23$; CZ: $F_{2,18} = 0.06$, $p = 0.94$). Therefore, the amplitude of the early MRP component was comparable in the pre-training trial across each training day. There was a significant main effect of training type on early MRP amplitude post-training relative to pre-training evident at electrode site CZ (CZ: $F_{2,18} = 3.45$, $p = 0.05$; FCZ: $F_{2,18} = 1.65$, $p = \text{NS}$). The *a priori* contrasts revealed that this training-related difference in early MRP amplitude at CZ was because of an enhanced negativity

following inphase BMT relative to the other training interventions (CZ: $F_{1,18} = 6.83$, $p = 0.02$) (Fig. 2-4A & B). There was no significant difference between early MRP amplitude following BMT when comparing antiphase BMT and repetitive unimanual training (CZ: $F_{1,18} = 0.06$, $p = \text{NS}$) (Fig. 2-4B). Further, Figure 2-4B shows that for the inphase BMT intervention, the early MRP was significantly more negative post-training compared to pre-training for the unimanual test task. There were no pre/post differences in early MRP amplitude following either the antiphase BMT or repetitive unimanual movement training (Fig. 2-4B). Lastly, there were no significant main effects of training type (inphase, antiphase or repetitive unimanual) on the amplitude of either the late MRP or the RAP when comparing pre- versus post-training trials (Fig. 2-4A, C & D).

There were no significant effects of training time (pre- vs post-training) on RT following any type of training (inphase: $F_{1,9} = 0.931$, $p = \text{NS}$; antiphase: $F_{1,9} = 0.143$, $p = \text{NS}$; repetitive unimanual training: $F_{1,9} = 0.82$, $p = \text{NS}$). There were also no significant effects of training time (pre- vs post-training) on movement time (MT) following any type of training (inphase: $F_{1,9} = 0.864$, $p = \text{NS}$; antiphase: $F_{1,9} = 1.1$, $p = \text{NS}$; repetitive unimanual training: $F_{1,9} = 1.39$, $p = \text{NS}$). Figures 2-5A, B and C show the correlation analyses between early MRP differences and RT following inphase BMT ($r = -0.77$, $p < 0.01$), antiphase BMT ($r = -0.46$, $p = \text{NS}$), and repetitive unimanual training ($r = 0.22$, $p = \text{NS}$). Additionally, there were no significant correlations between the early MRP differences and MT following any type of training. Figure 2-6 shows grand average contingent negative variations (CNV) derived from the pre- and post-training unimanual movement trials for each of the three

types of training. There were no significant main effects of training type at either electrode site (FCZ or CZ) when comparing the CNV in pre- versus post-training trials.

Bimanual training trial

As shown in Figure 2-7A & B, group average early MRP amplitudes significantly increased in amplitude in the last 40 repetitions compared to the first 40 repetitions of inphase bimanual movement training (FCZ: $F_{2,18} = 4.11$, $p = 0.03$; CZ: $F_{2,18} = 6.07$, $p = 0.01$; FC3: $F_{2,18} = 3.49$, $p = 0.05$). Conversely, the early MRP did not change in amplitude in the last 40 repetitions compared to the first 40 repetitions of antiphase bimanual movement training or repetitive unimanual training. Task performance was not assessed in trial 2 due to task accuracy exhibiting a ceiling effect. Accuracy was based upon the subject's ability to move the cursor into the target within two seconds following the cue to move. This time constraint was achieved frequently; therefore, a ceiling effect was encountered.

Discussion

The purpose of the present study was to determine if cortical excitability is differentially modulated for a cued unimanual task in response to cued inphase versus antiphase BMT. The hypothesis that cued inphase BMT more so than cued antiphase BMT or repetitive unimanual training (control) would induce cortical excitability modulations within regions subserving motor preparation and execution was partially supported. Results indicated that reaction time (RT) did not significantly change in the post-unimanual trial for inphase BMT for the group as a whole, but looking at the correlation analysis, practice of a novel short duration (~45 minutes) visually cued inphase BMT task was associated with increased preparatory excitability for a similar cued

unimanual movement task that correlated with a behavioural enhancement. More specifically, cued inphase BMT increased the amplitude of the early MRP (Fig. 2-4A & B) component that was significantly associated with a decrease in RT for some individuals (Fig. 2-5A). However, inphase BMT was not associated with an increase in executory excitability, measured by the late MRP component (Fig. 2-4C). Training strategies such as cued antiphase BMT or repetitive cued unimanual training did not affect cortical excitability and therefore any component of the MRP (Fig. 2-4B,C & D) or behaviour. The ERP data revealed that learning effects were not due to a change in arousal or visual cue anticipation since the contingent negative variation (CNV) (Walter, Cooper, Aldridge, McCallum, & Winter, 1964) was not modulated in response to any type of training in the current study (Fig. 2-6). Instead visuomotor learning was exhibited as an increase in preparatory cortical excitability denoted as an amplitude increase of the early MRP component in the last 40 repetitions of cued inphase BMT (Fig. 2-7A & B) that ultimately transferred to the post-training trial (Fig. 2-4A & B). The early MRP component occurred during the preparatory phase of movement; therefore, it was most likely linked with activity originating from the supplementary motor area (SMA). Previous work has shown visuomotor learning to increase preparatory SMA activity related to the task (Petersen, van Mier, Fiez, & Raichle, 1998; Staines et al., 2002). The present study further demonstrated that inphase BMT preferentially increased preparatory excitability that was associated with a behavioural enhancement versus antiphase BMT or repetitive unimanual training, and these modulations were shown to occur within a short-duration (~45 minutes).

Early stage plasticity

Cortical and behavioural modulations can occur within the early stages of learning (Classen et al., 1998; Karni et al., 1998; Kleim et al., 2004). The early stage of learning possibly reflects a change in GABAergic activity leading to the unmasking of latent horizontal connections (Jacobs & Donoghue, 1991; Karni et al., 1998; Nudo et al., 2003). Unmasking is the initial stage of long-term potentiation (LTP) or the mechanism underlying plasticity (Rioul-Pedotti, Friedman, Hess, & Donoghue, 1998). It may have been possible that short-term cued inphase BMT more so than cued antiphase BMT increased excitability within a region subserving motor preparation, in the post-training trial, by initializing the early phase of LTP; however, we do not have direct evidence of this assertion.

The cued MRP versus the self-paced BP

The cue-related MRP used in the current study had a similar distribution as the Bereitschaftspotential (BP); an ERP extracted from an EEG recording around self-paced movement onset (Deecke et al., 1969; Deecke, 1987; Deecke & Lang, 1996). We observed that the cued MRP, just as the self-paced BP, exhibited an early slow negativity (early MRP) beginning between 1300-1600 ms prior to movement onset, followed by a sharper negativity that peaked approximately 150 ms after movement onset (late MRP). Also similar to the early BP, the early MRP was distributed over frontal electrodes, but maximal at FC3, and the late MRP was lateralized to the hemisphere (left) contralateral to the moved wrist, again maximal at electrode site FC3. The early negativity of the BP (early BP) is usually maximal at electrode sites CZ and FCZ and likely reflects preparatory activity predominantly within the SMA (Cui et al., 1999; Deecke et al., 1969; Deecke, 1987;

Deecke & Lang, 1996; Jahanshahi & Hallett, 2003; Praamstra, Stegeman, Horstink, & Cools, 1996). The late component is usually lateralized to the contralateral primary motor cortex (M1), in the region of the hand representation (Rossi et al., 2000; Shibasaki & Hallett, 2006). Lastly, we consistently observed a re-afferent potential (RAP) that peaked after movement onset before 350 ms that most likely represented movement-related sensory feedback to primary sensorimotor cortex (Colebatch, 2007; Deecke et al., 1969; Deecke & Lang, 1996; Shibasaki & Hallett, 2006).

Due to the similarities between the cue-related MRP and self-paced BP we assumed that it was possible that the same cortical areas generated the components of these two ERPs, but we do acknowledge that the cued MRP may represent a different cortical network other than the predominant regions that generate the BP (SMA, M1 and S1). This is a possibility since the early component of the MRP in the present study was lateralized to electrode site FC3, as was the late component. Localization of the cued MRP versus the self-paced BP requires further investigation and as such contributes to a limitation of the current study.

Localization of the early MRP

The early MRP component observed in response to a visually cued movement in the present study may be generated by a different cortical region other than the SMA that is shown to generate the early BP component of a self-generated movement. Human (Jancke, Loose, Lutz, Specht, & Shah, 2000; Koch et al., 2006; Sugiura et al., 2001) and non-human primate studies (Hoshi & Tanji, 2006; Riehle & Requin, 1989) reveal that the preparatory stage of an externally cued movement (visually or acoustically) primarily activates the dorsal portion of the lateral premotor cortex (PMd) versus the SMA that is predominantly active

during the initial stages of self-generated movement. What is interesting is that in studies of healthy individuals with ‘virtual lesions’ to the SMA induced by repetitive TMS (Serrien & Brown, 2002; Steyvers et al., 2003) and in studies of Parkinson’s patients (Almeida, Wishart, & Lee, 2002; Almeida, Wishart, & Lee, 2003; Johnson et al., 1998; Swinnen et al., 1997) that exhibit a decrease in basal ganglia and SMA excitability, can execute a unimanual or an inphase bimanual movement when the task is externally cued; however, they are unable to execute a task that is self-generated or antiphase in nature. Parkinson’s patients also present with an attenuated early BP component during self-generated movement, but it remains intact during externally triggered movement (Jahanshahi et al., 1995). This finding points to the importance of the basal ganglia and SMA in self-generated movement and complex bimanual movement, but it highlights that other cortical regions are activated during movements that are externally triggered or of inphase bimanual movement. In a study by Seitz et al. (2004) it was reported that a patient whom had suffered a lesion to the corpus callosum exhibited an increase in activation within the PMd, lateral occipital cortex and cerebellum during the execution of an inphase bimanual task with an external cue. The lateral PM cortex was also reported by Samuel et al. (1997) to be highly activated in Parkinson’s patients during a cued inphase bimanual task. Therefore, it is possible that the inphase BMT task with external cuing used in the current study increased activation of the lateral premotor cortex (most likely the dorsal portion), evident by the increase of the early MRP component (shown to be maximal at electrode site FC3). To confirm a differential localization between the early MRP and early BP, further study is required.

Kinematic parameters and the MRP versus the BP

Studies investigating the self-paced Bereitschaftspotential (BP) have reported that various kinematic characteristics can alter the amplitude of the specific components of the BP (early BP, late BP and RAP) for example movement velocity (MT) and range of motion (ROM) (Slobounov & Ray, 1998; Slobounov, Ray, & Simon, 1998; Slobounov, Rearick, & Chiang, 2000; Slobounov, Rearick, Simon, & Johnston, 2000). Therefore, due to the similarities between the BP and MRP, it was necessary to consider MT and ROM as confounding variables to the results in the present study. We found that movement velocity (MT) did not change in the post- versus pre-training trial following inphase BMT. We also found that MT was not correlated to the change in early MRP amplitude following inphase BMT. Therefore, we do not attribute the enhancement of the early MRP amplitude to changes in movement velocity. We also do not attribute early MRP amplitude changes to a modulation of movement amplitude (ROM) since movement amplitude was held constant due to cursor movement calibration (detailed in methods). As an aside, force production itself has been found to have no effect on any component of the BP (Slobounov & Ray, 1998; Slobounov et al., 1998; Slobounov et al., 2000; Slobounov, Rearick et al., 2000); therefore, we did not measure force production in the present experiment.

Inphase BMT and M1 excitability

We had hypothesized that performance enhancement following inphase BMT would be accompanied by an increase in late MRP component amplitude since there is extensive reporting of training related plasticity in the M1 (Classen, Liepert, Hallett, & Cohen, 1999; Kleim, Barbay, & Nudo, 1998; Nudo & Milliken, 1996; Nudo et al., 1996). In a study by Stinear and Byblow (2002) it was observed that there was a disinhibition of

homologous muscle representations within the M1 during inphase bimanual movement compared to antiphase movement. Additionally, Carson et al. (2004) reported a facilitation of M1 representations using TMS during contralateral movement of the homologous muscle representation. It is difficult to say why inphase BMT preferentially facilitated the early MRP component associated with movement preparation versus the late MRP associated more directly with M1 motor execution. Perhaps the late component of the cue-related MRP does not represent M1 excitability, or more practice time was required to enhance M1 excitability, or the cue-related MRP is not sensitive enough to measure within session modulations of the M1.

The second hypothesis that repetitive unimanual training would induce an amplitude increase of the late MRP (denoting M1 excitability) was also not supported. This finding is not too surprising since the unimanual task was simple to execute. In order for learning-related plasticity to occur within the M1 the task must be novel or skilled (Kleim et al., 1998; Nudo et al., 2003). In a study by Kleim (1998) rats were divided into two groups, an unskilled movement-training group and a skilled movement-training group. The unskilled movement task required rats to press a lever to retrieve a food pellet and the skilled movement group were required to reach through an opening in the cage to grasp a food pellet out from a well. The study found that M1 cortical representations for the wrist and digits used in the skilled task expanded, whereas no change occurred in response to unskilled movement.

Bimanual training and reaction time

Looking at the behavioural measure specifically, results showed that RT did not significantly change in the post-training trial of inphase BMT in the group analysis.

However, it is evident in the inphase BMT correlation analysis (Fig. 2-5A) that some individuals exhibited an increase in the amplitude of the early MRP component with concomitant decrease in RT. Therefore, these individuals responded to the cued inphase BMT paradigm in terms of cortical excitability and behavioural modulations, while other participants did not respond. Also, those participants that responded to the inphase bimanual training in the post-training trial also showed an increase in preparatory excitability in the later portion (last 40 repetitions) of the inphase bimanual training trial (trial 2) (Fig. 2-7). The relationship between SMA activity and RT has been demonstrated previously. In a study of Parkinson's disease patients, Filipovic et al. (1997) reported that RT increased as SMA activity decreased. On a similar note, Di Russo et al. (2005) reported that traumatic brain injury patients who presented with a decrease in medial frontal lobe activity also presented with an increase in RT. Lastly, a lesion to the SMA leads to a deficit in its functional roles such as timing of sequential movement (Halsband, Ito, Tanji, & Freund, 1993), movement planning (Tanji & Shima, 1994) and initiating motor plans (Viallet, Vuillon-Cacciuttolo, Legallet, Bonnefoi-Kyriacou, & Trouche, 1995). Disturbance of each of these functional roles increase RT. It is not clear why SMA activity increased during the inphase BMT block (trial 2) perhaps cortical disinhibition induced by inphase movement increased preparatory activity and subsequently decreased RT; however, this is pure speculation since we do not have evidence of this and studies of inphase movement have focused purely upon M1 excitability (Stinear & Byblow, 2002; Stinear & Byblow, 2004a). We would also like to acknowledge that although RT was chosen as the behavioural measure for the current study, additional behavioural measures could have been employed such as peak to movement velocity, EMG characteristics or

movement error rate. We do not wish to claim that cued inphase BMT specifically targets RT only, other behavioural characteristics could also exhibit modulation.

As discussed above, the localization of the early MRP is not known. We cannot confirm if the early MRP component is generated predominantly by the SMA that has been reported to generate the early BP component. There is evidence that externally triggered movements and inphase bimanual movements enhance excitability within the dorsal premotor cortex (Hoshi & Tanji, 2006; Jancke et al., 2000; Koch et al., 2006; Riehle & Requin, 1989; Samuel et al., 1997; Seitz et al., 2004; Sugiura et al., 2001). In a study by Mochizuki et al. (2005) a ‘virtual lesion’ to the left dorsal premotor cortex caused an increase in choice reaction time. Therefore, if the increase in early MRP amplitude was an enhancement of PMd excitability versus SMA activity, it remains possible for behaviour to be influenced.

Lastly, even though the present results indicated that inphase BMT increased preparatory activity leading to a subsequent behavioural enhancement, we do not wish to discount antiphase BMT as a possible training strategy to enhance cortical excitability and behaviour. Differing cortical regions are predominantly active during external versus internally generated movement (Hoshi & Tanji, 2006; Jancke et al., 2000; Koch et al., 2006; Riehle & Requin, 1989; Sugiura et al., 2001) and during inphase versus antiphase movement (Almeida et al., 2002; Almeida et al., 2003; Immisch et al., 2001; Johnson et al., 1998; Sadato et al., 1997; Serrien & Brown, 2002; Steyvers et al., 2003; Swinnen et al., 1997). Therefore, it is possible that antiphase BMT did not induce observed cortical excitability modulations because the cue-related MRP was not an appropriate measurement tool for antiphase BMT modulations. Further study of the localization of the MRP versus

the BP is required to understand the appropriate measurement tool to gauge cortical activity changes in response to both types of movement training.

Conclusion

The most relevant findings of the present study are three fold: 1) the MRP can be used to assess cortical excitability modulations for a cued one-handed task following cued inphase BMT within a single ~45 minute session. 2) Cued inphase BMT increased preparatory excitability linked to enhanced behaviour for a one-handed task, and 3) the MRP can be used as a possible measure of within session cortical excitability modulations in response to cued inphase BMT in the stroke patient population. Understanding the neurophysiological mechanisms underlying the behavioural changes associated with BMT is required so that affective rehabilitative protocols can be optimized and novel approaches developed to increase motor recovery following stroke. Mechanistic information may also lead to the development of other measurement tools with the potential to assess cortical activity changes in association with behavioural enhancement during a treatment regime in order to quantify its effectiveness.

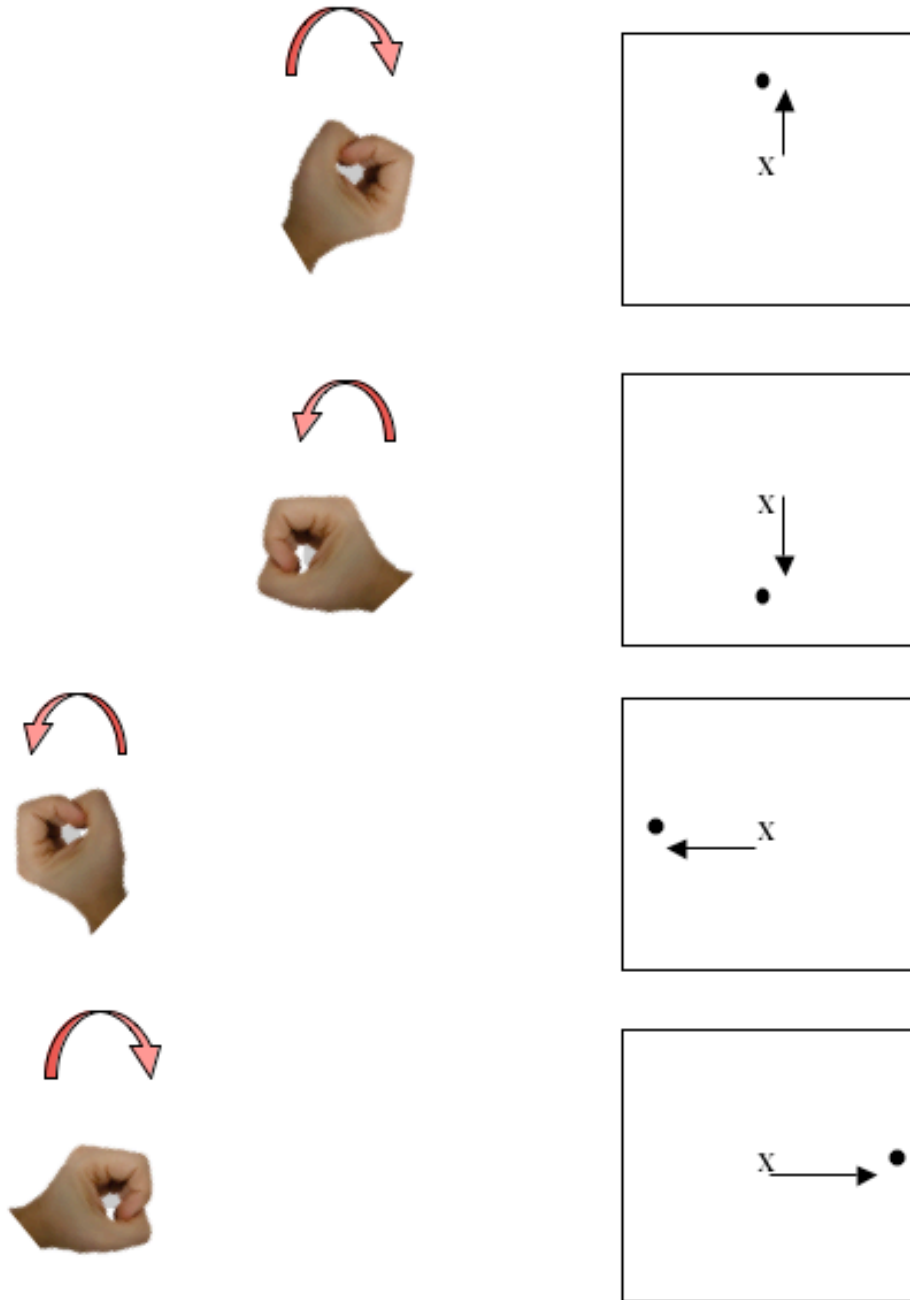


Figure 2-1 - Right and left wrist movement corresponding to cursor movement on the computer screen. (A) Right wrist extension controlled upward movement of the cursor, (B) right wrist flexion controlled downward movement, (C) Left wrist extension controlled leftward movement and (D) left wrist flexion controlled rightward movement of the cursor.

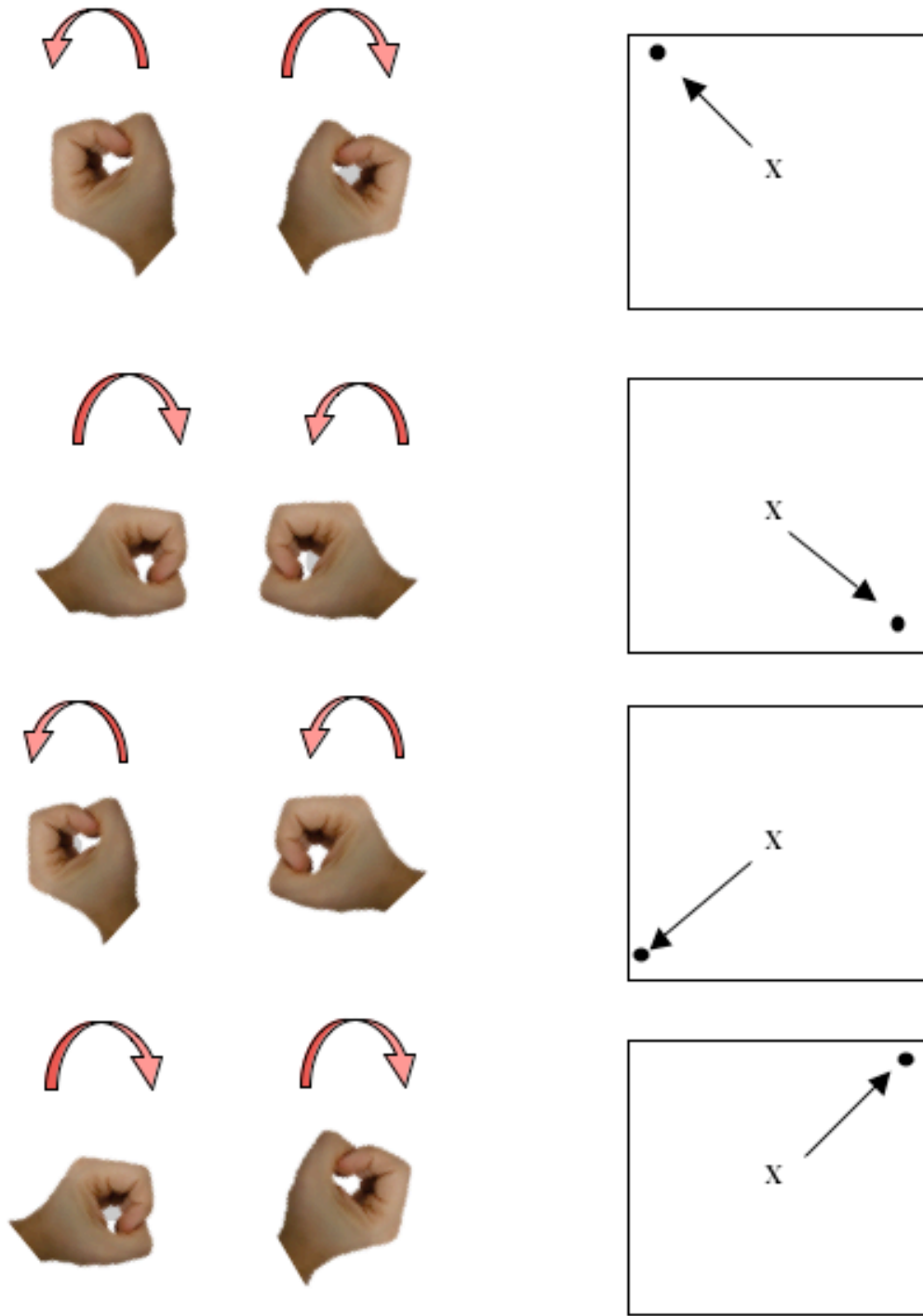


Figure 2-2 - Bimanual wrist movement corresponding to cursor movement on the computer screen. (A & B) Inphase bimanual movement. (C &D) Antiphase bimanual movement

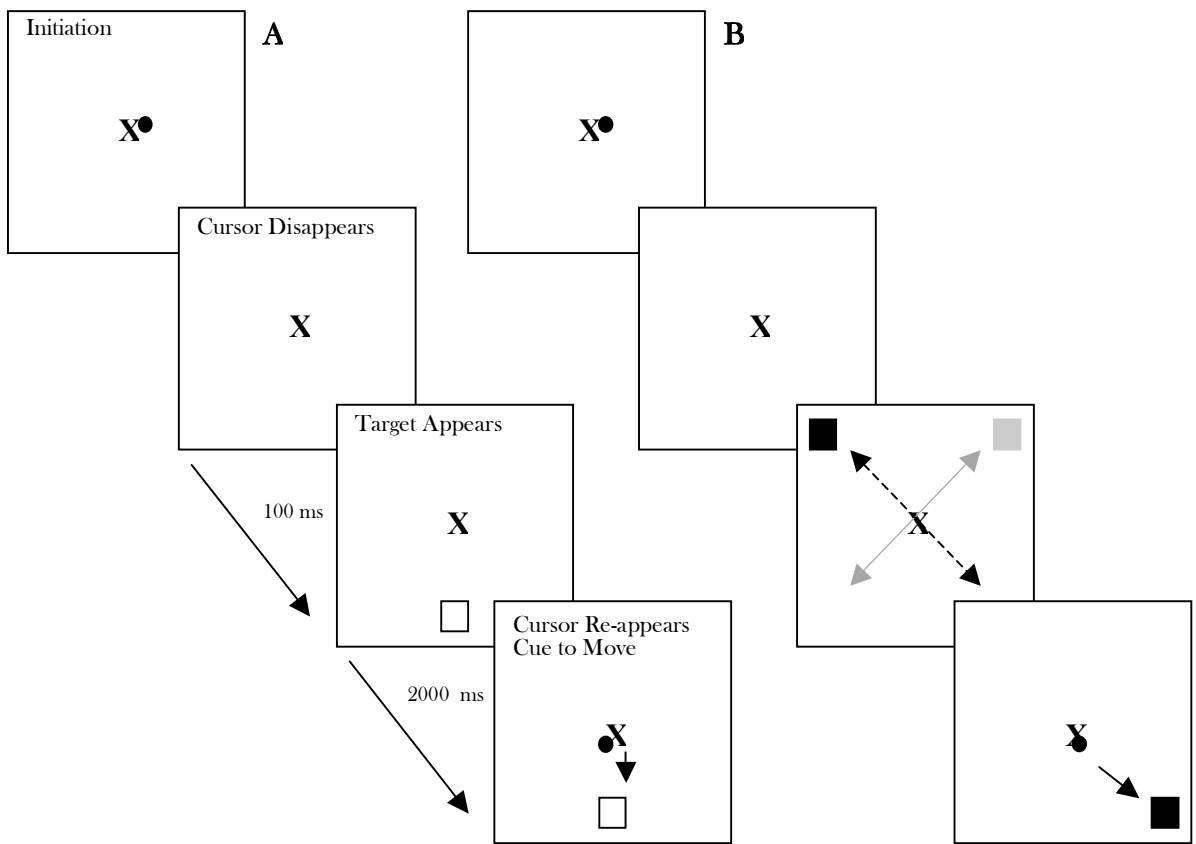


Figure 2-3 - (A) Steps to complete one repetition during the pre- and post-training unimanual movement task.
 (B) Steps to complete one repetition during the inphase bimanual movement training (black target) and antiphase bimanual movement training (grey target).

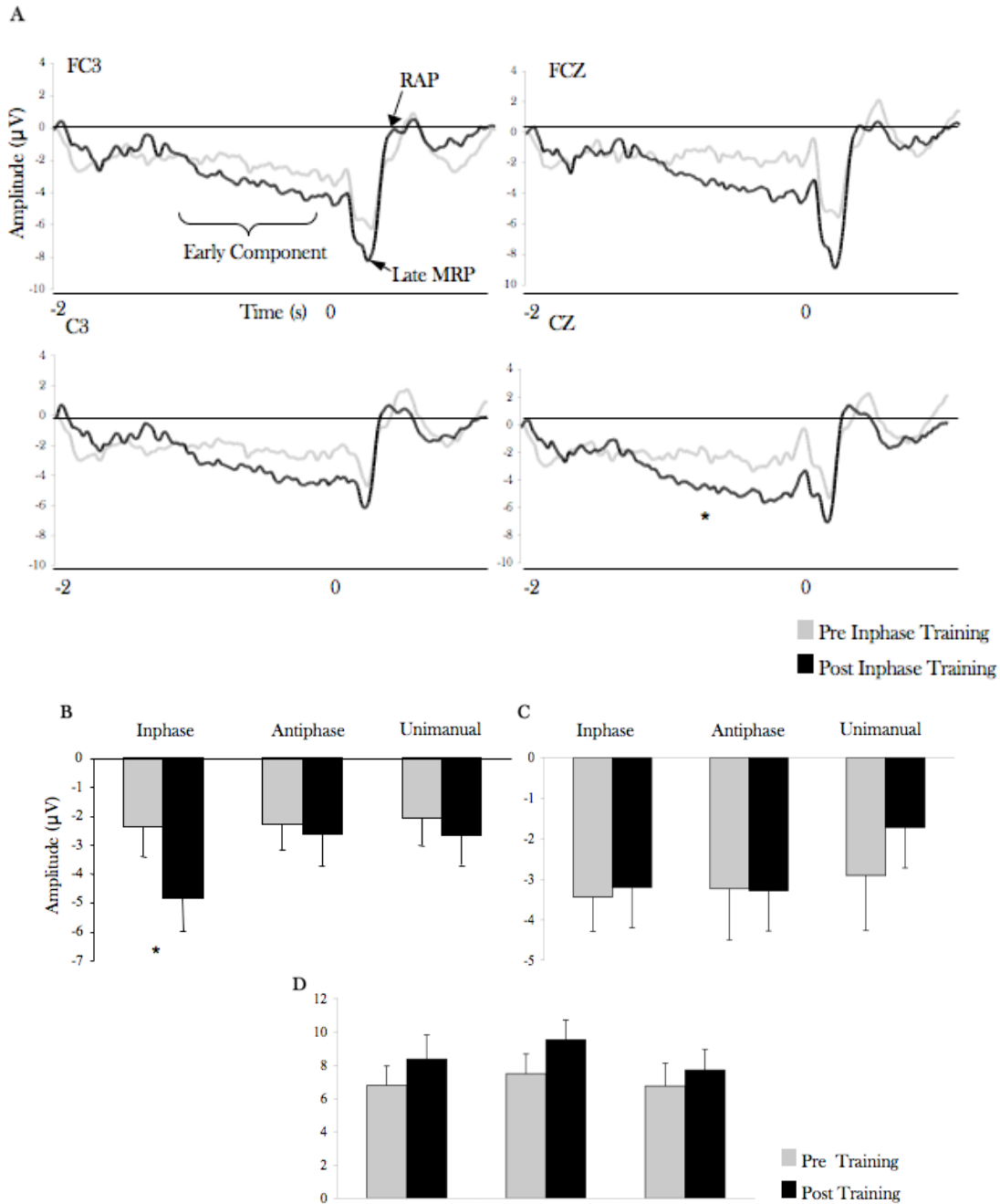


Figure 2-4 - (A) Grand average MRPs ($n=10$) time-locked to cued movement onset of the right wrist prior to (pre-training grey trace) and following (post-training black trace) practice of the inphase bimanual visuomotor training task at 4 electrode sites (FCZ, CZ, C3 and FC3). (B) Group mean ($\pm SE$, $n=10$) early MRP amplitudes in the pre-training (grey bars) and post-training (black bars) condition for the three types of visuomotor movement training: inphase bimanual, antiphase bimanual and repetitive unimanual. (C) Group mean ($\pm SE$, $n=10$) late MRP amplitudes in the pre-training (grey bars) and post-training (black bars) condition for the three types of visuomotor movement training: inphase bimanual, antiphase bimanual and repetitive unimanual. (D) Group mean ($\pm SE$, $n=10$) RAP amplitudes in the pre-training (grey bars) and post-training (black bars) condition for the three types of visuomotor movement training: inphase bimanual, antiphase bimanual and repetitive unimanual. Data is shown for electrode site CZ. * Indicates $p < 0.05$.

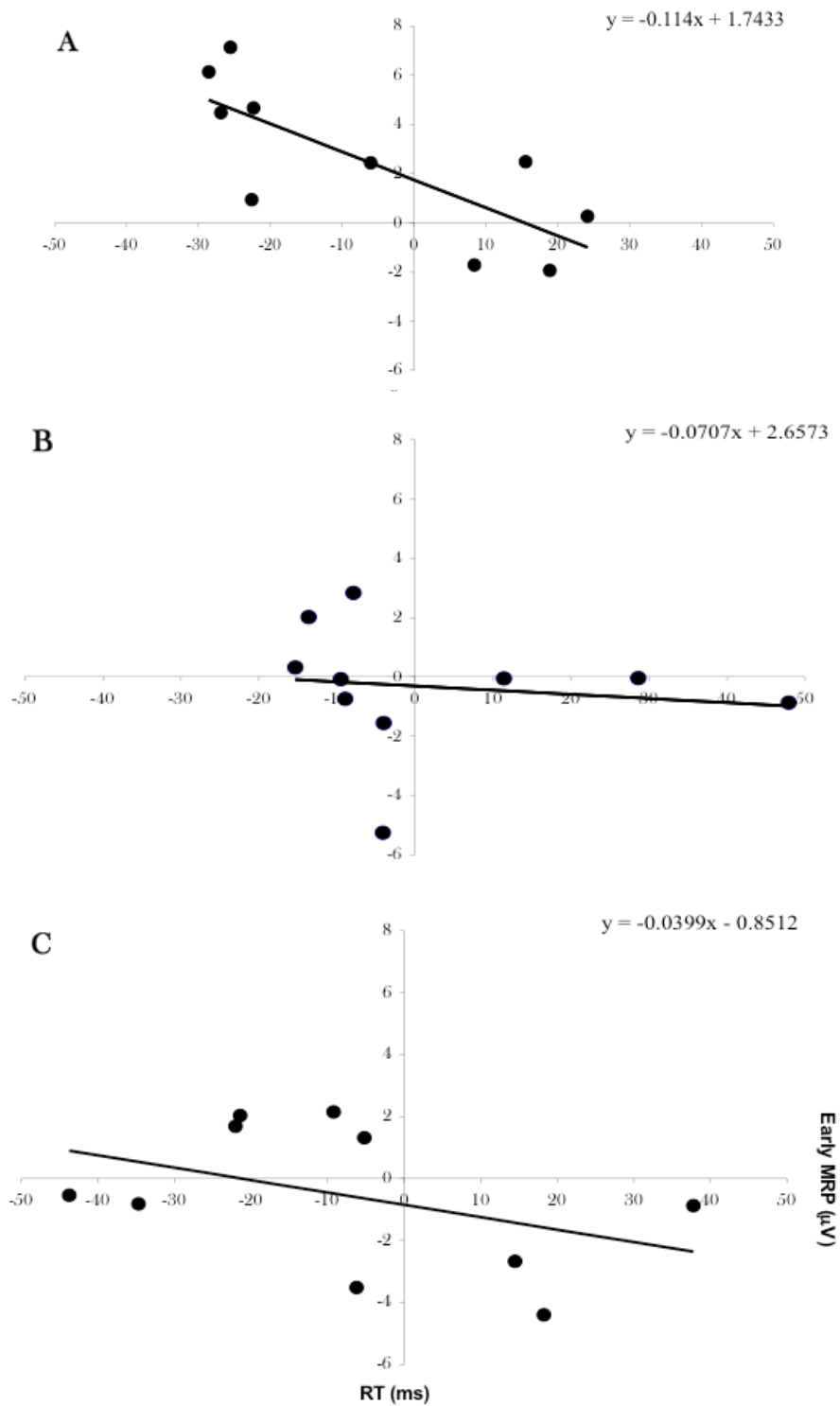


Figure 2-5 - (A, B & C) Correlation analysis between the post-training minus pre-training difference in early MRP amplitude and reaction time for the (A) inphase (B) antiphase and (C) repetitive unimanual visuomotor training. MRPs were measured from CZ (n=10). Indicates $p < 0.05$.

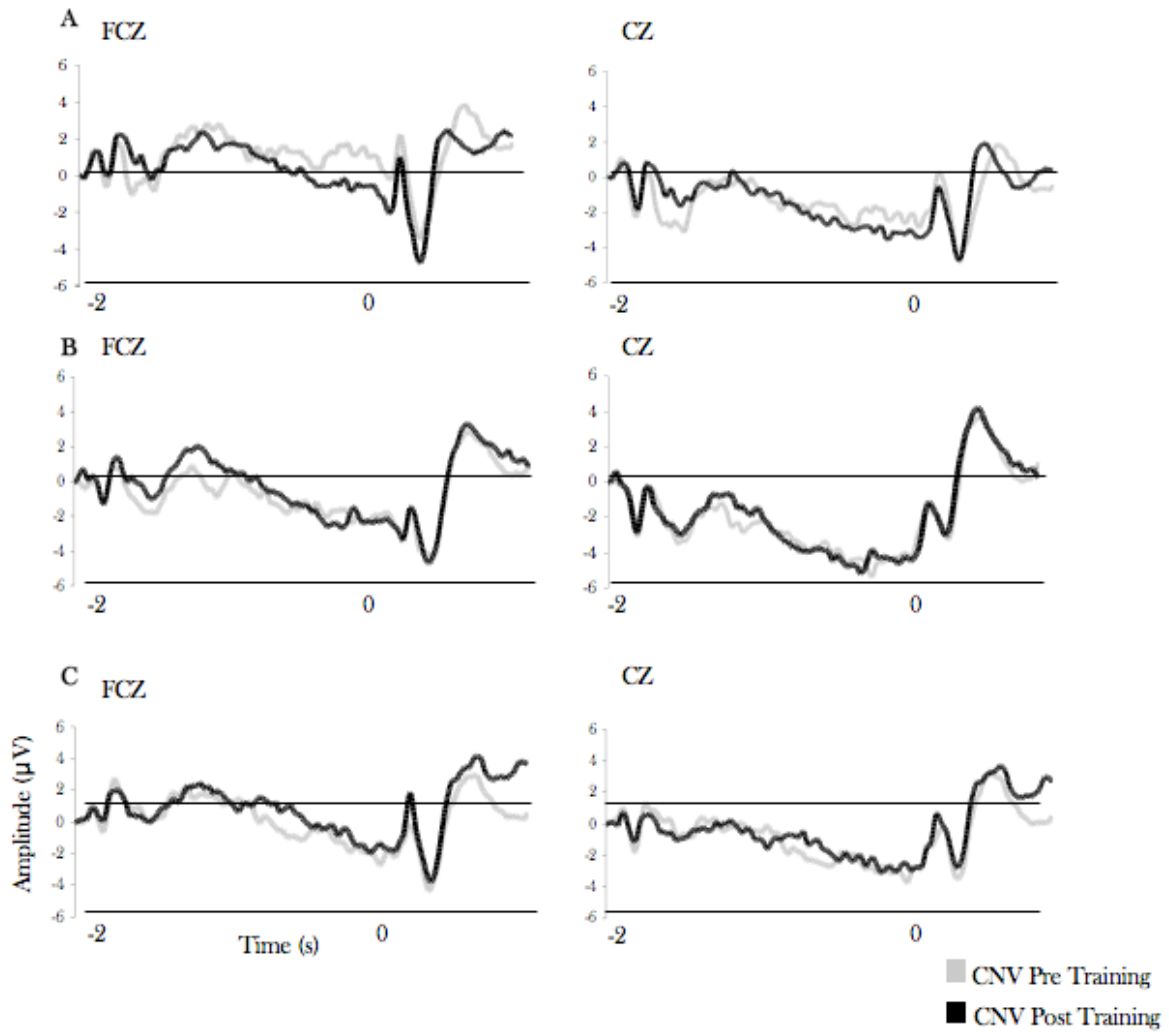


Figure 2-6 - Grand average CNVs (n=10) time-locked to the cue to move before (pre-training grey trace) and following (post-training black trace) practice of the three types of visuomotor training in 2 electrode sites (FCZ, CZ). (A) Inphase bimanual,(B) antiphase bimanual and (C) repetitive unimanual.

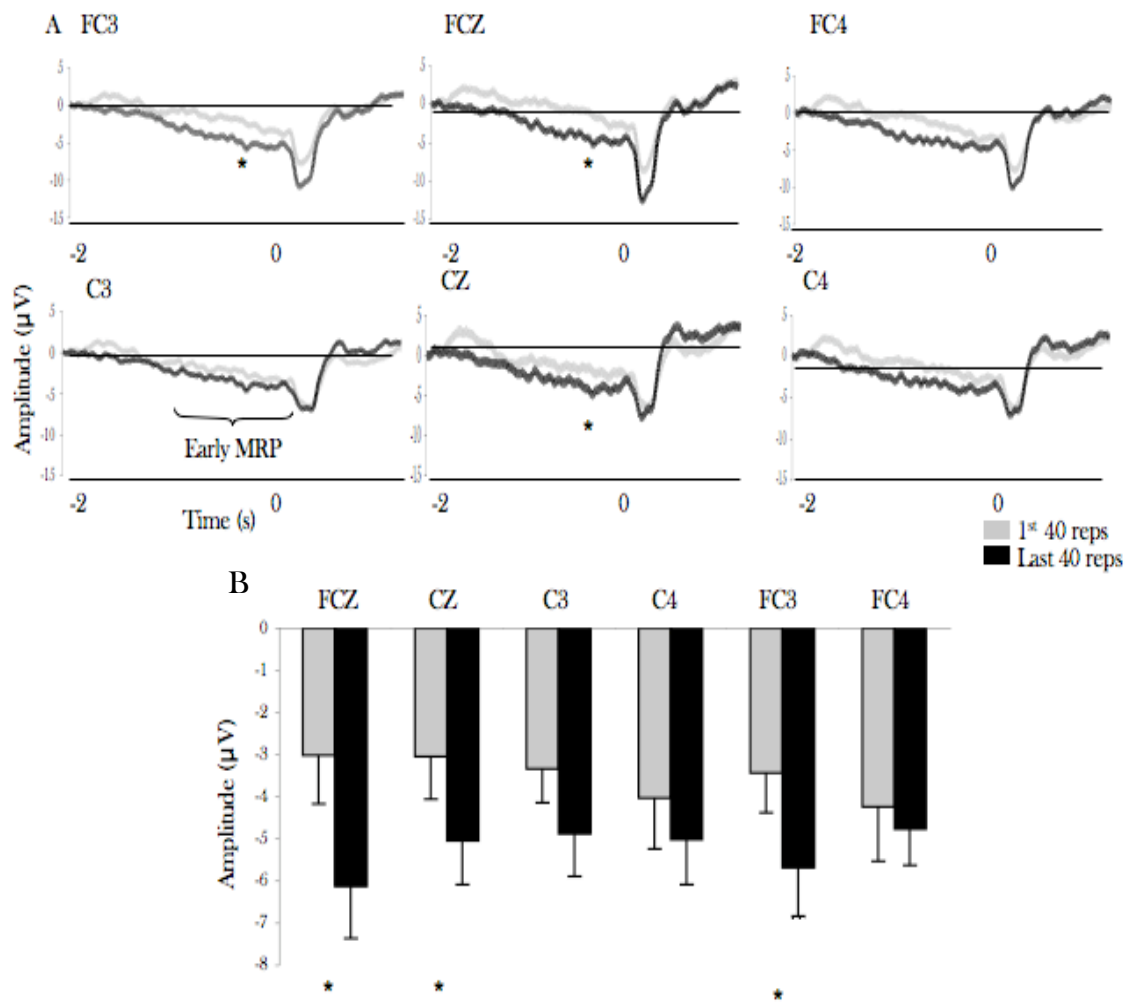


Figure 2-7 - (A) Grand average MRPs ($n=10$) time-locked to cued movement onset of the right wrist in the first 40 repetitions (grey trace) versus the last 40 repetitions (black trace) of the inphase bimanual visuomotor training task (trial 2) at 6 electrode sites (FCZ, CZ, C3, C4, FC3 and FC4). (B) Group mean (\pm SE, $n=10$) early MRP amplitudes in the first 40 repetitions (grey bars) and last 40 repetitions (black bars) for inphase BMT at 6 electrode sites (FCZ, CZ, C3, C4, FC3 and FC4). * Indicates $p < 0.05$.

Chapter Three - Cued inphase bimanual training adaptations imposed upon a self-paced task and cue-related versus self-paced event-related potential source localization

Smith, A.L. & Staines, W. R.

Overview

The present study consisted of two experiments to indirectly (experiment one) and directly (experiment two) investigate the cortical localization of the cue-related movement-related potential (MRP) versus the self-paced Bereitschaftspotential (BP), with particular interest in the localization of the early component. We were interested to determine if there was a common cortical network underlying the cue-related MRP versus the self-paced BP. In experiment one EEG was recorded from 22 electrodes to record the self-paced BP before and following cued inphase bimanual movement training (BMT). Ten healthy volunteers participated in three trials: a pre and post one-handed trial comprising 80 repetitions of self-paced right wrist flexion (to measure the self-paced BP); interspersed with one session of cued inphase bimanual movement training (BMT) (to measure the cue-related MRP). Two specific hypotheses were investigated: 1) the cue-related early MRP component observed in our previous studies was generated by another cortical region other than the SMA; therefore, cued inphase BMT will not effect the amplitude of the self-paced early BP component. 2) However, the amplitude of the cue-related early MRP component would increase in amplitude in the last 40 repetitions of cued inphase BMT as observed in our previous studies. Results showed that cued inphase BMT did not affect the amplitude of the early BP component; however, the amplitude of the early MRP component increased in the last 40 repetitions of cued inphase BMT. These findings support the hypothesis that cued inphase BMT does not primarily modulate SMA excitability.

Experiment two recorded EEG from 64 electrode sites and consisted of an additional 10 healthy volunteers who performed 80 repetitions of self-paced and visually cued right wrist flexion. Source localization of the self-paced BP and cue-related MRP components was investigated using standardized low-resolution brain electromagnetic tomography (sLORETA). We hypothesized that 1) the early MRP component would be generated predominantly by an area overlying the lateral premotor cortex, and the early BP component would be generated predominantly by the SMA. 2) In terms of the late component and re-afferent potential of the cue-related MRP and self-paced BP components both would be predominantly generated by the M1 and S1 respectively. Results indicated that the primary generator of the cue-related early MRP component was the lateral premotor region, contrasting from the SMA that underlies the generation of the self-paced early BP component. The late and RAP components of both ERPs however were generated by similar regions namely the M1 and S1 respectively. The results of these two experiments provided needed insight into the cortical localization of the cue-related early MRP component and point to specific measures required to detect modulatory effects of cued inphase BMT.

Introduction

Chapter 2 indicated that the cue-related movement-related potential (MRP) is a useful measurement tool to gauge within session cortical excitability modulations in response to cued inphase bimanual movement training (BMT) versus antiphase BMT or repetitive unimanual training. Our findings from Chapter 2 have determined that the early component of the cue-related MRP, denoting preparatory cortical excitability, increased in amplitude following a cued inphase BMT paradigm, replicating our previous findings

(Smith & Staines, 2006). Cortical excitability modulation was observed in the last 40 repetitions of the training paradigm that ultimately transferred to a similar unimanual task, and was linked to a behavioural enhancement in some individuals. These experiments (Smith & Staines, 2006 & Chapter 2) were the first to use the cue-related **MRP** as a measure of learning-related adaptations in response to **BMT** in the healthy population. An important finding was that cortical excitability modulations could be measured within a short duration of a single session of **BMT**. However, the localization of the early component of the cue-related **MRP** remains unknown and imposes a limitation to the interpretation of our previous findings. Therefore, the experiments of the current chapter were designed to address the overall thesis objective, which was to determine the generators of the cue-related **MRP**, an **ERP** associated with the preparation and execution of a cued movement versus the **Bereitschaftspotential (BP)**, a similar **ERP** associated with self-paced movement.

The cue-related **MRP** that we utilized to measure preparatory and executory excitability (Smith & Staines, 2006 & Chapter 2) in response to a visually cued movement, presented similarly to another **ERP** called the **Bereitschaftspotential (BP)** (Fig. 3-1). Traditionally, the **BP** is extracted from an **EEG** recording 2 seconds prior to and 1 second following self-paced movement onset and is typified by several components. The first component is a slow negativity typically subdivided into two segments: 1) the early component, beginning 1.5 to 2 seconds prior to movement onset, and a later steeper slope called the negative slope (**NS**), occurring approximately 500 ms prior to movement onset. The early **BP** component is maximal in frontocentral electrode sites (**FCZ, CZ**) and is symmetrically distributed. The second component is a peak negativity occurring slightly

after movement onset (termed the late component), maximal in contralateral electrodes corresponding to the primary motor cortex (C1/C3 or C2/C4) for hand movement according to the international 10-20 system. Lastly, the re-afferent potential (RAP); a positive deflection occurring before 350 ms after movement onset (Barrett, Shibasaki, & Neshige, 1985; Deecke, Scheid, & Kornhuber, 1969; Deecke, Grozinger, & Kornhuber, 1976; Kornhuber & Deecke, 1965; Kristeva, Keller, Deecke, & Kornhuber, 1979; Kutas & Donchin, 1980; Shibasaki, Barrett, Halliday, & Halliday, 1980; Shibasaki & Hallett, 2006).

According to the literature, the self-paced early BP component is predominantly generated by motor preparatory excitability from the supplementary motor area (SMA) (Cui, Huter, Lang, & Deecke, 1999; Jahanshahi & Hallett, 2003; Praamstra, Stegeman, Horstink, & Cools, 1996). Several patient-based studies have found that persons who have decreased SMA activation due to cortical pathology or injury also present with an attenuation of the early BP component whilst the other components (late BP component and RAP) remain intact (Dick et al., 1989; Feve, Bathien, & Rondot, 1994; Jahanshahi et al., 1995; Shimizu & Okiyama, 1993; Simpson & Khuraibet, 1987). The late BP component is primarily generated by the contralateral primary motor cortex (M1) and most likely represents pyramidal cell activation at motor execution (Rossi et al., 2000; Shibasaki & Hallett, 2006). Lastly, the re-afferent potential (RAP) is primarily generated by the primary somatosensory cortex (S1) and is thought to reflect sensory feedback regarding the movement (Colebatch, 2007; Shibasaki & Hallett, 2006).

Based upon the similar presentation of the cue-related MRP and self-paced BP, we concluded in our previous studies that the cue-related early MRP component represented SMA excitability as well (Smith & Staines, 2006). However, an interesting observation

from our previous study (Smith & Staines, 2006) and our most current study (Chapter 2) was that the early MRP component generated in response to a cued wrist flexion movement was not maximal at the electrode sites overlying the SMA region (FCZ, CZ). Instead, the early MRP component was maximal at electrode sites FC1 or FC3, which overlie the lateral premotor cortex. Jahanshahi et al. (1995) reported that the early BP component of patients with Parkinson's disease was attenuated during self-initiated right index finger extension, but remained robust during acoustically cued right index finger extension. Since the early component of the BP is reportedly linked primarily with SMA activation, the authors (Jahanshahi et al., 1995) concluded that the early component of the cue-related MRP must be generated predominantly by a different cortical region other than the SMA; due to the lateralization of the cue-related early MRP component to electrode site FC4; the lateral premotor cortex seemed a likely candidate.

The dorsal portion of the lateral premotor cortex (PMd) has been shown to be primarily active during movements that are visually or acoustically triggered in humans (Jancke, Loose, Lutz, Specht, & Shah, 2000; Koch et al., 2006; Sugiura et al., 2001) and non-human primates (Hoshi & Tanji, 2006; Riehle & Requin, 1989); whereas predominant activation of the SMA underlies self-initiated movement. In studies of Parkinson's disease patients with damage to the basal ganglia leading to a subsequent decrease in SMA activation, self-initiated movement is difficult to perform, but patients can perform externally triggered movement comparable to healthy control subjects (Almeida, Wishart, & Lee, 2002; Almeida, Wishart, & Lee, 2003; Johnson et al., 1998; Swinnen et al., 1997). The ability to execute externally triggered movement is also evident in studies of 'virtual

lesions' of the SMA following repetitive transcranial magnetic stimulation (TMS) (Serrien & Brown, 2002; Steyvers et al., 2003).

Due to the differences observed in the maximal activation of the cue-related early MRP component versus the self-paced early BP component observed in our previous studies, and the current literature regarding the localization of internal versus externally triggered movement, we conducted two experiments. Cued inphase BMT has been reported to increase the amplitude of the cue-related early MRP component. We hypothesize that the early MRP component is primarily generated by the lateral premotor cortex. Conversely, the self-paced early BP component is primarily generated by the SMA; therefore, each early component is most likely primarily generated by differing cortical regions. Due to the differential cortical localization of the early MRP and early BP components we hypothesize that specific training types can differentially modulate both ERP components; therefore, in experiment one we hypothesized that 1) the self-paced early BP component will not exhibit modulation in response to cued inphase BMT. 2) However, the amplitude of the cue-related early MRP component will increase in amplitude in the last 40 repetitions of cued inphase BMT as observed in our previous studies.

The second experiment was to directly determine the prominent cortical generators of the self-paced BP versus the cue-related MRP. We hypothesized that 1) the cue-related MRP and self-paced BP would be similar in latency; however, the amplitude of the self-paced early BP component would be greater. 2) the cue-related early MRP component would be generated predominantly by an area overlying the lateral premotor cortex, and the early BP component would be generated predominantly by the SMA. 3) In terms of

the late component and re-afferent potential of the cue-related MRP and self-paced BP components both would be predominantly generated by the M1 and S1 respectively.

Materials & Methods

Subjects

Twenty healthy, normal participants participated in the study, ten each in 1 of 2 experiments (Experiment one: 6 male, 4 female; age range 21-33; Experiment two: 4 male, 6 female; age range 22-37). All were right-handed by self-report and did not report any history of neurological impairments. Participants provided written informed consent and were paid a nominal fee for their participation. The Office of Research Ethics at the University of Waterloo and the research ethics board at the Toronto Rehabilitation Institute approved the experimental procedures.

EMG & EEG Recording Procedures

Scalp electroencephalographs (EEG) were recorded from 22 channels in Experiment one and 64 channels in Experiment two using the international 10-20 system guidelines and an electrode cap (Quick-Cap, Neuroscan, Compumedics, NC). These channels were recorded to determine the topography of the movement related potential and Bereitschaftspotential; however not all were included in quantitative analysis. All EEG channels were referenced to linked electrodes placed on the left and right mastoid processes. Vertical and horizontal eye movements were monitored with bipolar recordings above and below the left eye and at the lateral aspect of the left and right eyes respectively. Electromyography (EMG) was also recorded from the right flexor carpi radialis (FCR) muscle using bipolar electrodes placed longitudinally over the muscle bellies in Experiments one and two. All channels were amplified (20,000x), low pass filtered (50

Hz), digitized at a rate of 250 Hz (Neuroscan, Compumedics, NC) and impedance was below 5 k Ω . All post processing of the EEG data was performed using Neuroscan® (Compumedics, NC).

Behavioural Task

Subjects were seated in a dimly lit room, in front of a computer monitor with arms and head supported. The medial aspects of the bilateral forearms were supported with elbows flexed to 90° and the shoulder in forward flexion ~0-10°. The wrist was oriented in a neutral position so that flexion and extension of the wrist occurred in the horizontal plane. This position was maintained for all trials. Subjects grasped two handles of a custom made wrist movement device that rotated in clockwise and counter clockwise directions (Fig. 3-2)[for this and subsequent studies a custom made wrist movement device was used during the task. Appendix one details a small methodological study confirming that the new wrist device did not increase EMG activity of the wrist musculature compared to the goniometric sensors of Chapter 2). These handles were linked to potentiometers that measured wrist flexion and extension during visually cued movement tasks. Subjects rested the 5th metacarpale of the hands on the bottom portion of the handle; therefore, the musculature of the wrists and arms were relaxed prior to movement. The handles, in conjunction with a customized program written in LabVIEW (National Instruments, Austin, TX), allowed the subjects to control a cursor on a computer monitor by flexing and extending the wrists in the horizontal plane. Shown in Fig. 3-3 right wrist extension controlled upward movement of the cursor, and right wrist flexion controlled downward movement of the cursor. Left wrist extension controlled leftward movement of the cursor

and left wrist flexion controlled rightward movement of the cursor. Simultaneous right/left wrist flexion/extension produced diagonal movement of the cursor on the screen (Fig. 3-4).

For experiment one subjects came into the lab to perform three movement blocks as follows: pre-training self-paced unimanual movement (self-paced right wrist flexion - 80 repetitions), cued inphase bimanual movement training (combinations of right/left wrist flexion/extension - 160 repetitions) and post-training self-paced unimanual movement (self-paced right wrist flexion - 80 repetitions). Pre and post-training trials were identical and required subjects to perform self-paced right wrist flexion movements every 5-6 seconds. The cued inphase bimanual movement training (Fig. 3-5B) involved producing cursor movements to visual targets using combinations of left and right wrist flexion and extension movements for 160 repetitions. As shown in Fig. 3-5B all trials would begin with the subject bringing the cursor to a center position (X). Subjects were allowed to determine the length of the rest period between trials. Following this, the cursor would disappear, and a visual target would appear after a 100 ms delay. For the cued inphase bimanual movement-training task (Fig. 3-5B - black target), the target appeared randomly, and at varying distances along the black diagonal line shown in the diagram, for 160 repetitions within the top left and bottom right quadrants of the task box. Therefore, cued inphase bimanual training required movements of equal amplitude to move the cursor to the target. Importantly, these movements involved activation of homologous muscle groups in both the left and right forearms. Targets appeared for 80 repetitions within each of the two quadrants.

Two seconds following target appearance (preparation period), the cursor would reappear, and the subject was to move the cursor to the center of the target as quickly and

accurately as possible. Following a successful trial, a message would appear on the screen displaying total response time (reaction time + movement time) for that trial. Subjects had a maximum of 2 s to reach the target before the trial ended. An individual trial was deemed successful if the target was reached within 2 s.

For experiment two, subjects performed two trials; one consisting of 80 repetitions of self-paced right wrist flexion and 80 repetitions of cued right wrist flexion. The steps to complete the self-paced task are described above. The steps to complete the unimanual cued task was similar to the above description except one target would appear at the bottom centre of the task box and would require right wrist flexion in response to the cue to movement (Fig. 3-5A)

Event-related potentials

Event-related potentials were extracted from the EEG by averaging individual, artifact-free epochs, time-locked to the onset of movement (movement related potentials or MRPs). Prior to averaging, individual epochs containing artifacts (i.e. from blinks or muscle contractions), defined as deflections greater than 80 μV , were removed from further analysis. Averaged epochs extended from 2000 ms prior to movement onset to 1000 ms after movement onset. Preceding averaging, the MRP was filtered with a 5 Hz low-pass filter.

The pre and post BP of experiment one and the self-paced trial of experiment two consisted of three sub-components, an early slow negativity with an onset of ~ 1300 - 1860 ms prior to movement (early BP), a sharper negativity beginning ~ 100 - 150 ms prior to movement onset and peaking between ~ 0 and 190 ms immediately following the onset of movement (late BP). Lastly, a positive deflection, the re-afferent potential (RAP) was

evident ~340-370 ms after movement onset. The early BPs in experiment one and two were maximal over frontocentral electrode sites (CZ, FCZ, and C1). The late BP was lateralized and maximal over electrode site C1 (experiment one) and C3 (experiment two). The early MRPs of experiment two were distributed over frontocentral electrode sites and maximal at FC1. The late MRP was lateralized and maximal over electrode site FC1.

The latency of the late BP was determined as the peak of negativity between 0 to +190 ms after the onset of movement (onset of movement occurred at time zero). For the early BP, amplitudes were quantified by calculating the mean amplitude from -1000 ms to -50 ms before movement onset. Late MRP amplitudes were taken as the peak-to-peak value from the mean amplitude value of the early BP to the peak negativity of the late BP between 0 to +190 ms after movement onset. The re-afferent potential (RAP) amplitude was taken as the peak-to-peak value from the peak negativity of the late BP (0 to +190 ms after movement onset) to the peak of the RAP that occurred between +340 to +370 ms after movement onset.

Data Analysis

Cued inphase BMT has been reported to increase the amplitude of the cue-related early MRP component. We hypothesize that the early MRP component is primarily generated by the lateral premotor cortex. Conversely, the self-paced early BP component is primarily generated by the SMA; therefore, each early component is most likely primarily generated by differing cortical regions. Due to the differential cortical localization of the early MRP and early BP components we hypothesize that specific training types can differentially modulate both ERP components; therefore, the self-paced early BP component will not exhibit modulation in response to cued inphase BMT. To test this

hypothesis we used repeated measures one-way ANOVAs comparing average amplitudes of the early and late BPs and the RAP from the post-training block to those from the pre-training block. Our second hypothesis was 2) the amplitude of the early cue-related MRP component will increase in amplitude in the later portion of cued inphase BMT (trial 2) as observed in previous studies (Smith & Staines, 2006). To test this hypothesis we used repeated measures one-way ANOVAs comparing average amplitudes of the early and late MRP and the RAP from the last 40 repetitions to those from the 1st 40 repetitions of cued inphase BMT (trial 2). To limit the number of comparisons, statistical tests were performed over specific electrode positions, identified by visual inspection of the topographical distribution of the BP and MRP. For the pre- versus post- self-paced unimanual movement analysis frontocentral sites CZ, FCZ, C1 and FC1 were analyzed. For the cued inphase block (trial 2) CZ, FCZ, C1, C2, FC1 and FC2, were analyzed.

In experiment two we hypothesized that 1) the cue-related MRP and self-paced BP would be similar in latency; however, the amplitude of the self-paced early BP component would be greater. To test this hypothesis we used separate repeated measures one-way ANOVAs to determine if there were any differences in the amplitudes of the three different components of the MRP and BP (early component, late component and re-afferent potential). 2) the early MRP component would be generated predominantly by an area overlying the lateral premotor cortex, and the early BP component would be generated predominantly by the SMA. 3) In terms of the late component and re-afferent potential of the cue-related MRP and self-paced BP components both would be predominantly generated by the M1 and S1 respectively. To test these hypotheses we

used a source localization method incorporating the averaged MRP and BP data, digitized electrode positions and structural MR image for each subject.

sLORETA analysis

The averaged BP and MRP event-related potentials, MR images and digitized electrode positions were the data files inputted into a software package that computed current density reconstructions, used for source localization (Curry v6, Compumedics Neuroscan, NC). The first step in source localization was the estimation of noise in the data. Noise was estimated using the prestimulus interval (-3000 ms to -2016 ms). Prior to noise estimation this interval was baseline corrected using a constant setting and high-pass filtered (frequency = 1.0; width = 2.0). Baseline correcting and filtering the noise estimation interval (-3000 ms to -2016 ms) enhanced the probability of this interval only containing noise related data. This assumption was confirmed by the mean global field power (MGFP) plot that showed after baseline correction. Mean global field power (MGFP) gives a quick overview of the EEG time courses, by collapsing all electrodes into a single averaged trace. With MGFP one can easily distinguish a time range with meaningful signal from noise (Curry v.6.0 User Manual, 2007). The noise estimation interval contained low signal content; therefore, validating that the interval could be used for noise estimation. In all cases the noise was computed below 1 μV (average was 0.28 μV).

MRI data sets were linearly interpolated to create 3-dimensional images of each subject's cortex. A boundary element model (BEM) of the head compartments was computed by the triangulation of the various compartments (skin, inner skull and outer skull). Mean triangle edge lengths for the BEM surfaces were 9, 8 and 6 mm respectively. Fixed conductivities of each surface were specified as 0.33, 0.0042 and 0.33 S/m

respectively. Lastly, a reconstructed head model, housing the three compartments was created and consisted of approximately 5000 nodes and 10 000 triangles. The final step was the projection of the electrode positions onto the skin surface. Detailed description of the methods used for MRI processing and source reconstruction can be found in the following references (Fuchs, Wagner, Kohler, & Wischmann, 1999; Fuchs, Wagner, & Kastner, 2001) (Curry v.6.0 User Manual, 2007).

Current density analysis of the four components of the BP and MRP (early BP, NS, late component and re-afferent potential) was conducted using the sLORETA process (Pascual-Marqui, 2002) within the Curry version 6 (Compumedics Neuroscan, NC) software package. This process finds a solution to the inverse problem by assuming similar cortical activation of proximate locations, followed by a standardization of the current density; therefore, producing images of cortical activation without localization bias (Greenblatt, Ossadtchi, & Pflieger, 2005; Pascual-Marqui, 2002; Sekihara, Sahani, & Nagarajan, 2005). The inverse problem is the computation of cortical excitability localization based on extracranial measurements such as EEG or MEG (Pascual-Marqui, 2002). Using the sLORETA method, the maximal current density calculated at a given time was taken as the source of the particular component. We computed sLORETA images for each individual subject and group averaged data for the four components of the BP and MRP in the following time ranges: early BP component: -1840 ms to -1156ms, negative slope: -1000 ms to -64 ms, the late component: ~ -20 ms to 190 ms and re-afferent potential: ~190 ms to 415 ms.

Results experiment one

Pre- versus post-training self-paced unimanual movement – group analysis

The early BP was maximal over frontocentral electrode sites (CZ: μV 3.82) and had an onset latency of approximately 1715-1762 ms prior to movement onset. The late BP peaked after movement onset at approximately 163-174 ms. The scalp distribution of the late BP was lateralized to the left hemisphere and was maximal over C1 ($-9.54 \mu\text{V} \pm 2.35$). The re-afferent potential (RAP) was maximal at CZ ($6.47 \mu\text{V} \pm 1.05$) with latency around 370 ms after movement onset.

Shown in Fig. 3-6 there were no significant task-related differences in the early BP (FCZ: $F_{1,9} = 0.33$, $p = 0.58$; CZ: $F_{1,9} = 0.37$, $p = 0.55$; C1: $F_{1,9} = 0.11$, $p = 0.75$; FC1 : $F_{1,9} = 0.01$, $p = 0.92$), late BP (FCZ: $F_{1,9} = 1.16$, $p = 0.31$; CZ: $F_{1,9} = 1.14$, $p = 0.31$; C1: $F_{1,9} = 1.14$, $p = 0.27$; FC1 : $F_{1,9} = 0.66$, $p = 0.45$) or RAP (FCZ: $F_{1,9} = 1.96$, $p = 0.19$; CZ: $F_{1,9} = 0.28$, $p = 0.61$; C1: $F_{1,9} = 0.45$, $p = 0.52$; FC1 : $F_{1,9} = 1.65$, $p = 0.23$) amplitude of the self-paced BP following cued inphase bimanual movement training.

Cued Bimanual Training Trial

The cued early MRP was maximal over frontocentral electrode sites (FC2: μV 3.57) and had an onset latency of approximately 1814-1855 ms prior to movement onset. The late MRP peaked after movement onset between 58-72 ms. The scalp distribution of the cued late MRP was lateralized to the left hemisphere and was maximal over FC2 ($11.08 \mu\text{V} \pm 1.88$). The cued re-afferent potential (RAP) was maximal at FC1 ($12.06 \mu\text{V} \pm 1.27$) with latency of approximately 256 ms after movement onset.

Shown in Fig. 3-7A & B, the cued early MRP significantly increased in amplitude in the last 40 repetitions compared to the first 40 repetitions of cued inphase bimanual

movement training (FCZ: $F_{1,9} = 8.9$, $p = 0.015$; CZ: $F_{1,9} = 5.7$, $p = 0.04$; C1: $F_{1,9} = 5.4$, $p = 0.04$; C2 : $F_{1,9} = 6.7$, $p = 0.03$; FC1 : $F_{1,9} = 5.6$, $p = 0.04$; FC2 : $F_{1,9} = 13.2$, $p = 0.005$; FC3 : $F_{1,9} = 4.1$, $p = 0.07$; FC4 : $F_{1,9} = 7.4$, $p = 0.02$). This replicates previous findings. Task performance was not assessed due to task accuracy exhibiting a ceiling affect. Lastly, the contingent negative variation (CNV) did not change in amplitude during the last 40 repetitions compared with the first 40 repetitions of cued inphase bimanual movement training (Fig. 3-8)

Results experiment two

The early MRP was maximal over frontocentral electrode sites (greatest at FC1: $1.63 \mu\text{V} \pm 1.23$) and had an onset latency of approximately 1830-1700 ms prior to movement onset. The late MRP peaked after movement onset at approximately 128-133 ms. The scalp distribution of the late MRP was lateralized to the left hemisphere and was maximal over FC1 ($-7.74 \mu\text{V} \pm 1.5$). The re-afferent potential (RAP) was maximal at FC1 ($10.04 \mu\text{V} \pm 1.4$) with latency occurring before 300 ms following movement onset.

The early BP component was maximal over frontocentral electrode sites (greatest at FCZ: $-3.59 \mu\text{V} \pm 1.14$) and had an onset latency of approximately 1845-1775 ms prior to movement onset. The late BP peaked after movement onset around 129-137 ms. The scalp distribution of the late BP was lateralized to the left hemisphere and was maximal over C3 ($-7.78 \mu\text{V} \pm 1.28$). The re-afferent potential (RAP) was maximal at CZ ($7.36 \mu\text{V} \pm 1.27$) with latency occurring before 340 ms following movement onset.

Firstly, a one-way repeated measures ANOVA comparing the amplitude of the early BP to that of the early MRP was significant (Fig. 3-9). The amplitude of the early BP was

significantly larger. This difference was evident at electrode sites FCZ, C1, FC1 and FC3 (FCZ: $F_{1,9} = 8.38$, $p = 0.018$; CZ: $F_{1,9} = 0.827$, $p = \text{NS}$; C1: $F_{1,9} = 4.96$, $p = 0.05$; C3: $F_{1,9} = 3.12$, $p = \text{NS}$; FC1: $F_{1,9} = 12.15$, $p = 0.007$; FC3: $F_{1,9} = 8.98$, $p = 0.015$). A one-way repeated measures ANOVA also revealed that the amplitude of the late BP component was significantly greater when compared to the amplitude of the late MRP component (Fig. 3-9); however, the difference was only significant at electrode site CZ (CZ: $F_{1,9} = 6.17$, $p = 0.035$). Lastly, when comparing the MRP versus the BP there was a trend for the amplitude of the RAP to be of greater amplitude during the cued MRP task (Fig. 3-9) (FCZ: $F_{1,9} = 3.78$, $p = 0.084$; CZ: $F_{1,9} = 1.37$, $p = \text{NS}$; C1: $F_{1,9} = 3.8$, $p = 0.083$; C3: $F_{1,9} = 2.37$, $p = \text{NS}$; FC1: $F_{1,9} = 5.09$, $p = 0.05$; FC3: $F_{1,9} = 3.53$, $p = 0.093$). There was no difference present when comparing the latency of the three components of the MRP and BP.

sLORETA Results

sLORETA localization of the initial segment of the early component

Source localization of the initial portion of the cue-related early MRP component revealed a more predominant activation of the lateral premotor cortex in most subjects (Fig. 3-10). In comparison, source localization of the initial segment of the self-paced early BP component revealed predominant activation of the supplementary motor region (Fig. 3-11). Fig. 3-12, row A, displays the sLORETA localization maps of the cortical regions that exhibited activation during the initial time period of the early component for the averaged cued MRP (left column) and averaged self-paced BP (right column) (Tables 3-1 & 3-2).

Following sLORETA analysis the initial early component of the averaged cue-related MRP

showed predominant activation within the left middle frontal gyrus, just anterior to the left precentral gyrus; an area overlying the lateral premotor cortex. Conversely, the initial time period of the early BP component exhibited activation within the paracentral lobule, a region corresponding to the SMA.

sLORETA localization of the second segment of the early component

Fig. 3-12, row B, displays the sLORETA localization maps for the activation patterns of the second early component time period (we named the negative slope according to current BP nomenclature) for the averaged MRP (left column) and averaged BP (right column) (Tables 3-1 & 3-2). sLORETA analysis revealed that the medial frontal gyrus and superior frontal gyrus of the left cortex, just anterior to the left precentral gyrus, were predominantly activated during this time range. When considering the averaged BP, the medial frontal gyrus was activated as well as the left precentral gyrus.

sLORETA localization of late component

Fig. 3-12, row C, displays the sLORETA localization maps for the cortical activation patterns of the late component for the cued MRP (left column) and self-paced BP (right column) (Tables 3-1 & 3-2). The late MRP component showed with activation within the left superior frontal gyrus and left precentral gyrus; corresponding to the primary motor cortex, whilst the late BP component predominantly showed activation within the left precentral gyrus, an area associated with the primary motor cortex as well.

sLORETA localization of re-afferent component

Lastly, Fig. 3-12, row D, displays the sLORETA brain maps for the cortical regions most active during the time period of the re-afferent potential (Tables 3-1 & 3-2). The RAP of the averaged MRP (left column) showed with activation of the left postcentral

gyrus, an area related to the primary sensory cortex, and the RAP of the averaged BP showed with activation within the left precentral gyrus, left postcentral gyrus and paracentral lobule.

Discussion

Cued inphase BMT has been reported to increase the amplitude of the cue-related early MRP component (Chapter 2). We hypothesized that the early MRP component was primarily generated by the lateral premotor cortex. Conversely, the self-paced early BP component is primarily generated by the SMA. Results from experiments one and two support the hypothesis that the early component of the cue-related MRP and self-paced BP are predominantly generated by differing cortical regions (Fig. 3-12) and are differentially modulated by specific training types. Experiment one reported that the early BP component, elicited by a self-paced unimanual movement, was not modulated in response to cued inphase BMT (Fig. 3-6). This result indicated that supplementary motor cortical excitability was not modulated in response to cued inphase BMT; therefore the cue-related early MRP component observed in our previous experiments was most likely not predominantly generated by the SMA.

The second hypothesis of experiment one that predicted training-related modulations of the cue-related early MRP component in the last 40 repetitions of cued inphase BMT was supported (Fig 3-7) and replicated our previous findings (Chapter 2). Since the observed enhancement of the cue-related early MRP component in the last 40 repetitions of cued inphase BMT did not transfer to modulations of the self-paced early BP component of the post-unimanual trial, this result further supported the hypothesis that cued inphase BMT does not modulate SMA excitability. If the cue-related early MRP

component was representative of predominant SMA excitability then an enhancement of the self-paced early BP component should have been evident since the cue-related early MRP component in the last 40 repetitions of cued inphase BMT increased in amplitude. In our previous studies (Smith & Staines, 2006 & Chapter 2) an increase of the cue-related early MRP component amplitude in the last 40 repetitions of cued inphase BMT had transfer effects to the post-unimanual task.

The localization of the early MRP versus the early BP was confirmed in experiment two by source localization methods (sLORETA) (Figs. 3-10, 3-11 & 3-12) (Tables 3-1 & 3-2). Experiment two demonstrated that the cue-related MRP and self-paced BP, although similar in latency, they differ in terms of amplitude (Fig. 3-9) and sites of maximal activation of the various components (Fig. 3-12). But most importantly, experiment two confirmed that the BP was generated by the SMA, M1 and S1, which previous studies have found (Colebatch, 2007; Deecke, 1987; Shibasaki et al., 1980; Shibasaki & Hallett, 2006), but the cue-related MRP is generated most likely by the lateral premotor cortex, in addition to the M1 and S1 (Fig. 3-12). Experiment one is the first experiment to show that cued inphase bimanual movement training has differential modulatory affects upon event-related potentials. Specifically, experiment one highlighted that the cue-related MRP, utilized in Chapter 2, is a more appropriate measure of cortical excitability change in response to inphase BMT, whereas the self-paced BP is not an appropriate measure of the underlying training-related adaptations induced by cued inphase BMT. This is an important result because it opens up the possibility of utilizing certain event-related potentials as measures of cortical modulations in response to specific types of movement training, and these ERPs

are sensitive enough to assess within session, short-term training-related cortical excitability modulations.

The self-paced BP versus the cue-related MRP

We are not the first to hypothesize a differential cortical generator subserving the cue-related early **MRP** component versus the self-paced early **BP** component. In a study by Jahanshahi et al. (1995) this issue was explored indirectly by investigating the difference between the self-paced **BP** and cue-related **MRP** of normal healthy individuals to those with Parkinson's disease. Parkinson's disease is a pathology characterized by a disruption of dopaminergic neurons within the basal ganglia, which ultimately hinders activation of the **SMA**, an area heavily connected to the basal ganglia. The authors reported that the amplitude of the self-paced early **BP** component was of greater amplitude in healthy control subjects versus Parkinson's patients. However, this difference in early component amplitude was not evident when observing the cue-related early **MRP** component. Instead the early component of the cue-related **MRP** was comparable to the healthy control data. Jahanshahi et al. (1995) further reported that the early component of the self-paced **BP** was maximal at electrode site **FCZ**, a site overlying the **SMA**; this is in line with current literature regarding the **BP**. On the other hand, the early **MRP** component associated with a cued movement was lateralized and maximal at electrode site **FC4**, a region corresponding to the lateral premotor cortex. Therefore, Jahanshahi et al. (1995) concluded that the localization of the early **BP** component was most likely different than the early component of the cue-related **MRP**. More specifically, it was thought that the self-paced early **BP** component, whilst generated by the **SMA**, the cue-related early **MRP** component most likely was generated predominantly by the lateral premotor cortex;

however, the authors (Jahanshahi et al., 1995) at the time could not confirm this assertion based solely on ERP data.

The present studies were designed to indirectly (experiment one) and directly (experiment two) investigate the localization of the early component of the self-paced BP and cue-related MRP, in addition to the late component and re-afferent potential of both ERPs (experiment two). Based upon our previous findings (Chapter 2) that cued inphase BMT enhanced the amplitude of the cue-related early MRP component for a unimanual task; we hypothesized that if the early component of the self-paced BP and cue-related MRP are both generated by the SMA then cued inphase BMT should also increase the amplitude of the self-paced early BP component as well. This hypothesis was not supported. Cued inphase BMT did not affect the amplitude of the self-paced early BP component (Fig. 3-6). However, the early cue-related MRP component observed during the inphase bimanual training paradigm (trial 2) did exhibit an increase in amplitude in the later portion of the training session (Fig. 3-7), replicating previous findings (Smith & Staines, 2006 & Chapter 2). Based upon the literature regarding the self-paced BP, the early BP component, evident in the pre and post trials of experiment one, most likely represented activation of the SMA (Colebatch, 2007; Shibasaki & Hallett, 2006). Hence, we concluded that SMA excitability was not influenced by cued inphase BMT.

The Bereitschaftspotential of experiment one followed the same topographic pattern as reported in previous studies (Colebatch, 2007; Deecke et al., 1969; Deecke et al., 1976; Deecke, 1987; Shibasaki & Hallett, 2006). The early BP component was maximal at electrode site CZ, a position overlying the SMA region; the late BP component was maximal at site C1, an area associated with the primary motor cortical representation of

the hand. In experiment two the early BP component was maximal at electrode site FCZ, another site associated with the SMA. The late BP component was lateralized to site C3, an M1 region overlying the hand representation. Conversely, the early component of the cue-related MRP was maximal at site FC1 as was the late MRP component, an area associated with the lateral premotor cortex.

sLORETA self-paced BP & cue-related MRP localization

The sLORETA images showed evidence of differential early component localization between the self-paced BP and cue-related MRP (Fig. 3-12). Specifically, the averaged BP data (Fig. 3-12) showed the early BP component with predominant activation of the SMA, the late BP component with contralateral M1 activation and the RAP with primary sensory cortical activation. The averaged data for the cue-related MRP (Fig. 3-12) was different when observing the early MRP component. The early MRP component was lateralized to the contralateral lateral premotor area, whilst the late MRP component and RAP followed the same pattern as the BP; the late MRP component activated the contralateral M1 region and RAP activated the primary sensory cortex. This finding is comparable with several studies demonstrating the activation of differential premotor areas during the execution of self-paced and externally triggered movement. Goldberg (1985) suggested that the lateral premotor cortex, cerebellum and parietal lobe would dominate during externally triggered movements, whereas the SMA and basal ganglia would predominant self-paced movement (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003). In a study by Debaere (2003) movements generated by internal versus external guidance revealed a dissociative network involved in these two modes of movement production. Debaere (2003) showed that self-initiated movement exhibited

greater activation within the SMA, basal ganglia, cingulate motor cortex, inferior parietal, frontal operculum and cerebellar dentate nucleus. Comparably, visually guided movement showed greater activation of the dorsal and ventral premotor cortex, inferior temporal gyrus, superior parietal cortex, thalamus and cerebellum. Outlined in the introduction, investigations of human and non-human primates revealed that externally triggered movement primarily activated the dorsal portion of the lateral premotor cortex (PMd). Inactivation of the SMA region by way of 'virtual lesion' or pathology such as Parkinson's disease reported that self-initiated movement was difficult or impossible; however, externally triggered movement, either visually or acoustically, was possible and was comparable to healthy control data (Almeida et al., 2002; Almeida et al., 2003; Hoshi & Tanji, 2006; Jancke et al., 2000; Johnson et al., 1998; Koch et al., 2006; Riehle & Requin, 1989; Sugiura et al., 2001; Swinnen et al., 1997). Samuel et al. (1997) also reported predominant activation of the dorsal premotor cortex in patients with Parkinson's disease during externally cued inphase bimanual movement. Perhaps due to the nature of the cued visuomotor bimanual task in experiment one, which required a movement with visual cuing, the lateral premotor region that has been shown to be involved in the integration of proprioceptive and visual information during visually guided movement and externally triggered movement could have been upregulated (Debaere et al., 2003). This upregulation may have enhanced the amplitude of the early MRP component in the later portion of the cued inphase BMT task, but did not affect SMA activity, measured by the early BP component since the SMA region is not particularly implicated in externally cued movement.

Lateral premotor cortex and learning

The dorsal portion of the lateral premotor cortex (PMd) is functionally divided into the rostral and caudal segments. The caudal portion of the PMd is similar to the SMA in that both regions are active during preparatory and executory phases of movement (Boussaoud, 2001; Gomez, Fu, Flament, & Ebner, 2000; O'Shea, Johansen-Berg, Trief, Gobel, & Rushworth, 2007; Schluter, Rushworth, Passingham, & Mills, 1998; Simon et al., 2002) and send projections to the primary motor cortex (M1) and spinal cord (Barbas & Pandya, 1987; Dum & Strick, 1991; He, Dum, & Strick, 1993; Huang et al., 2009; Mochizuki, Huang, & Rothwell, 2004; Muakkassa & Strick, 1979; O'Shea, Sebastian, Boorman, Johansen-Berg, & Rushworth, 2007; Picard & Strick, 2001). In comparison, the rostral segment of the PMd is more closely related to the pre-SMA whereby both regions do not project to the M1 or spinal cord, and are more related to cognitive aspects of motor control (Barbas & Pandya, 1987; Dum & Strick, 1991; He et al., 1993; Muakkassa & Strick, 1979; Picard & Strick, 2001). Bilateral PMd regions are highly connected interhemispherically (Boussaoud, Tanne-Gariepy, Wannier, & Rouiller, 2005; Chouinard & Goodale, 2007). As mentioned above the PMd cortex is active during externally triggered movement versus internally generated movement, it is also reported to show adaptive changes during the acquisition of visuomotor conditional tasks (Lee & van Donkelaar, 2006; Mitz, Godschalk, & Wise, 1991; Xiao, 2005). A lesion to the PMd removes the ability to execute cued associations (Halsband & Passingham, 1982; Halsband & Passingham, 1985; Halsband & Freund, 1990; Passingham, 1988; Petrides, 1982; Petrides, 1986). From this evidence we conclude that the visually cued inphase BMT paradigm of experiment one increased excitability of the lateral premotor cortex, most

likely the dorsal portion, and this excitability modulation increased the amplitude of the early **MRP** component in the later portion of the training paradigm (trial 2).

The findings of the two experiments conducted in this study revealed that: 1) cued inphase **BMT** does not affect the amplitude of the early **BP** component, associated with **SMA** excitability for a unimanual movement. 2) The amplitude of the cue-related **MRP** increased in the last 40 repetitions of cued inphase **BMT** and represented learning-related adaptations. 3) The early component of the cue-related **MRP**, observed in trial 2 of experiment one and in our previous works, is not associated with predominant excitability of the **SMA**. 4) The early cue-related **MRP** is associated with activation of the lateral premotor cortex. 5) The late component and **RAP** of both the cue-related **MRP** and self-paced **BP** are associated with activation of the **M1** and **S1** respectively. Even though the cue-related **MRP** is similar to the self-paced **BP** in terms of latency, some fundamental differences are evident when considering the amplitude and localization of the early component. Understanding the cortical sources of the cue-related **MRP** versus the self-paced **BP** are important for future studies investigating cortical excitability modulations in response to bimanual movement training in the stroke patient population. These **ERPs** may be a useful measurement method to gauge within-session cortical modulations in response to rehabilitative protocols.

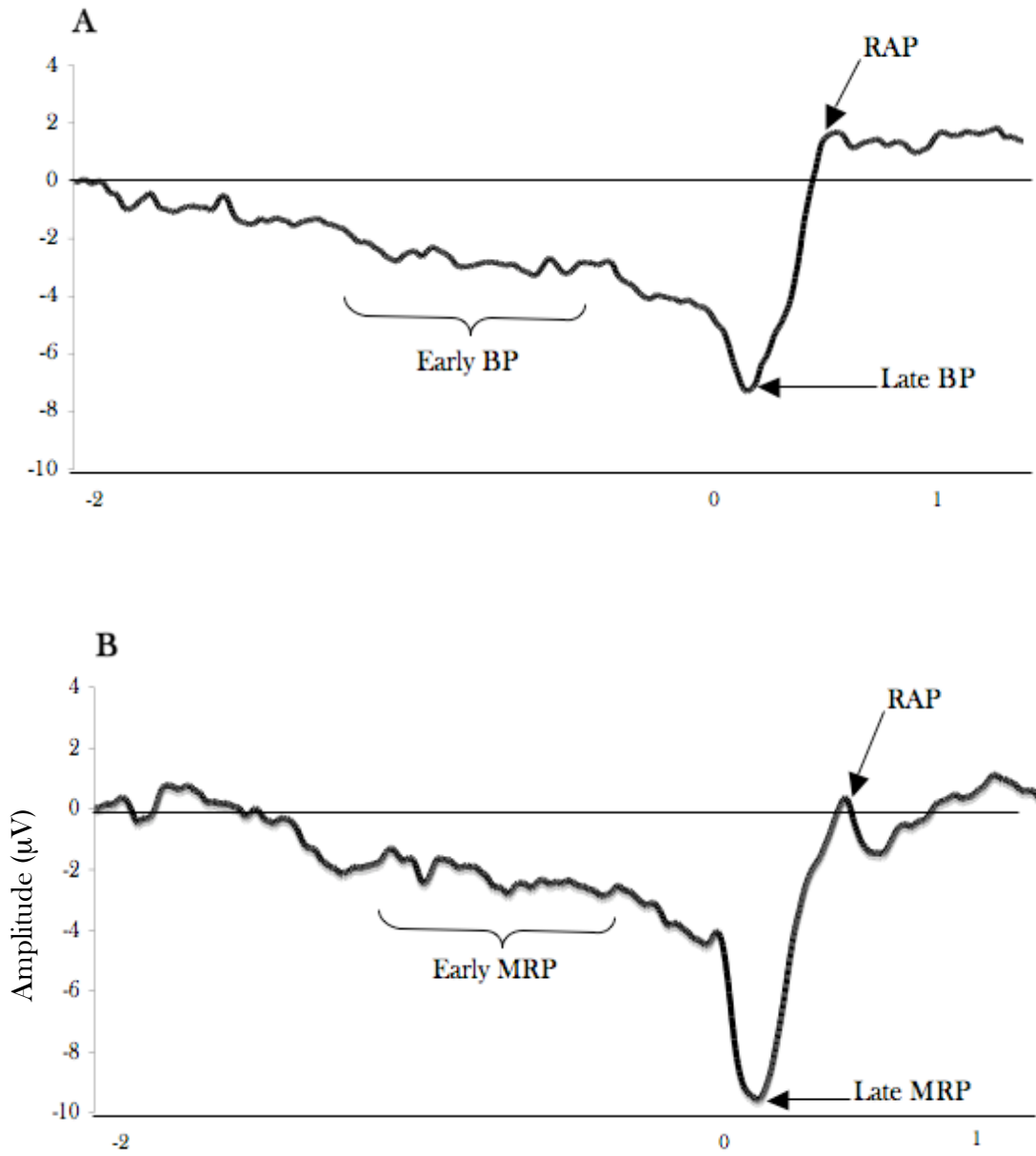


Figure 3-1 - (A) the self-paced Bereitschaftspotential and three main components. (B) The cue-related MRP and three main components.

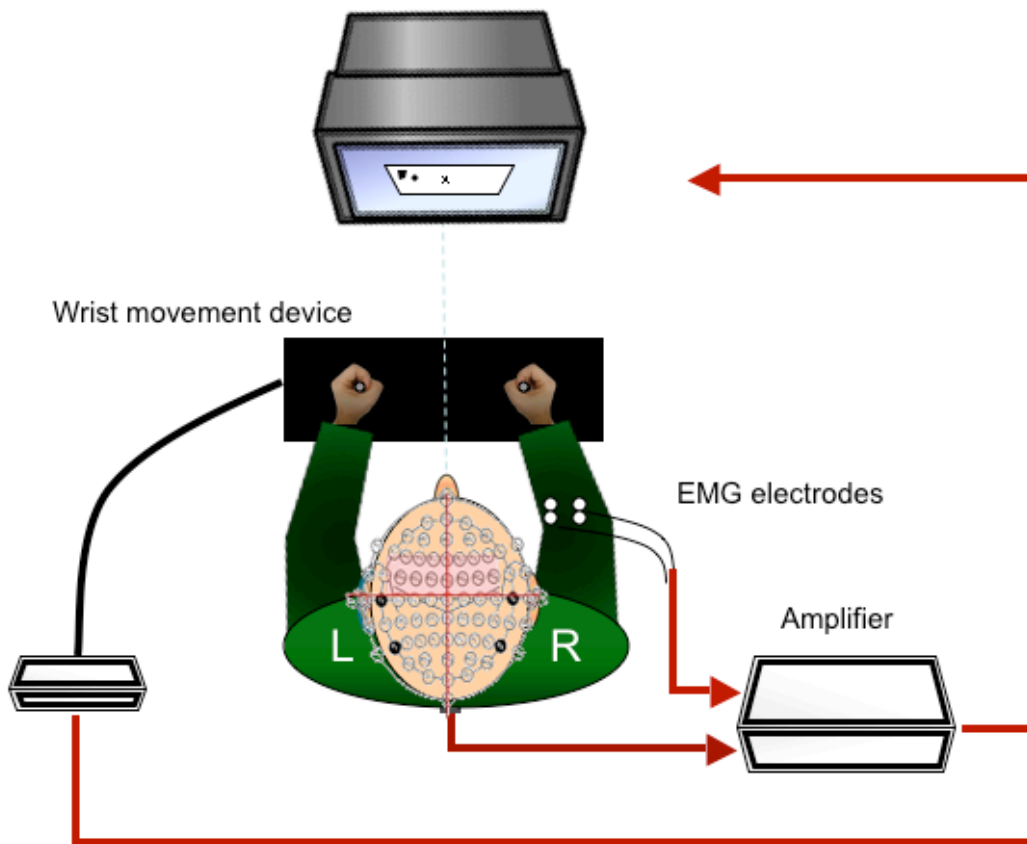


Figure 3-2 - Topview of the subject position during the task with custom made wrist movement device

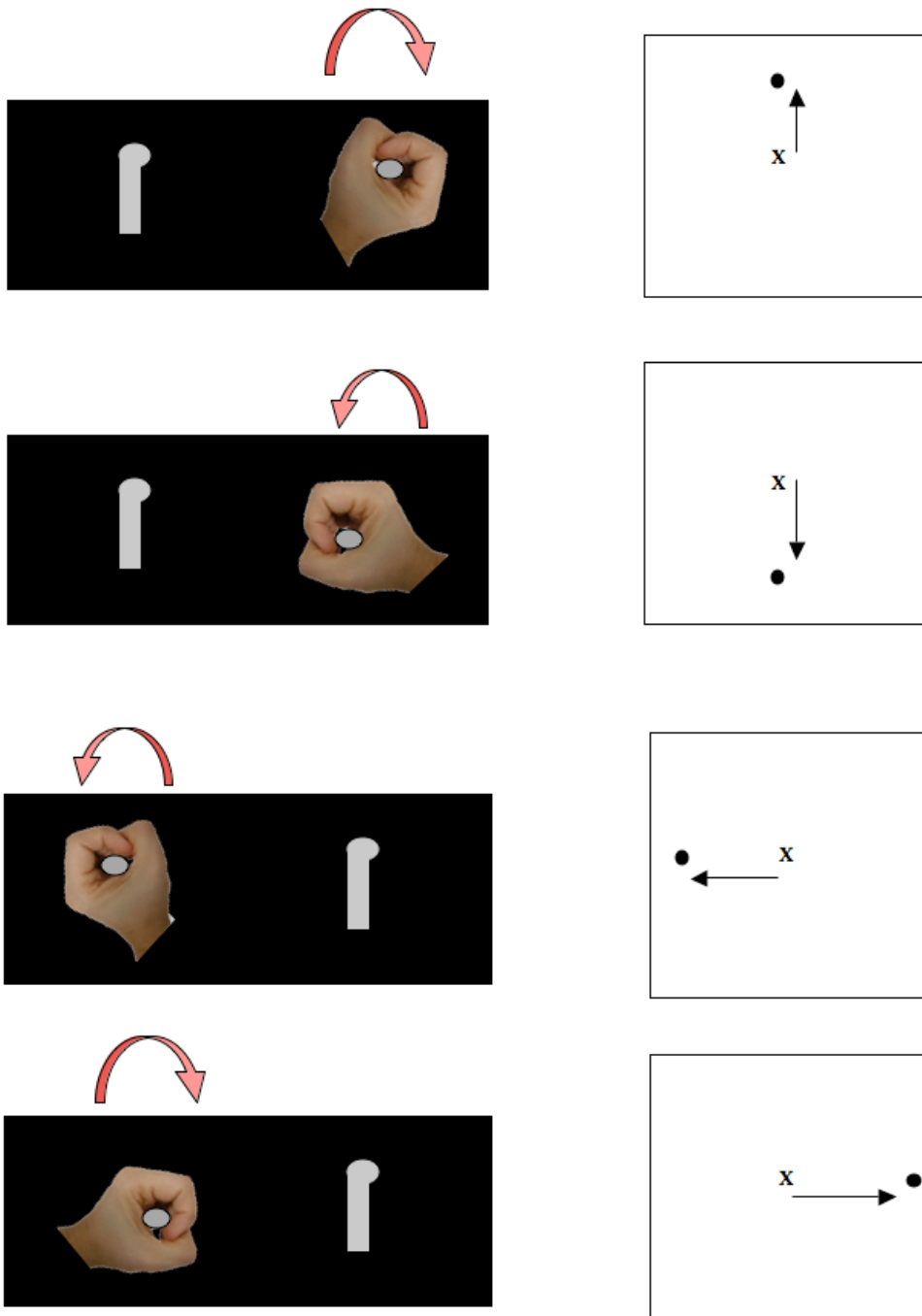


Figure 3-3 - Wrist movement and corresponding cursor movement

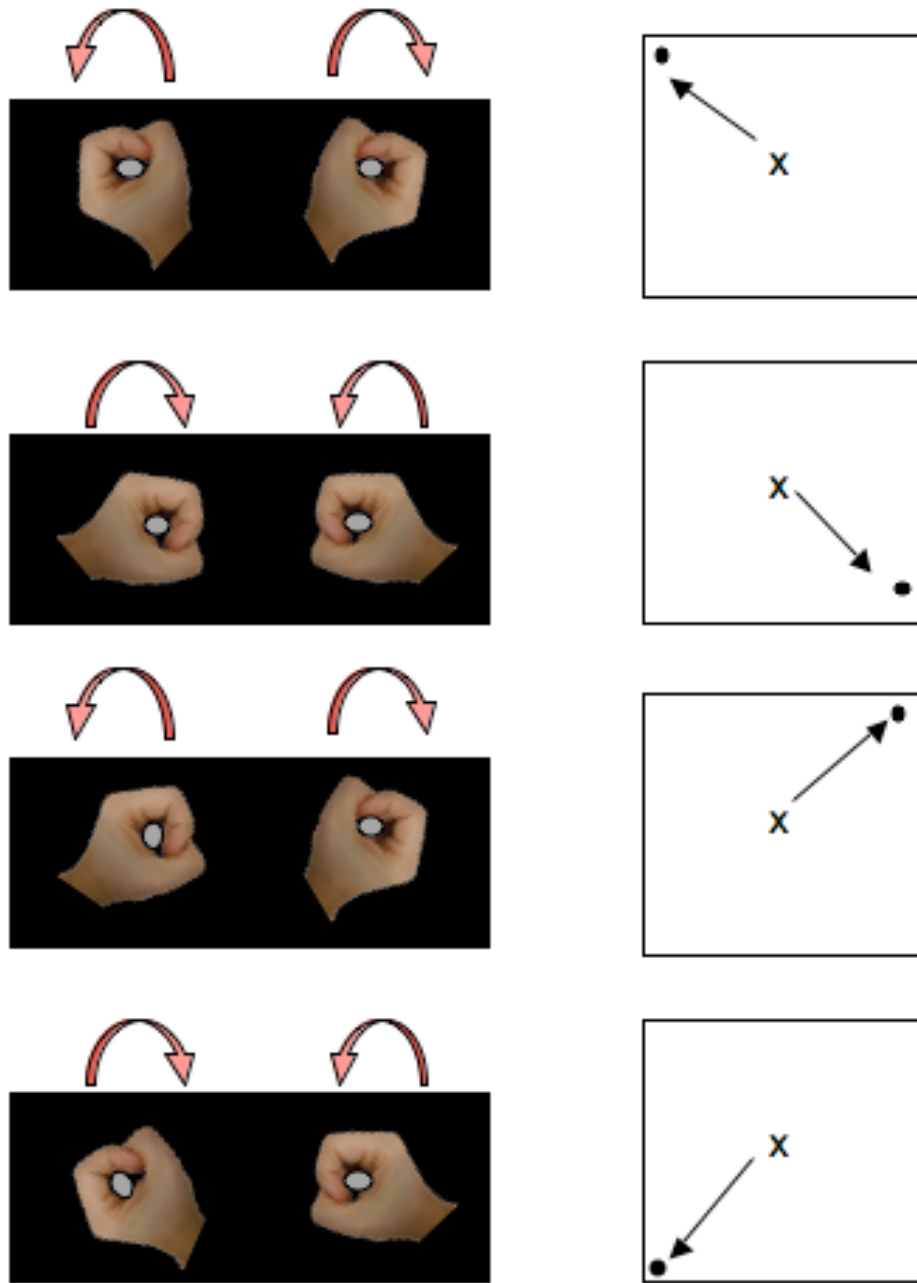


Figure 3-4 - Bimanual wrist movement and corresponding cursor movement

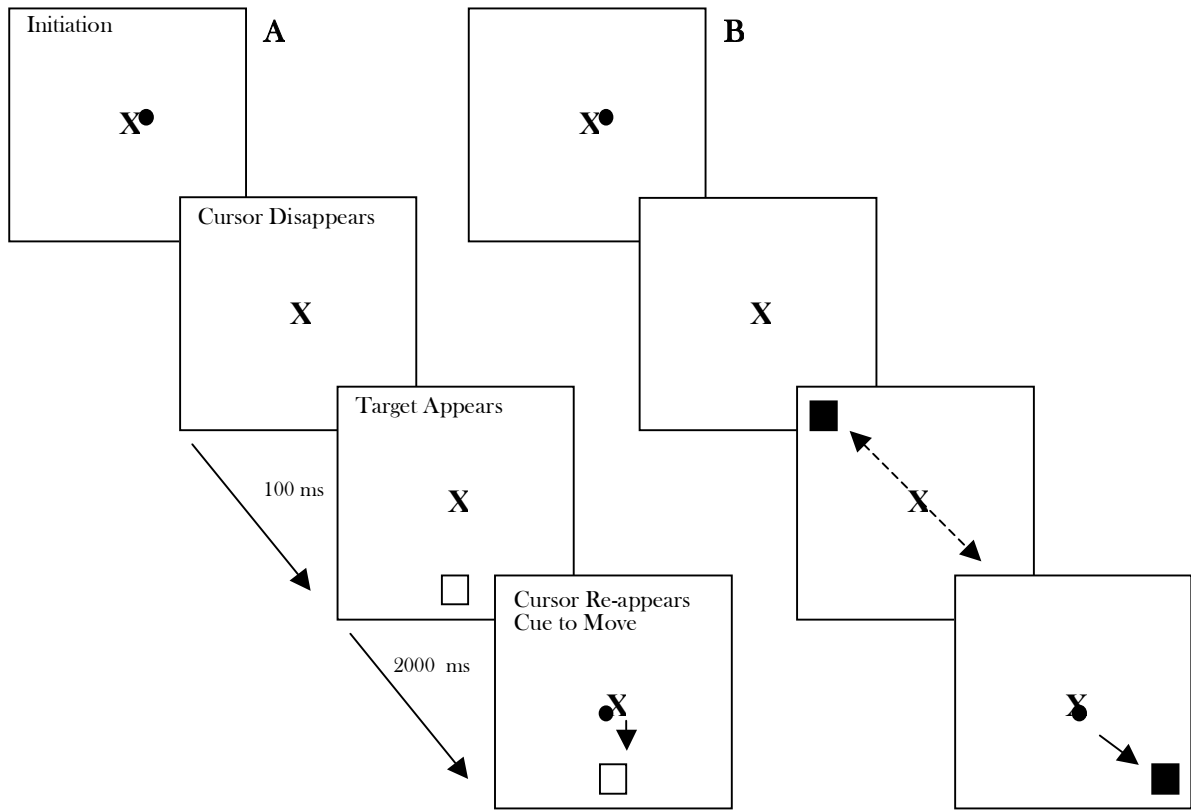


Figure 3-5 - Steps to complete one repetition during (A) cued unimanual movement and (B) inphase bimanual movement training (trial 2).

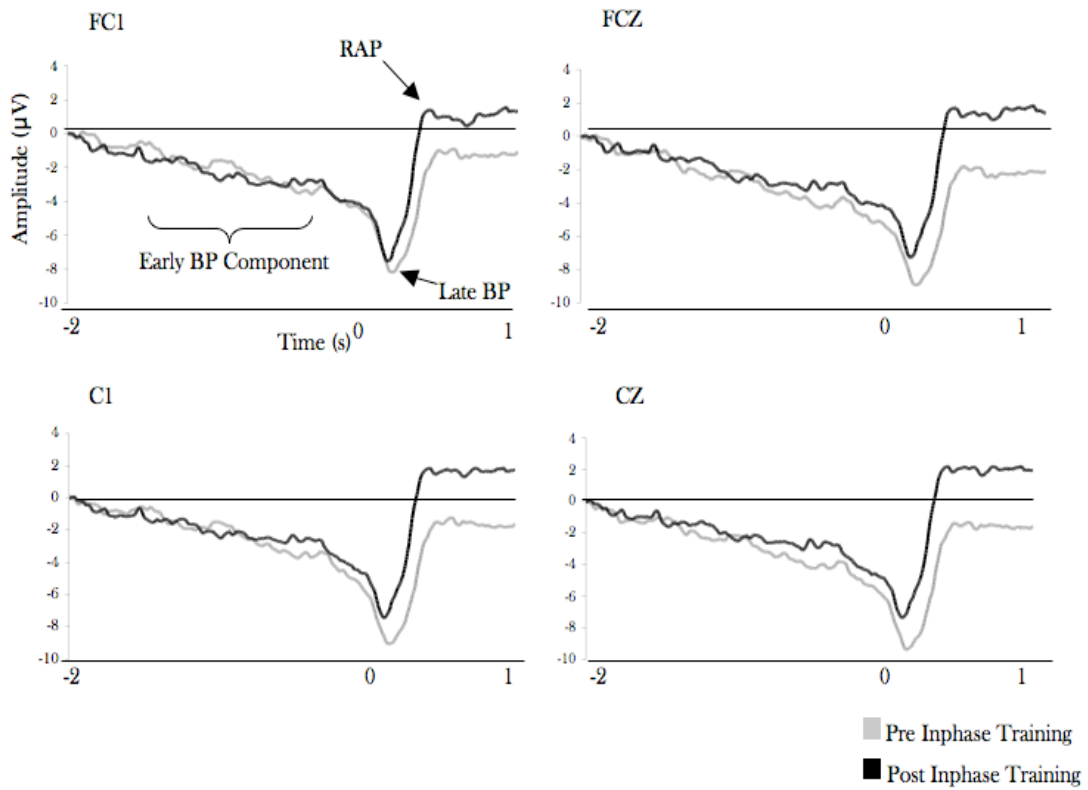


Figure 3-6 - A) Grand average self-paced BPs (CZ, C1 & FC3 n=10; FCZ n=9) time-locked to self-paced movement onset of the right wrist prior to (pre-training grey trace) and following (post-training black trace) practice of the cued inphase bimanual visuomotor training task at 4 electrode sites (FCZ, CZ, C1 and FC3).

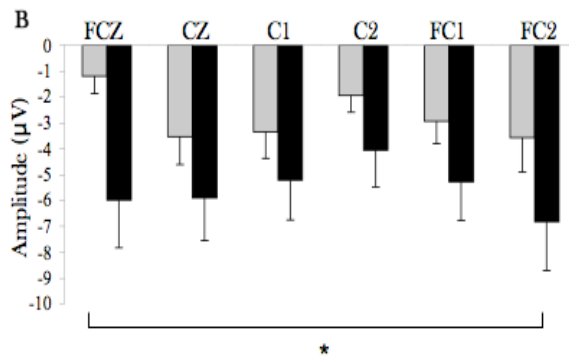
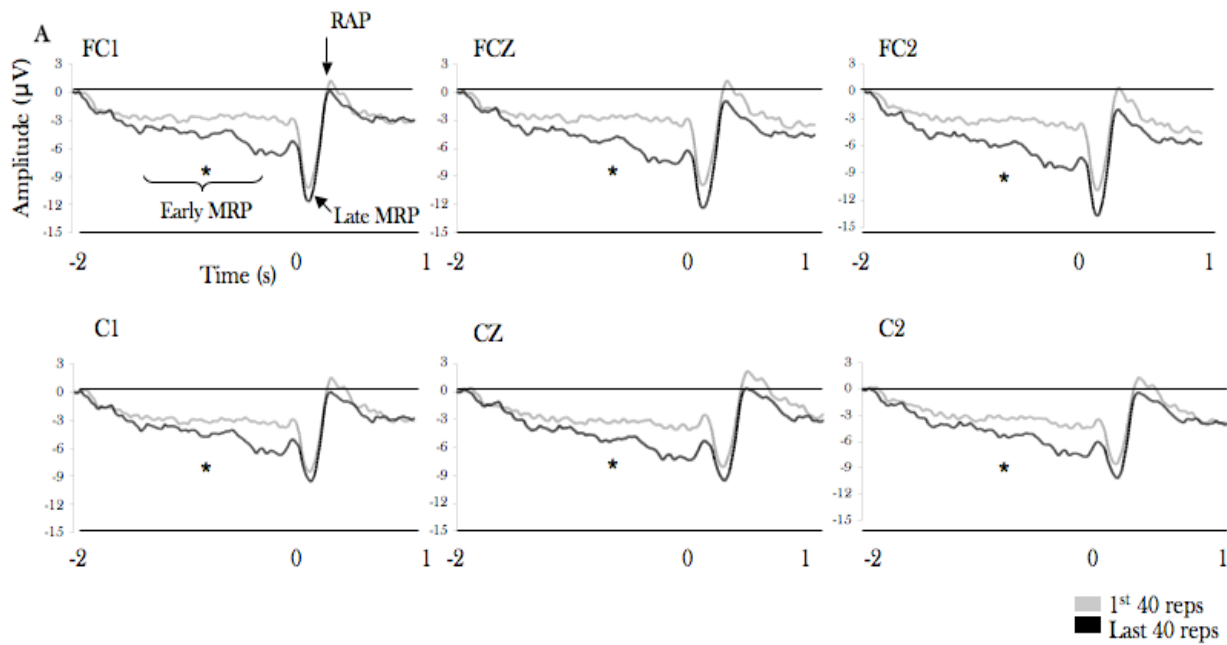


Figure 3-7 - (A) Grand average cued MRPs (CZ, C1, C2, FC1 & FC2 n=10; FCZ n=9) time-locked to cued movement onset of the right wrist in the first 40 repetitions (grey trace) versus the last 40 repetitions (black trace) of the inphase bimanual visuomotor training task (trial 2) at 6 electrode sites (FCZ, CZ, C1, C2, FC1 and FC2). (B) Group mean (\pm SE) of the early MRP amplitudes in the first 40 repetitions (grey bars) and last 40 repetitions (black bars) of cued inphase bimanual visuomotor movement training. * Indicates $p < 0.05$.

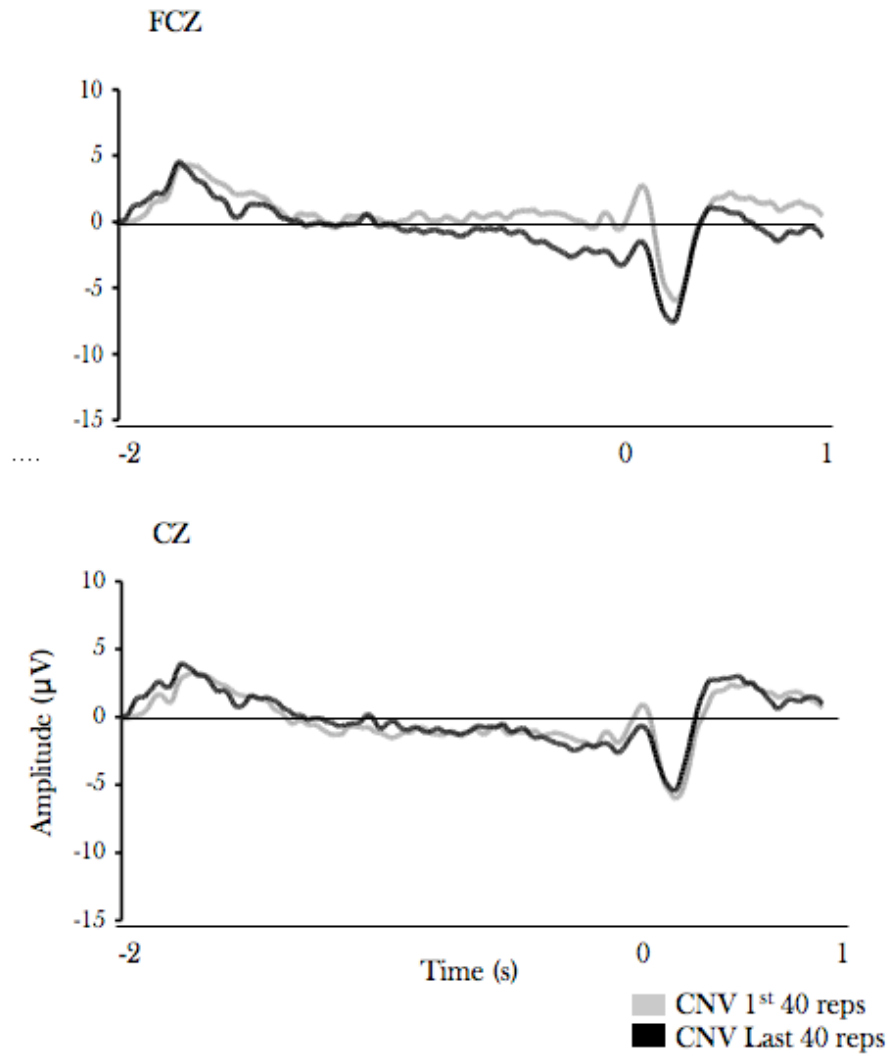


Figure 3-8 - Grand average CNVs (CZ n=10; FCZ n=9) time-locked to the cue to move in the first 40 repetitions (grey trace) versus the last 40 repetitions (black trace) of the cued inphase bimanual visuomotor training task in 2 electrode sites (FCZ, CZ).

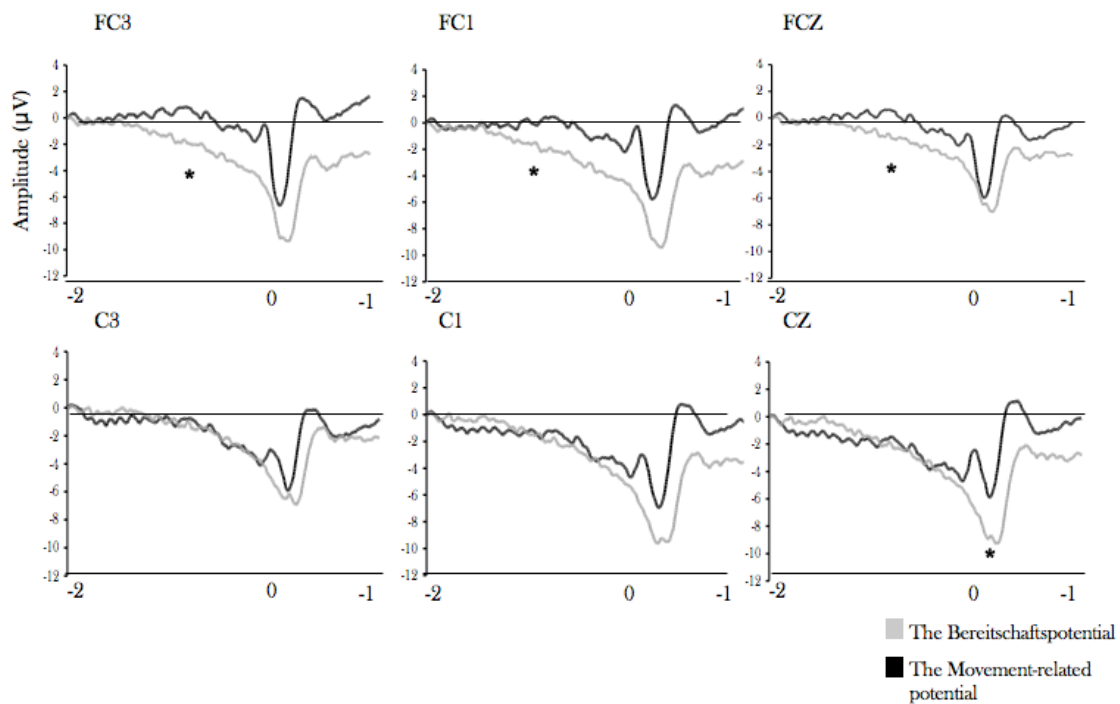


Figure 3-9 - (A) Grand average self-paced BPs (grey trace) time-locked to self-paced movement onset of the right wrist and grand average cue-related MRPs (black trace) time-locked to cued movement onset of the right wrist at 6 electrode sites (FCZ, CZ, C1, C3, FC1 and FC3). * Indicates $p < 0.05$.

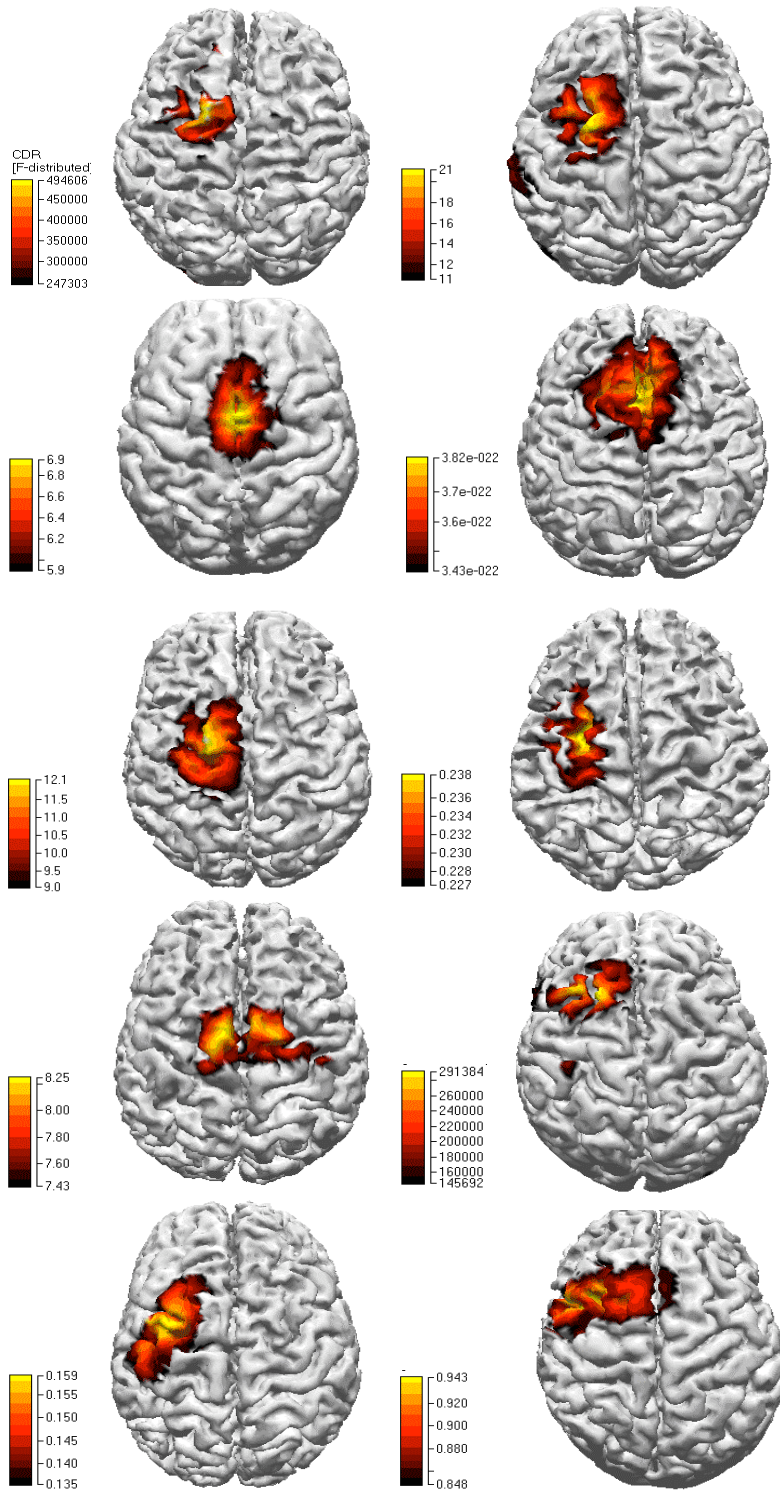


Figure 3-10 - Current density reconstruction of the early MRP for all subjects. The early MRP was specified as a range between -1850 to -1000 ms before cued movement onset. The scale is an F-distribution, higher values correspond to greater activation (indicated by the colour yellow).

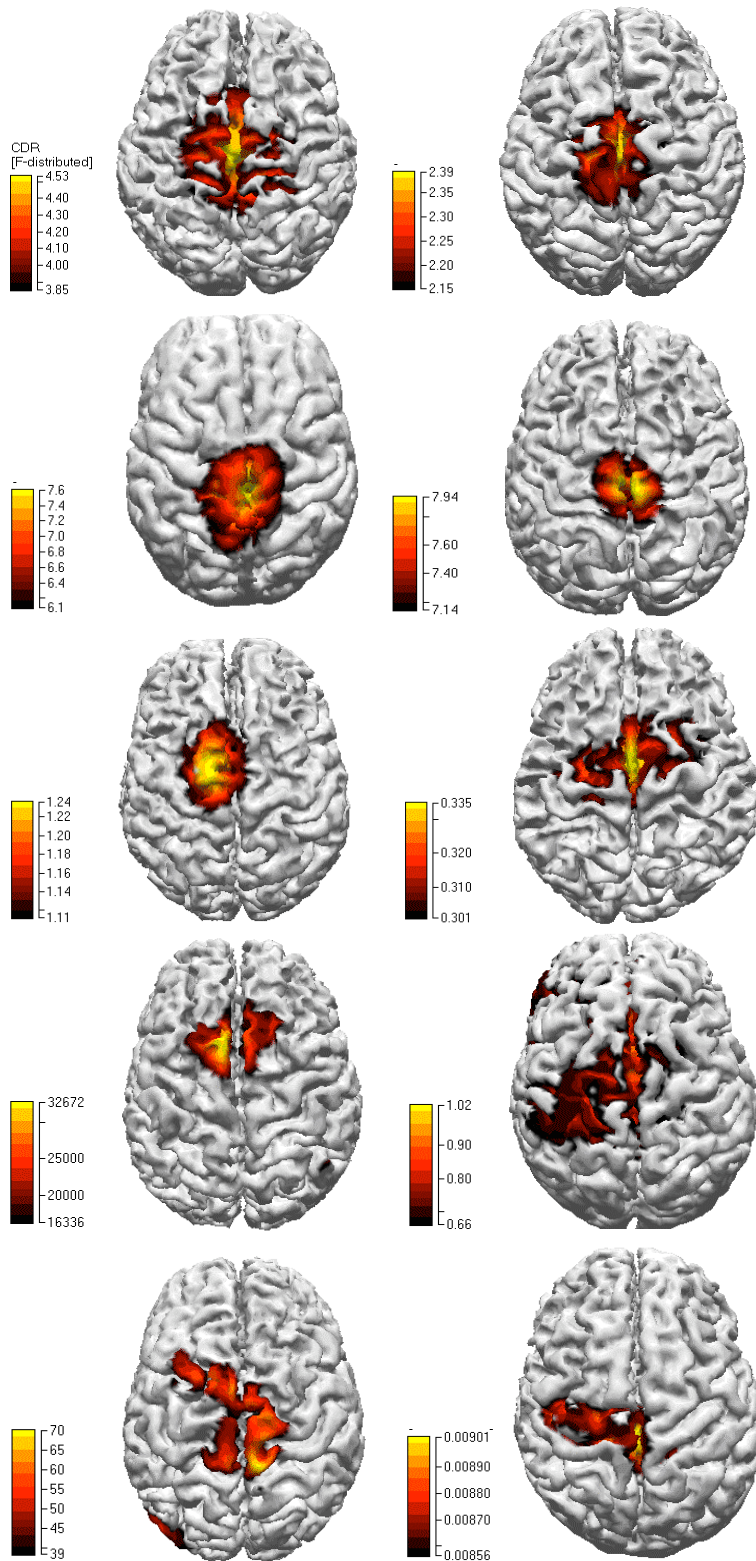


Figure 3-11 - Current density reconstruction of the early BP for all subjects. The early BP was specified as a range between -1850 to -1000 ms before self-paced movement onset. The scale is an F-distribution, higher values correspond to greater activation (indicated by the colour yellow).

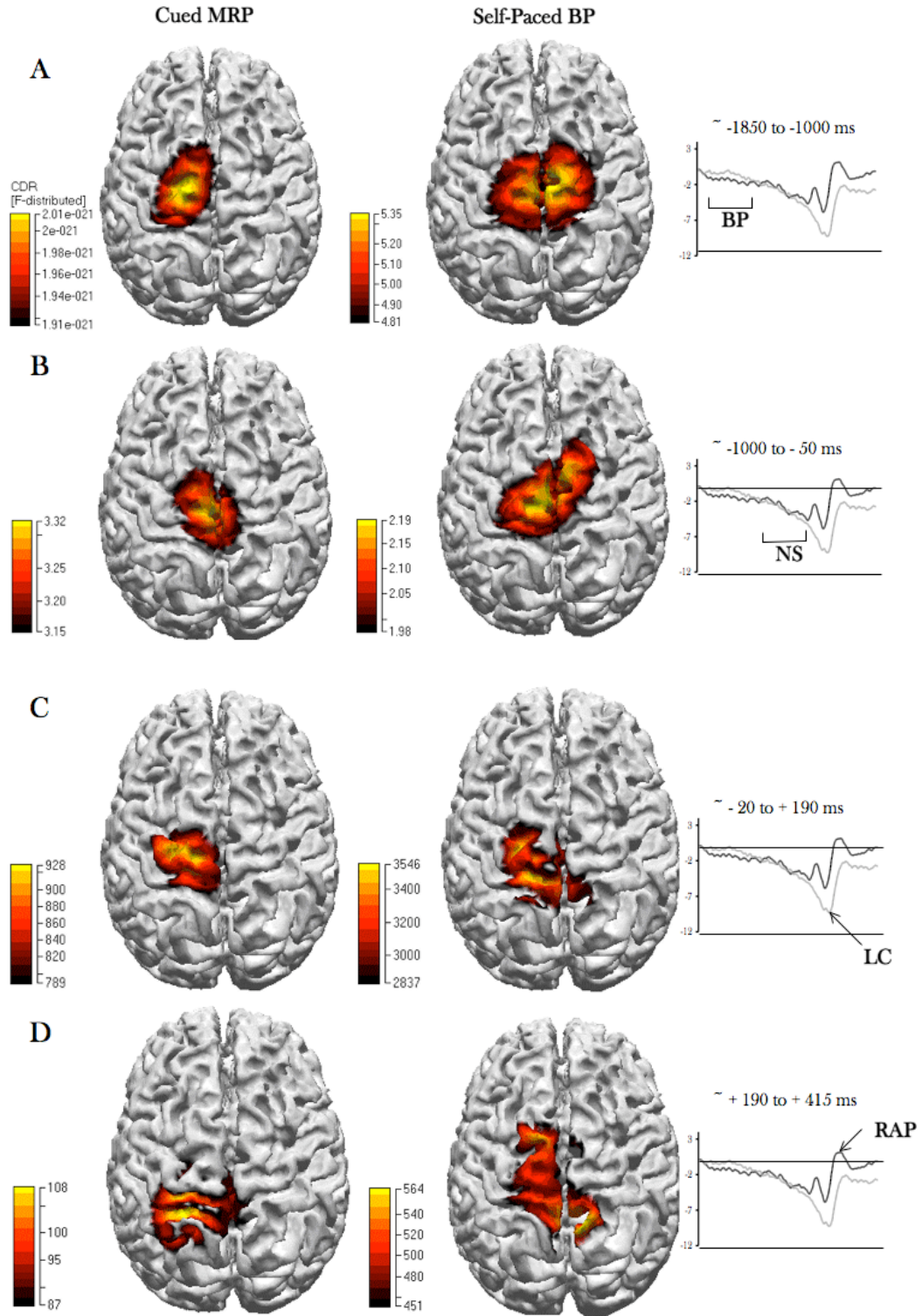


Figure 3-12 - Grand average current density reconstruction results for the (A) early MRP and early BP component, (B) later portion of the early MRP and BP components (negative slope), (C) the late MRP and BP components and (D) the RAP of the MRP and BP. The scale is an F-distribution, higher values correspond to greater activation (indicated by the colour yellow).

| MRP Component | Medial Frontal Gyrus | Left Middle Frontal Gyrus | Left Superior Frontal Gyrus | Left Precentral Gyrus | Left Postcentral Gyrus | Paracentral Lobule |
|---------------------------|----------------------|---------------------------|-----------------------------|-----------------------|------------------------|--------------------|
| Early MRP Component | | x | | | | |
| MRP Negative Slope | x | | | | | |
| Late MRP Component | | | x | x | | |
| MRP Re-afferent Potential | | | | | x | |

Table 3-1 - Areas of activation determined by current density reconstruction during the four components of the cue-related MRP.

| BP Component | Medial Frontal Gyrus | Left Middle Frontal Gyrus | Left Superior Frontal Gyrus | Left Precentral Gyrus | Left Postcentral Gyrus | Paracentral Lobule |
|--------------------------|----------------------|---------------------------|-----------------------------|-----------------------|------------------------|--------------------|
| Early BP Component | | | | | | x |
| BP Negative Slope | x | | | x | | |
| Late BP Component | | | | x | | |
| BP Re-afferent Potential | | | | x | x | x |

Table 3-2 - Areas of activation determined by current density reconstruction during the four components of the self-paced BP.

Chapter Four - Influential kinematic parameters and the cue-related MRP

Smith, A.L. and Staines, W.R.

Overview

The cue-related movement-related potential (MRP) is an event-related potential (ERP) extracted from an EEG recording preceding and following cued movement onset. The present study investigated a variety of kinematic parameters that may influence the components of the cue-related MRP representing preparation, execution and movement-related sensory feedback. Ten healthy participants were required to perform a cued right wrist flexion task under different kinematic conditions. Subjects performed 40 repetitions of cued right wrist flexion with varying speeds of movement, imposed loads at movement onset or as an inertial load, and range of motion. We hypothesized that the components of the cue-related MRP would be modulated in response to the various kinematic parameters. Results indicated that the imposed kinematic conditions had variable effects upon the components of the cue-related MRP. The component primarily affected was the re-afferent potential (RAP) a component related to movement-related sensory feedback. These data will inform future training-related studies in the healthy and stroke patient populations that utilize the cue-related MRP as a measure of cortical excitability modulation in response to motor training.

Introduction

The cue-related movement-related potential (MRP) typically elicited by a visual or acoustically cued movement is an event-related potential (ERP) that is not well understood. The cue-related MRP has been measured in previous studies (Cui & MacKinmon, 2009;

Jahanshahi et al., 1995; Jankelowitz & Colebatch, 2002; Smith & Staines, 2006); however, the certain kinematic parameters that influence the components of the cued MRP remain unclear. Understanding how various movement parameters influence the amplitude of the cue-related MRP would inform the design and control of future training-related studies utilizing the cue-related MRP as a measure of learning-related cortical adaptation.

The cue-related MRP is quite similar in presentation to the Bereitschaftspotential (BP), an ERP associated with the preparation and execution of a self-paced movement (Cui & Mackinnon, 2009; Jahanshahi et al., 1995; Jankelowitz & Colebatch, 2002). The self-paced BP contains three components; 1) The early BP component, reflecting preparatory excitability within the SMA (Hallett & Toro, 1996; Praamstra et al., 1996); some divide the early component further into a later segment called the negative slope (NS), a segment associated with preparatory and executory excitability of the SMA and M1 (Shibasaki & Hallett, 2006). 2) The late BP component denoting primary motor cortical excitability at motor execution (Jahanshahi & Hallett, 2003; Shibasaki & Hallett, 2006), and lastly 3) the re-afferent potential (RAP) conveying primary sensory cortical excitability pertaining to movement-related feedback (Colebatch, 2007; Deecke et al., 1969; Deecke & Lang, 1996; Shibasaki & Hallett, 2006). The cortical generators of the cue-related MRP are most likely comparable when considering the late MRP and RAP (M1 and S1); however, the predominant generator of the early MRP component seems to be the lateral premotor cortex, a region associated with increased excitability in response to an externally triggered movement, whereas the SMA underlies the early BP amplitude (Hoshi & Tanji, 2006; Jancke et al., 2000; Koch et al., 2006; Riehle & Requin, 1989; Sugiura et al., 2001).

Previous studies report that the amplitude of the later portion of the early BP component (negative slope) (Hink, Deecke, & Kornhuber, 1983; Kutas & Donchin, 1974b) and late BP component (Becker & Kristeva, 1980; Kutas & Donchin, 1977; Nishihira, Araki, & Ishihara, 1989; Shibata, Moritani, & Kubota, 1993; Slobounov & Ray, 1996; Wilke & Lansing, 1973) increases in amplitude in response to an increase in an external load placed upon the musculature; indicating that force modulates the components of the self-paced BP related to executive excitability (Kristeva, Cheyne, Lang, Lindinger, & Deecke, 1990; Siemionow et al., 2000). However, in a subsequent study by Slobounov et al. (2002) it was demonstrated that increased force output during a movement reduces the rate of movement and attenuates the BP, but if rate of movement is held constant, force production itself does not influence the amplitude of the BP.

Grunewald and Grunewald-Zuberbier (1980; 1983) report that early BP amplitude is greater during increased movement rate versus slow and smooth ramped movement. Slobounov et al. (1998a; 1998b) have reported a similar finding of increased late BP component and RAP amplitude with increased movement rate. Looking at the effect of range of motion (ROM), Slobounov et al. (1999; 2000) reported that as ROM increased so too did the amplitude of the later portion of the early component (negative slope) and late BP component. Overall, the aforementioned studies indicate that the self-paced BP is influenced by a combination of factors including: movement rate (speed), and range of motion; however it is debatable whether force production influences the self-paced BP.

Due to the similarities between the self-paced BP and cue-related MRP, the current study was designed to investigate kinematic parameters that may influence the cue-related MRP. We hypothesized that movement speed and ROM would modulate the cue-related

MRP. Varying loads placed upon the musculature at movement onset or as an inertial load, would influence the components of the cue-related MRP as well, and the two types of load exposures would influence the MRP comparably. Overall, this work attempts to establish better understanding of the kinematic parameters that influence the cue-related MRP to inform future training-related studies in the healthy and stroke patient populations.

Materials & Methods

Subjects

Ten healthy, normal participants (2 male, 8 female; age range 22-35) participated in the study, each providing written informed consent. All were right-handed by self-report and did not report any history of neurological impairments. Participants were paid a nominal fee for their participation. The Office of Research Ethics at the University of Waterloo and the research ethics board at the Toronto Rehabilitation Institute approved the experimental procedures.

EMG & EEG Recording Procedure

Electromyography (EMG) was recorded from the right flexor carpi radialis (FCR) muscle using bipolar electrodes placed longitudinally over the muscle belly. Scalp electroencephalographs (EEG) were recorded from 22 electrodes using the international 10-20 system guidelines and an electrode cap (Quick-Cap, Neuroscan, Compumedics, NC). These channels were recorded to determine the topography of the MRP; however, not all were included in quantitative analysis. All EEG channels were referenced to linked electrodes placed on the left and right mastoid processes. Vertical and horizontal eye movements were monitored with bipolar recordings above and below the left eye and at the lateral aspect of the left and right eyes respectively. All channels were amplified (20,000x),

low pass filtered (50 Hz), digitized at a rate of 250 Hz (Neuroscan, Compumedics, NC) and impedance was below 5 k Ω . All post-processing of the EEG data was performed using Neuroscan® (Compumedics, NC).

Assessing Maximum Force Production

A custom-made device was used to measure 3% and 5% of each subject's maximum force production (MFP) for right wrist flexion. The device consisted of a force transducer stabilized upon a flat surface. Linked to the force transducer was a strap that the subject would grasp with their right hand. Subjects were instructed to rest the ulnar aspect of the right forearm upon the stable surface, grasp the strap and perform three isometric MFPs of right wrist flexion. An amplifier linked to the transducer displayed MFP in grams of force. Three and five percent of MFP measured in grams of force was recorded for each subject (Table 4-1). A weight equating to 3% or 5% of MFP was added to conditions: 3% and 5% weight at movement onset and as an inertial load.

Behavioural Task

Subjects were seated in a dimly lit room, in front of a computer monitor with arms supported (Fig. 4-1). The medial aspects of bilateral forearms were supported with elbows flexed to 90° and the shoulder in forward flexion approximately 0-10°. The wrist was oriented in a neutral position so that flexion and extension of the wrist occurred in the horizontal plane. This position was maintained for all trials. A custom-made wrist movement device (Fig. 4-2A & B) was used to control a cursor on a computer screen by way of wrist flexion and extension. The device was placed upon the subject's lap (Fig. 4-1) and consisted of two handles that when grasped by bilateral hands, pivoted in clockwise and counter-clockwise directions in response to wrist flexion and extension. Each handle

was linked to a potentiometer embedded within the device housing which was in turn linked to a custom made behavioural program constructed through LabVIEW (National Instruments, Austin, TX). The 5th metacarpal of the subject's hand rested upon the bottom portion of the device handles. Shown in Fig. 4-3, right wrist extension controlled upward movement of the cursor, and right wrist flexion controlled downward movement of the cursor. Left wrist extension controlled cursor movement to the left and left wrist flexion controlled cursor movement to the right.

The fundamental procedure of all eight trials was identical and required subjects to move the cursor (8 mm in diameter) from a starting position to a target (1.5 cm²) displayed in the bottom-centre of the screen (Fig. 4-4). Movement of the cursor was calibrated for each subject so that maximal flexion or extension of the wrist would not allow cursor movement to over exceed the target location within the task box. Calibration prevented the subject from over shooting the target, therefore holding movement amplitude (ROM) constant. For each block, the target always appeared in the same position (bottom of the task box) and required subjects to make a right wrist flexion movement. For each block subjects performed 40 repetitions of visually cued right wrist flexion. As shown in Fig. 4-4, all trials would begin with the subject bringing the cursor to a center position (X). Following this, the cursor would disappear, and a visual target would appear after a 100 ms delay. The target always appeared for each repetition, with the same distance and the same position at the bottom-centre of the screen as described above. Two seconds following target appearance (preparation period), the cursor would reappear, and the subject was to move the cursor to the center of the target as quickly and accurately as possible. Following a successful trial, a message would appear on the screen displaying total response time

(reaction time + movement time) for that trial. Subjects had a maximum of 2 s to reach the target before the trial ended. An individual trial was deemed successful if the target was reached within 2 s. Subjects were allowed to determine the length of the rest period between repetitions.

All subjects came into the lab for one session to perform the eight blocks of visually cued movement under eight different kinematic constraints (Fig. 4-5) as follows: 1) 50% and 2) 20% range of motion (ROM). Calibration for these conditions consisted of placing a block on the wrist movement device that prevented the subject from exceeding the desired ROM and at the same time calibrating the cursor to reach the target location without overshooting it (Fig. 4-4). 3) & 4) Load applied (3% and 5% MFP) at movement onset with 100% ROM. The loads (Table 4-1) measured in grams were added to a custom made weight device consisting of a vessel to hold the weight linked to the right handle of the wrist movement device via a cable and pulley (Fig. 4-2). The cable was attached to the right handle of the wrist movement device and angled at approximately 30° to prevent the cable from slipping off the pulley during the task. Five percent MFP was chosen as the heaviest weight condition in order to expose the musculature to a heavy weight (on average 5% MFP equaled 450 g) while attempting to prevent fatigue. Three percent MFP was chosen to considerably lessen the weight but still expose the musculature to a light load. 5) Slow rate of movement with 100% ROM. Subjects were asked to respond slowly to the visual cue and move the cursor to the target location slowly as well. 6) Fast rate of movement with 100% ROM. This was the overall control condition, where the subject was to respond to the visual cue with speed and accuracy moving the cursor to the target using 100% ROM (approximately 80-90° of right wrist flexion). 7) & 8) Load applied (3% MFP)

to muscle before movement onset (inertial load) with 100% ROM, 8) 5% weight applied to muscle prior to movement onset (inertial load) with 100% ROM. These were calculated and applied as in conditions 3) and 4) above (Table 4-1). These inertial load conditions required an isotonic muscle contraction and were included in order to assess the influence of a load placed upon the musculature before movement onset in comparison to a load placed at movement onset (conditions 3 & 4). The order of the kinematic constraint block was randomized across subjects.

Event-related potentials

Event-related potentials were extracted from the EEG by averaging individual, artifact-free epochs, time-locked to the onset of cued movement (movement related potentials or MRPs), determined as the onset of EMG activity. Prior to averaging, individual epochs containing artifacts (i.e. from blinks or muscle contractions), defined as deflections greater than 80 μ V, were removed from further analysis. Averaged epochs extended from 2000 ms prior to 1000 ms after cued movement onset. Since a MRP has a frequency less than 1 Hz, the MRP was filtered with a 5 Hz low-pass filter.

The MRP consisted of three sub-components, an early slow negativity with an onset of approximately 1700-1800 ms prior to movement (early MRP), a sharper negativity beginning approximately 200 ms prior to movement onset and peaking between 0 and 90 ms immediately following the onset of movement (late MRP). Lastly, a positive deflection, resembling the re-afferent potential (RAP) commonly observed following self-paced movement, was evident approximately 200-250 ms after movement onset. The MRPs in this experiment were distributed over frontal electrode sites and maximal at FC1. The late MRP was lateralized and maximal over electrode site FC3.

Data Analysis

To test the first hypothesis that speed of movement would increase the amplitude of the cue-related MRP components, we used separate (for each electrode site) one-way repeated measures ANOVAs with movement rate as the factor (slow, fast) and individual MRP components as the dependent measures. To test the second hypothesis that force requirements (either at movement onset or as an inertial load) would increase the amplitude of the cue-related MRP components a 2 (load type - load at onset vs. inertial load) x 2 (load level - 3% weight vs. 5% weight) repeated measures ANOVA was conducted with each MRP component as the dependent measure. To test the third hypothesis that as range of motion requirements increased (20% to 50% to 100%) the amplitude of the cued MRP components would increase we used separate (for each electrode site) one-way repeated measures ANOVAs with condition type as the factor (20% ROM versus 50% ROM versus 100% ROM). The dependent measures were the early MRP, late MRP and RAP amplitudes in comparison to the three ROM conditions. *A priori* contrasts with Bonferroni correction were used to test the specifically hypothesized differences between the kinematic constraint conditions. To limit the number of comparisons, statistical tests were performed over specific electrode positions, identified by visual inspection of the topographical distribution of the MRP. For analysis we used frontocentral sites CZ, FCZ, C1, C3, FC1 and FC3. To assess behavioural effects, one-way repeated measures ANOVAs with reaction time (RT) and movement time (MT) as the dependent measure were conducted as appropriate.

Results

Behavioural Data

A one-way repeated measures ANOVA comparing movement time (MT) for the movement rate conditions was significant ($F_{1,9} = 101.3$, $p = 0.00$). Movement time was slower for the slow rate of movement condition versus fast (Fig. 4-6A). Reaction time (RT) was also slowest in the slow rate of movement condition ($F_{1,9} = 5.075$, $p = 0.05$) versus fast (Fig. 4-7A). A repeated measures ANOVA comparing MT for each load condition was not significant (Fig. 4-6B- $F_{3,27} = 2.3$, $p = 0.1$). Reaction time was also not variable across load conditions versus no load (Fig. 4-7B - $F_{3,27} = 0.42$, $p = 0.71$). For the range of motion (ROM) conditions MTs (Fig. 4-6B - $F_{2,18} = 1.258$, $p = 0.31$) and RT (Fig. 4-7B - $F_{2,18} = 0.56$, $p = 0.48$) were not significantly different.

EEG Data

MRP amplitude and speed of movement

There were no significant effects of rate of movement on either early or late MRP amplitudes for any of the electrodes tested (4-8 A, B & C). However, rate of movement did have a significant effect on RAP amplitude such that RAPs were enhanced in the fast versus slow movement conditions across all electrode sites (Fig. 4-8D - FCZ: $F_{1,9} = 18.54$, $p = 0.002$; CZ: $F_{1,9} = 19.96$, $p = 0.002$; C1: $F_{1,9} = 19.39$, $p = 0.002$; C3: $F_{1,9} = 19.95$, $p = 0.002$; FC1: $F_{1,9} = 21.2$, $p = 0.001$; FC3: $F_{1,9} = 20.26$, $p = 0.001$).

MRP amplitude and load type

A 2x2 repeated measures ANOVA revealed a significant main effect of load type on the amplitude of the early MRP at electrode sites CZ, C1 and C3 (Fig. 4-9A & B - CZ: $F_{1,9} = 7.1, p = 0.03$; C1: $F_{1,9} = 6.2, p = 0.04$; C3: $F_{1,9} = 9.1, p = 0.02$). There was a significant main effect of load level (3% versus 5%) on the amplitude of the RAP (Fig. 4-9A & D - FCZ: $F_{1,9} = 4.97, p = 0.05$; CZ: $F_{1,9} = 4.84, p = 0.06$; C1: $F_{1,9} = 7.36, p = 0.03$; C3: $F_{1,9} = 5.86, p = 0.04$; FC1: $F_{1,9} = 10.32, p = 0.01$; FC3: $F_{1,9} = 9.79, p = 0.01$). There was also a significant interaction between load type and load level for RAP amplitude (FCZ: $F_{1,9} = 12.72, p = 0.006$; CZ: $F_{1,9} = 8.23, p = 0.01$; C1: $F_{1,9} = 7.03, p = 0.03$; C3: $F_{1,9} = 5.86, p = 0.04$; FC1: $F_{1,9} = 9.61, p = 0.01$; FC3: $F_{1,9} = 9.2, p = 0.01$). Contrasts revealed that the amplitude of the RAP for the 3% inertial load condition was significantly attenuated compared to 3% load at onset (FCZ: $p = 0.03$; FC1: $p = 0.01$) and 5% inertial load conditions (FCZ: $p = 0.007$; CZ: $p = 0.01$; C1: $p = 0.03$; C3: $p = 0.04$; FC1: $p = 0.006$).

MRP amplitude and ROM

A repeated measures ANOVA of the data in Fig. 4-10 of MRP amplitudes (early, late, RAP) across ROM conditions were not significant at any of the electrode sites tested (Fig. 4-10). Therefore, varying ROM excursions did not modulate any of the MRP components.

Discussion

The cue-related MRP and movement speed

The hypothesis that as the speed of movement increased, the amplitude of the cue-related MRP components would increase as well (early MRP, late MRP and RAP) was

partially supported. The amplitude of the **RAP** significantly increased during movement with greater speed (Fig. 4-8), partially replicating findings by Slobounov et al. (1998a & 1998b). Larger **RAP** amplitude during a movement of enhanced speed could indicate that the speed of muscle recruitment provides greater sensory feedback in comparison to a slower movement. The amplitude of the early and late **MRP** (Fig. 4-8B & D) was not significantly modulated in response to movement speed, which is an interesting finding since non-human primate studies (Johnson, Coltz, & Ebner, 1999; Johnson & Ebner, 2000; Stark, Drori, Asher, Ben-Shaul, & Abeles, 2007) have reported increased firing rates of PMd related to direction and speed of a forthcoming movement, and the primary motor cortex (M1) is also reported to be involved in the velocity of movement (Ashe & Georgopoulos, 1994; Hamada, 1981; Hore & Flament, 1988; Johnson & Ebner, 2000; Moran & Schwartz, 1999; Schwartz, 1992; Schwartz, 1993; Stark et al., 2007).

The cue-related MRP and type of force

The second hypothesis that the **MRP** components would increase in amplitude in response to increased load, but would be comparable across differing load conditions (load at movement onset versus inertial load) was not supported. Curiously, the amplitude of the early **MRP** component was attenuated during the load at movement onset conditions versus inertial load (Fig. 4-9A & B). This novel observation alludes to the preparatory system assessing and forming an efficient motor output program to increase force production but only in the instance when the load can be predetermined as is the case in the inertial load conditions. During the load at movement onset conditions preparatory regions might not be able to form a motor program efficiently when the condition starts in a resting state, unaware of the force required to move the imposed load.

Modulation of early MRP amplitudes with load type is not due to a difference in response latency (RT) or movement speed (MT), since the averaged RT and MT between compared conditions was not different (Fig. 4-6B & 4-7B). These results do not replicate findings by Slobounov et al. (2002) who demonstrated that force does not modulate the amplitude of the self-paced BP if movement rate is held constant. Conversely, the present results show a significant increase in preparatory excitability only during loaded tasks that contain an inertial load despite comparable movement rate. Physiologically, the lateral PM cortex plays a role in force production (Chouinard, Leonard, & Paus, 2005; Nowak et al., 2009; Werner, Bauswein, & Fromm, 1991). The results of the current study demonstrate that lateral PM excitability is influenced by force production requirements in a specific manner.

In addition to the early MRP, RAP amplitude was significantly less for the 3% inertial load condition compared to the 5% inertial load condition and 3% load at onset condition (Fig. 4-9A & D). A significant interaction between load level and type was also evident. From this observation it seems that less feedback from the movement was required in response to the 3% versus 5% inertial loaded or 3% load at onset conditions. There was greater preparatory excitability during inertial load conditions, this might reflect efficient motor programming for the forthcoming movement. An efficient preparatory program may negate the need for increased sensory feedback, but this is purely speculation. The present data are unable to definitively disentangle the relationship between modes of force output and the components of the cue-related MRP.

Cue-related MRP and ROM

Range of motion did not affect the amplitude of the cue-related MRP (Fig. 4-10); therefore, the third hypothesis was not supported. This observation does not follow the results of the self-paced BP by Slobounov et al. (1999; 2000). These results seem to indicate that ROM is not a primary influential movement parameter. This is a surprising result since primate studies have reported variable lateral PM excitability in response to the preparation of variable movement amplitudes (Kurata, 1993; Park, Kim, & Ebner, 1988). This result highlights the need for further study of the kinematic parameters that may influence the cue-related MRP.

Conclusion

The results of the present study provide novel insight into the various kinematic parameters that may influence the components of the cue-related MRP. Such parameters include: force production, particularly inertial load, whereas range of motion did not seem to be a primary influence. Although, one of the components of the MRP was modulated in response to a fast rate of movement, we were unable to determine if movement speed indeed influenced the MRP since slowing movement speed transitioned the protocol into a self-paced BP paradigm. These data provide needed understanding of the cue-related MRP and will inform future training-related studies using the cue-related MRP as a measure of cortical excitability modulation in response to bimanual movement training in the healthy and stroke patient populations. However, further study is greatly required to fully understand the kinematic parameters that influence the cue-related MRP.

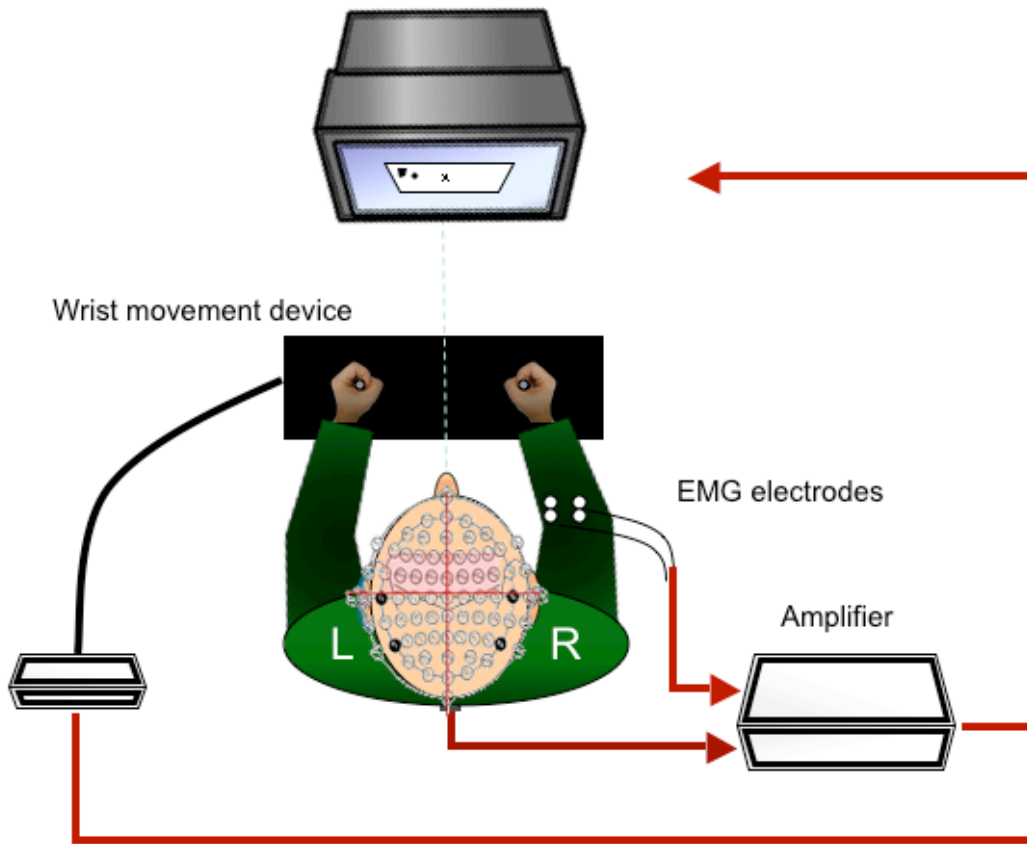


Figure 4-1 - Top view of the position of the subject using the custom-made wrist movement device. Flexion and extension of the wrists occurred in the horizontal plane by grasping bilateral movement device handles, which rotated in clock-wise and counter-clockwise directions.

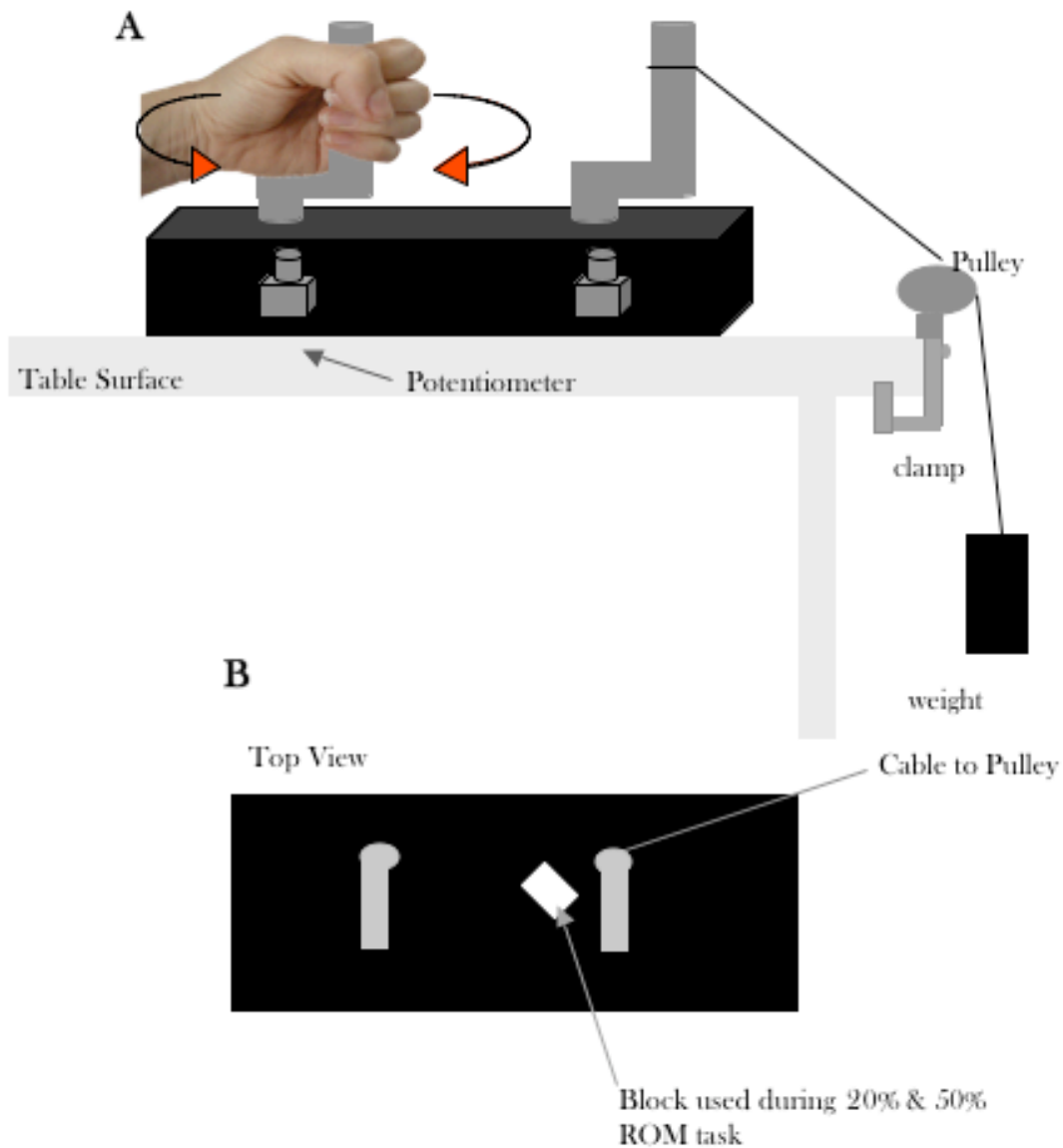


Figure 4-2 - (A) The custom-made wrist movement device consisting of two handles linked to two potentiometers. For the conditions with an applied weight, a weight linked via a pulley was attached to the right handle to impose a 3% or 5% tonic load upon the right wrist musculature. (B) The top view of the wrist movement device. One block was attached to the device to restrict right wrist movement during the restricted ROM conditions.

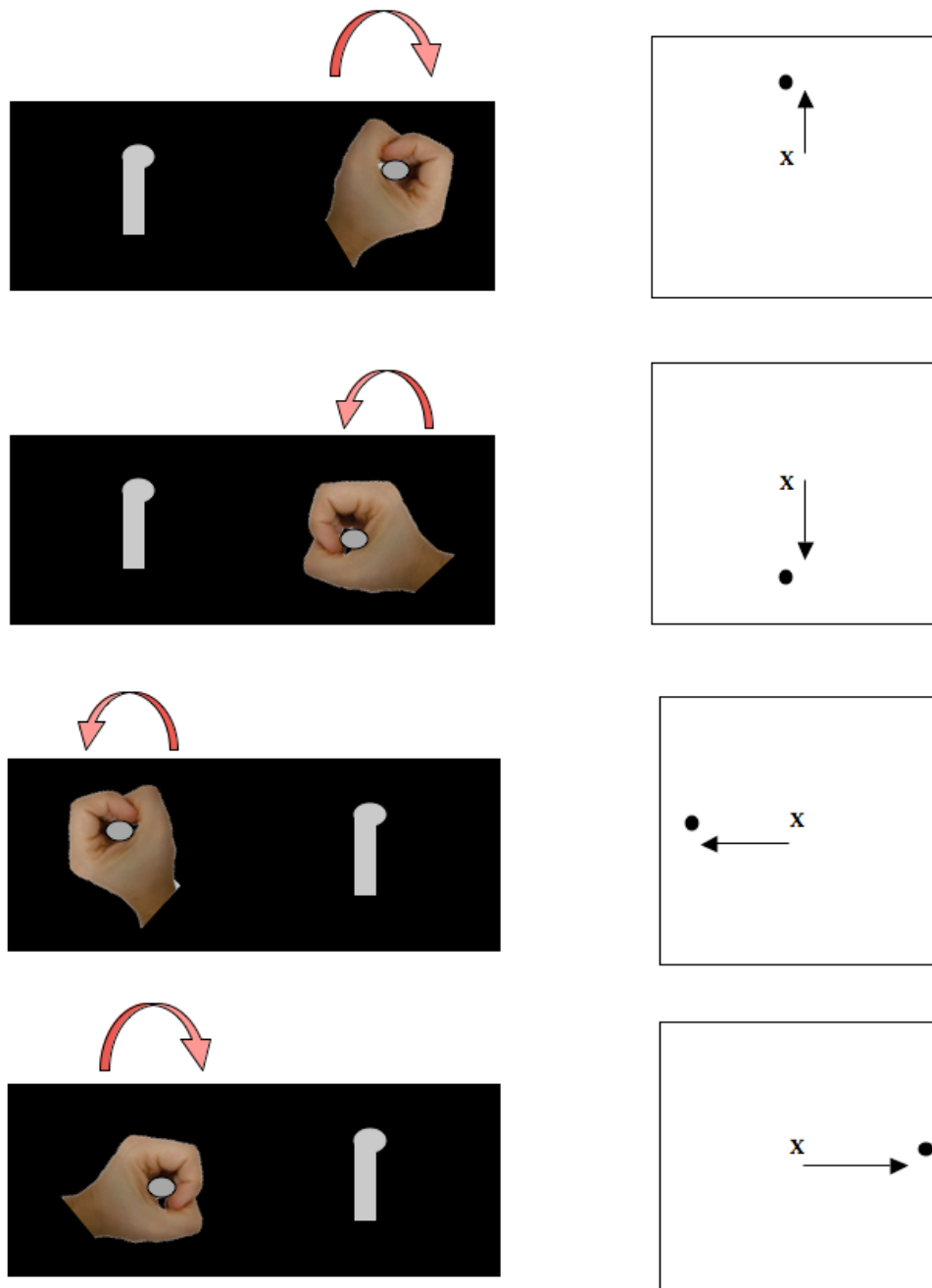


Figure 4-3 - (A) Wrist movement and corresponding cursor movement. (A) Right wrist extension controlled cursor displacement upward. (B) Right wrist flexion controlled downward movement of the cursor. (C) Left wrist extension controlled leftward movement of the cursor and (D) left wrist flexion controlled rightward movement of the cursor.

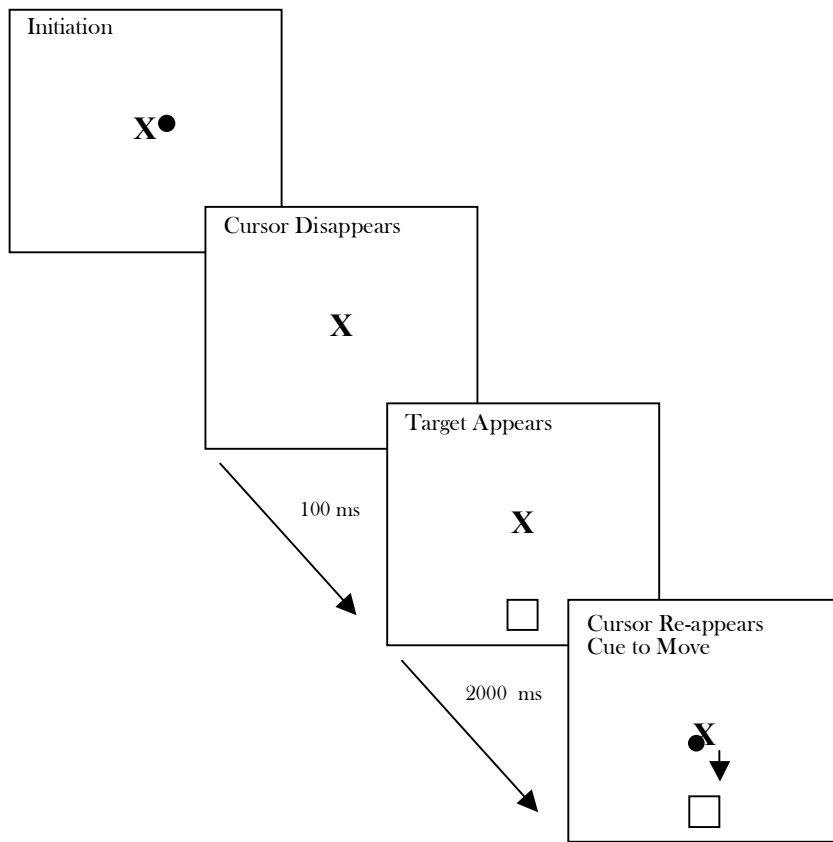


Figure 4-4 - Steps to complete one repetition during the unimanual movement task performed for each kinematic condition.

| ROM | FORCE | RATE |
|-----|---------------------------|------------------------|
| 50% | 3% Load at Movement Onset | FAST (control task) |
| 20% | 5% Load at Movement Onset | SLOW |
| | 3% Inertial Load | |
| | 5% Inertial Load | |

Figure 4-5 - A list of the 8 kinematic conditions.

| Subject | Maximum Force Production (g) | 3% MFP (g) | 5% MFP (g) |
|---------|------------------------------|------------|------------|
| 1 | 9000 | 270 | 450 |
| 2 | 9500 | 285 | 475 |
| 3 | 8200 | 246 | 410 |
| 4 | 8000 | 240 | 400 |
| 5 | 9800 | 294 | 490 |
| 6 | 15000 | 450 | 750 |
| 7 | 12000 | 360 | 600 |
| 8 | 9000 | 270 | 450 |
| 9 | 9200 | 276 | 460 |
| 10 | 9500 | 285 | 475 |

Table 4-1 - Maximum force production and corresponding 3% MFP in grams for each subject.

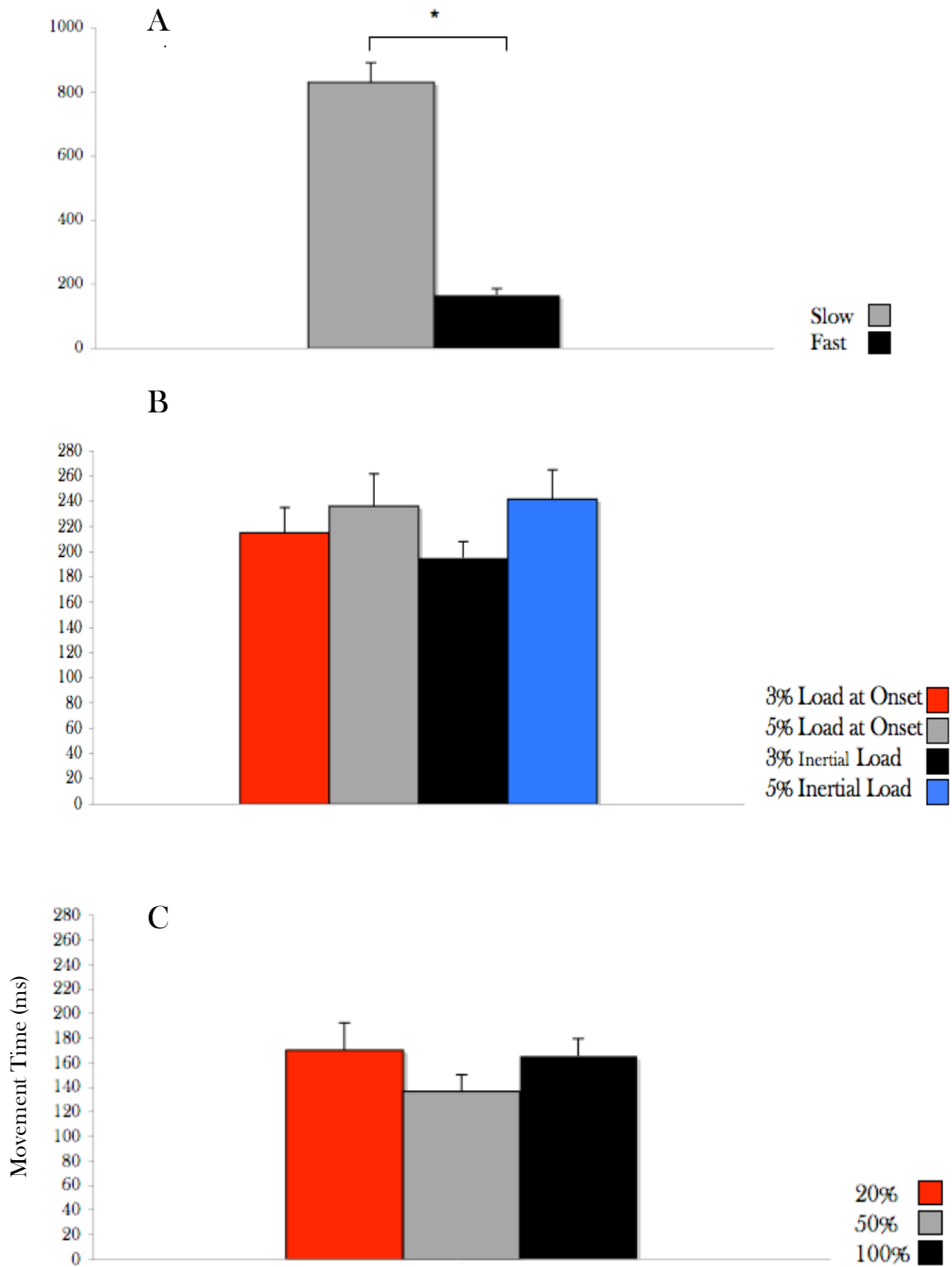


Figure 4-6 - Movement time for (A) rate of movement condition, (B) force type condition and (C) ROM condition.

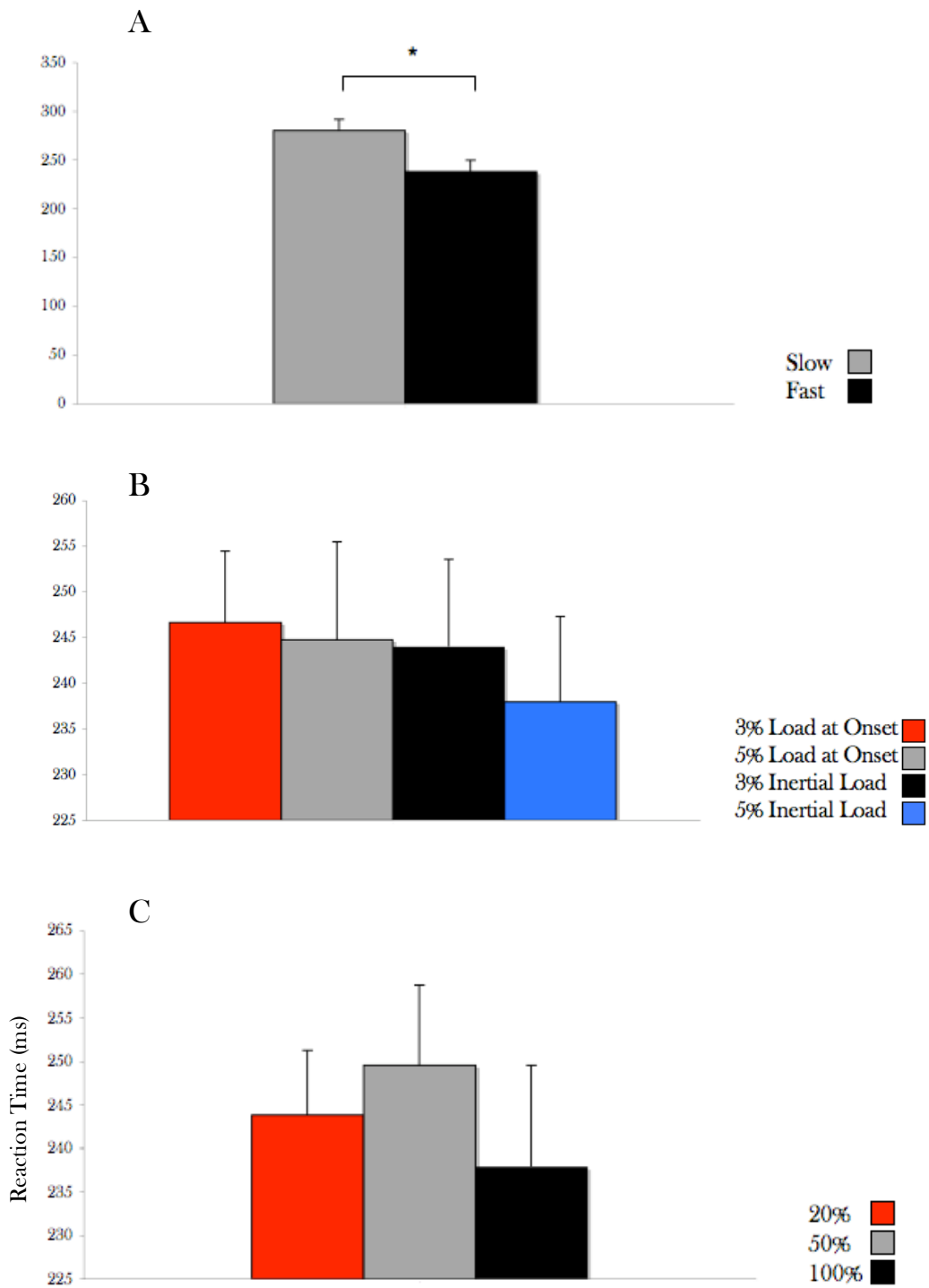


Figure 4-7 - Reaction time for (A) rate of movement condition, (B) force type condition and (C) ROM condition.

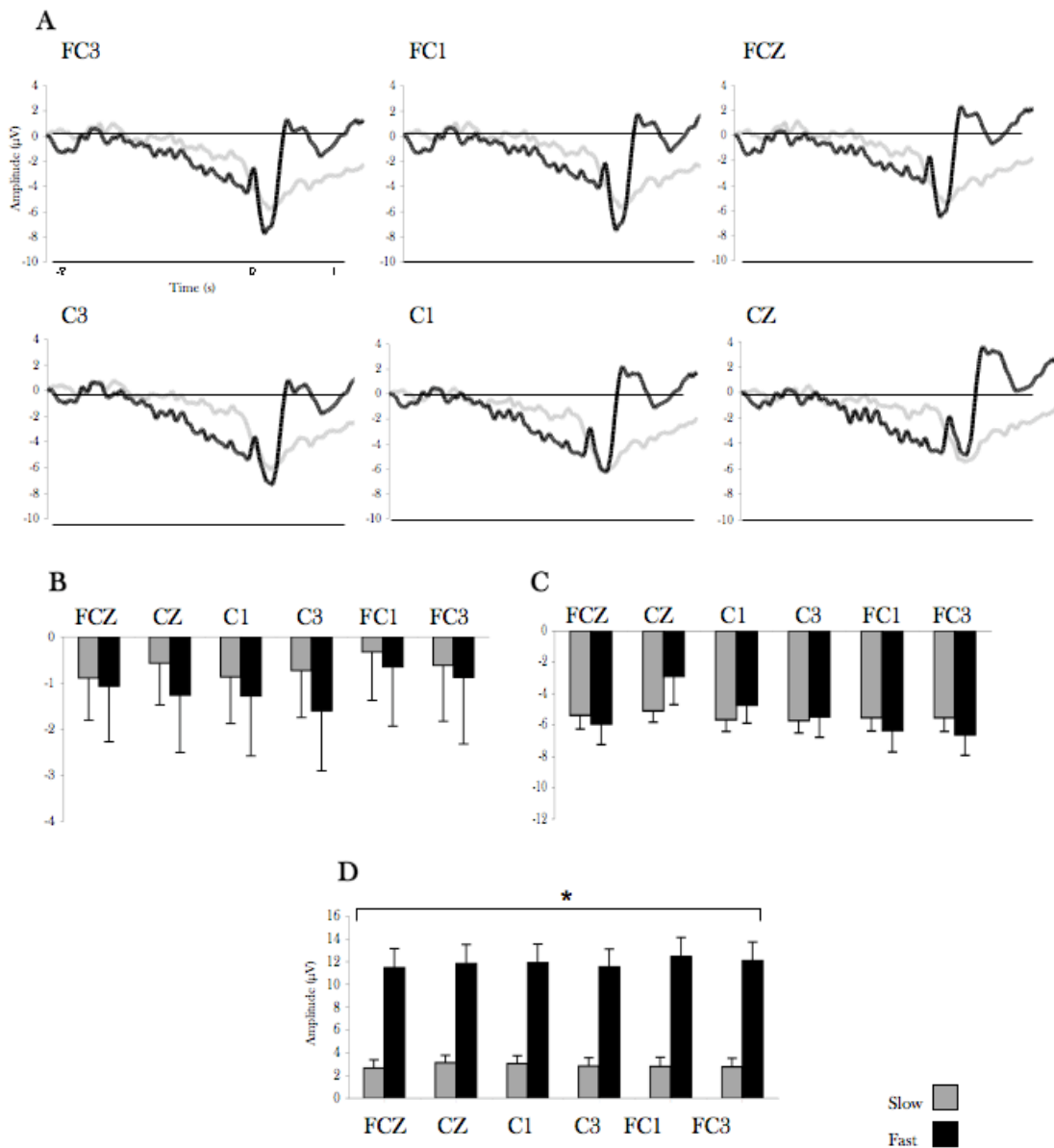


Figure 4-8 - (A) Grand average MRPs time-locked to cued movement onset of the right wrist for the slow movement condition (grey trace, $n=10$) and fast movement condition (black trace, $n=7$) at 6 electrode sites (FCZ, CZ, C1, C3, FC1 and FC3). (B) Group mean (\pm SE, $n=10$) early MRP amplitudes in the slow condition (grey bars) and fast condition (black bars). (C) Group mean (\pm SE, $n=10$) late MRP amplitudes in the slow condition (grey bars) and fast condition (black bars). (D) Group mean (\pm SE, $n=10$) RAP amplitudes in the slow condition (grey bars) and fast condition (black bars). All bar graphs $n=10$. * Indicates $p < 0.05$

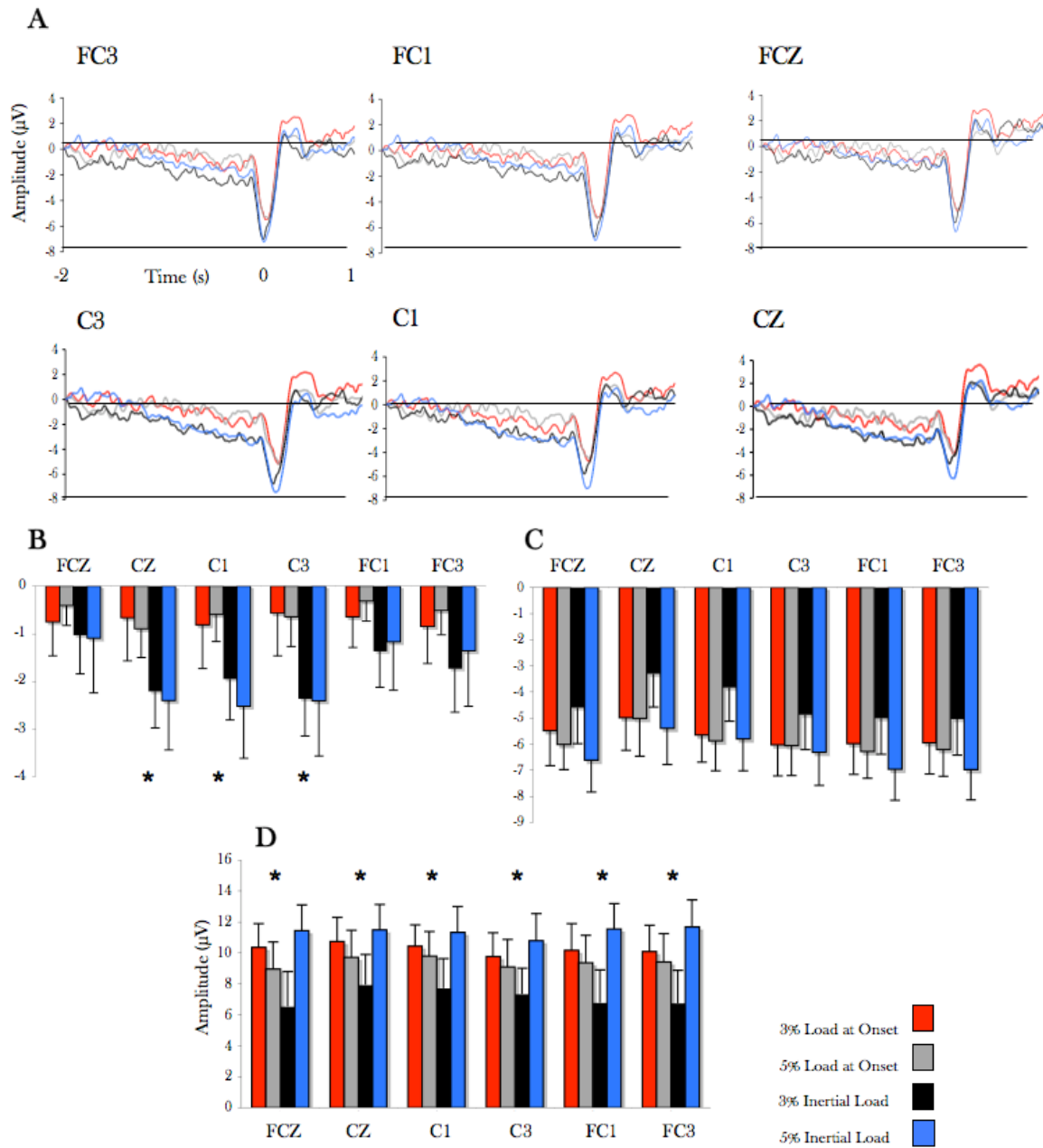


Figure 4-9 - (A) Grand average MRPs time-locked to cued movement onset of the right wrist for the 3% load at movement onset (red trace, $n=10$), 5% load at movement onset (grey trace, $n=10$), 3% inertial load (black trace, $n=9$), 5% inertial load (blue trace, $n=9$) at 6 electrode sites (FCZ, CZ, C1, C3, FC1 and FC3). (B) Group mean ($\pm\text{SE}$, $n=10$) early MRP amplitudes for the load conditions. (C) Group mean ($\pm\text{SE}$, $n=10$) late MRP amplitudes for the load conditions. (D) Group mean ($\pm\text{SE}$, $n=10$) RAP amplitudes for the load conditions. All bar graphs $n=10$. * indicates $p<0.05$

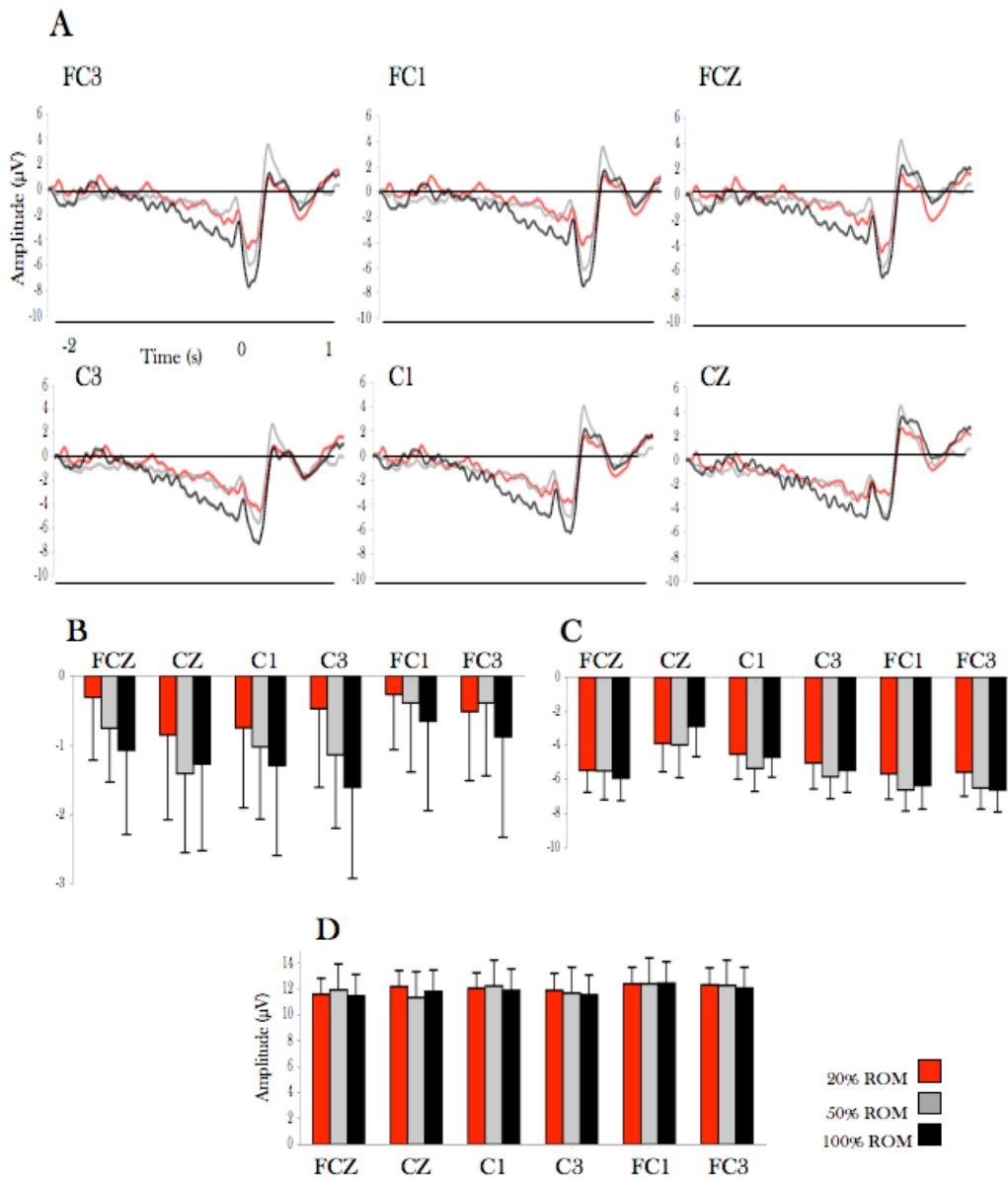


Figure 4-10 - (A) Grand average MRPs time-locked to cued movement onset of the right wrist for the 20% ROM (red trace, $n=10$), 50% ROM (grey trace, $n=10$) and 100% ROM condition (black trace, $n=7$) at 6 electrode sites (FCZ, CZ, C1, C3, FC1 and FC3). (B) Group mean ($\pm\text{SE}$, $n=10$) early MRP amplitudes in the 20% ROM (red bars), 50% ROM (grey bars) and 100% ROM condition (black bars). (C) Group mean ($\pm\text{SE}$, $n=10$) late MRP amplitudes in the 20% ROM (red bars), 50% ROM (grey bars) and 100% ROM condition (black bars). (D) Group mean ($\pm\text{SE}$, $n=10$) RAP amplitudes in the 20% ROM (red bars), 50% ROM (grey bars) and 100% ROM condition (black bars). All bar graphs $n=10$

Chapter Five - Cued inphase BMT effects upon the cue-related MRP with imposed unilateral mobility restriction

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Overview

As a first step to ascertain if the cue-related MRP can be recorded from and used as a measure of training-related adaptation in the stroke population, the present study was designed to investigate learning-related modulations of the cue-related MRP in response to cued inphase BMT with an imposed mobility restriction upon the right wrist of healthy participants. EEG was recorded from 22 electrode positions and the cue-related MRP extracted from the recording 2 seconds prior to and 1 second following cued movement onset of a pre and post-unimanual trial consisting of 40 repetitions of cued right wrist flexion, interspersed with 160 repetitions of cued inphase BMT. Left wrist movement was not restricted; however, the right wrist was limited to the terminal 30° of wrist flexion and a tonic load was placed upon the right forearm musculature to mimic lack of mobility and tonic muscle contraction that is observed in many stroke patients. We hypothesized that despite a lack of mobility and tonic muscle load of the right wrist 1) the amplitude of the early MRP component, reflecting preparatory excitability within the lateral premotor cortex, would increase following cued inphase BMT and would be linked to a behavioural enhancement (decrease in reaction time - RT), and 2) the amplitude of the early MRP component would increase in the last 40 repetitions of cued inphase BMT versus the first 40 repetitions; replicating our previous findings. Results indicated that despite a restriction of mobility and tonic muscle contraction of the right wrist, the early MRP component significantly increased following cued inphase BMT and was linked to a decrease in RT.

The amplitude of the early MRP component increased in amplitude in the last 40 repetitions of cued inphase BMT as well; replicating previous findings. These results indicate the potential to use the cued MRP as a measure of cortical excitability modulation in an individual with lack of mobility of the wrist, such as found in the stroke patient population.

Introduction

Stroke can cause a myriad of neurologic deficits, most commonly observed in the motor system (Rathore, Hinn, Cooper, Tyroler, & Rosamond, 2002). Currently there is a great deal of interest in training-related strategies to enhance motor recovery following a stroke (Cauraugh & Summers, 2005; Schaechter, 2004). This area of research has gained momentum from the dramatic increase in the understanding of plasticity. There is now a breadth of evidence demonstrating that reorganization of cortical connections does not only occur in response to injury-related reorganization, but in response to motor experiences as well (Kleim, Barbay, & Nudo, 1998; Nudo & Milliken, 1996; Nudo, Milliken, Jenkins, & Merzenich, 1996; Nudo, Wise, Si Fuentes, & Milliken, 1996; Nudo, Plautz, & Frost, 2001; Plautz, Milliken, & Nudo, 2000; Summers et al., 2007). The challenge is to elucidate the mechanisms underlying the recovery of motor function and to develop tools to assess early phases of brain plasticity associated with rehabilitative progress, ideally on a single-session basis, to guide optimal prescription of restorative therapeutic modalities after stroke (Cramer & Riley, 2008).

A number of stroke based motor rehabilitative studies have reported the advantageous use of bimanual movement training (BMT) for behavioural enhancements of the hemiparetic upper limb in some chronic stroke patients (Cauraugh & Kim, 2002; Luft

et al., 2004; McCombe Waller & Whittall, 2004; Mudie & Matyas, 2000; Rose & Winstein, 2004; Silvestrini, Cupini, Placidi, Diomedi, & Bernardi, 1998; Stinear, Barber, Coxon, Fleming, & Byblow, 2008; Stinear & Byblow, 2004; Summers et al., 2007; Whittall, McCombe Waller, Silver, & Macko, 2000), but the neurophysiological mechanisms underlying the behavioural improvement are not yet known. With the use of transcranial magnetic stimulation (TMS), Stinear et al. (2004; 2008) reported a balancing of hemispheric activation associated with a behavioural improvement of the stroke affected limb after active-passive bimanual training (APBT) involving active wrist flexion and extension of the unaffected wrist in conjunction with simultaneous passive flexion and extension of the affected wrist. Summers et al. (2007) also reported, in a TMS study, that a behavioural enhancement of the stroke affected limb following a bimanual dowel placing task was associated with a decrease in non-affected hemisphere activation. It would be highly advantageous to find a measurement tool that was relatively inexpensive, sensitive enough to detect within-session cortical excitability modulations in response to BMT and one that was correlated to behavioural improvements in order to assess the effectiveness of BMT from a single patient perspective. Based upon preliminary findings in the healthy population (Smith and Staines, 2006 & Chapter 2), the cue-related movement-related potential (MRP) may be a possible measurement tool to assess learning-related adaptations in response to BMT in the stroke population. However, we are unclear if this event-related potential (ERP) is recordable when wrist movement is compromised in terms of range of motion and the baseline 'resting' state of the musculature that produces the movement.

Many stroke patients suffer from limited mobility of their stroke-affected limb and have added tonic muscle contraction while the limb is at rest; this condition is termed spasticity. The clinical features of spasticity complicate the prospective use of the cue-related MRP as a measure of cortical excitability in stroke patients. As a preliminary step to ascertain the potential use of the cue-related MRP in the stroke population we investigated the training-related cortical adaptations induced upon the MRP in response to cued inphase BMT under a simulated spasticity condition imposed upon the right wrist of healthy participants. This study was undertaken to replicate the design of Chapter 2, to determine if the observed increase in the cue-related early MRP component remains evident following cued inphase BMT despite movement restriction and tonic muscle contraction of the right wrist. Conducting this type of study in the healthy population allowed us to observe learning-related adaptations of the cue-related MRP without the added complication of a cortical lesion and allowed us to establish healthy control data. We hypothesized that despite restriction of range of motion and an imposed tonic muscle contraction of the musculature controlling the right wrist: 1) the early MRP component would increase in the post-unimanual trial following cued inphase BMT and would be associated with a decrease in reaction time. 2) Amplitude of the early MRP component would increase in the last 40 repetitions of cued inphase BMT.

Materials & Method

Subjects

Ten healthy, normal participants (3 male, 7 female; age range 21-36) participated in the study, each providing written informed consent. All were right-handed by self-report and did not report any history of neurological impairments. Participants were paid a

nominal fee for their participation. The Office of Research Ethics at the University of Waterloo and the research ethics board at the Toronto Rehabilitation Institute approved the experimental procedures.

EEG recording procedure

EEG recording procedures were identical to those used in Chapter 2 (pg. 39).

Procedure for assessing maximum force output of wrist flexion

A custom-made device was used to measure each subject's maximum force production (MFP) for right wrist flexion as in Chapter 4. A weight equating to 3% maximal force for right wrist flexion was added to the right hand handle of the wrist movement device to impose a constant tonic 3% load upon the right forearm musculature throughout each trial. Table 5-1 displays the load used for each subject.

Behavioural task

All subjects came into the lab for a single session; to perform a pre and post visually cued right wrist flexion movement (40 repetitions), interspersed by one trial of cued inphase BMT (160 repetitions). Throughout the task right wrist movement was limited to the terminal 30° of wrist flexion in conjunction with an imposed 3% tonic load (Fig. 5-1). Movement was restricted with the use of two blocks placed in front of and in back of the right wrist device handle (Fig. 5-1B). Left wrist motion was not limited or imposed by a constant inertial load. Three percent of each subject's MFP calculated in grams of weight was determined and added to a vessel that was linked with the right handle of the wrist movement device via a cable and pulley situated approximately 30° in relation to the wrist movement device to prevent further hindrance of motion.

Subjects were seated in a dimly lit room, in front of a computer monitor with arms supported. The medial aspects of bilateral forearms were supported with elbows flexed to 90° and the shoulder in forward flexion ~0-10°. Flexion and extension of the wrist occurred in the horizontal plane. This position was maintained for all trials. Subjects grasped two separate handles of a custom made device that was placed on their lap (Fig. 5-1). The handles of the device pivoted in clockwise and counter-clockwise direction and were linked to two separate potentiometers within the device structure. When subject's grasped each of the handles they could flex and extend their wrists, in the horizontal plane. The custom made device, in conjunction with a customized program written in LabVIEW (National Instruments, Austin, TX), allowed the subjects to control a cursor on a computer monitor by flexing and extending the wrists (cursor control was needed for the visually cued task). Shown in Fig. 5-2, right wrist extension controlled upward movement of the cursor, and right wrist flexion controlled downward movement of the cursor. Left wrist extension controlled leftward movement of the cursor and left wrist flexion controlled rightward movement of the cursor. When an inphase bimanual movement was executed the cursor would travel along the diagonal direction displayed in Fig. 5-3.

The visually cued trial required subjects to move the cursor (8 mm in diameter) from a starting position to a target (1.5 cm²) displayed in the bottom-centre of the screen, identical to Chapter 2. Movement of the cursor was calibrated for each subject so that maximal flexion or extension of the wrist would not allow cursor movement to over exceed the target location. Calibration prevented the subject from overshooting the target, which would interfere with accuracy of the task and it held movement amplitude (ROM) constant. Due to the limitation of motion imposed upon the right wrist, calibration was important in

order to move the cursor to the target location despite lack of mobility. For the pre and post cued task (Fig. 5-4A), the target always appeared in the same position and required subjects to make a right wrist flexion movement using approximately the terminal 30° of right wrist flexion for 40 repetitions. With the exception of the restriction in ROM, the procedures were identical to those used for the pre- and post-training conditions described in Chapter 2.

For the inphase bimanual movement-training task the target appeared randomly, and at varying distances along the black diagonal line shown in the diagram, for 160 repetitions within the top left and bottom right quadrants of the task box. Importantly, these movements involved activation of homologous muscle groups in both the left and right forearms; however, the amplitude of movement allowed during right wrist flexion and extension was limited and held in the terminal 30° of right wrist flexion. Targets appeared for 80 repetitions within each of the two quadrants.

Event-related potentials

Event-related potentials were extracted from the EEG by averaging individual, artifact-free epochs, time-locked to the onset of movement (movement-related potentials or MRPs). Prior to averaging, individual epochs containing artifacts (i.e. from blinks or muscle contractions), defined as deflections greater than 80 μV , were removed from further analysis. Averaged epochs extended from 2000 ms prior to 1000 ms after movement onset. Preceding averaging, the MRP was filtered with a 5 Hz low-pass filter.

The pre and post MRP consisted of three sub-components, an early slow negativity with an onset \sim 1650-1900 ms prior to movement (early MRP), a sharper negativity beginning \sim 100-150 ms prior to movement onset and peaking between \sim 20 and 160 ms

immediately following the onset of movement (late MRP). Lastly, a positive deflection, the re-afferent potential (RAP) was evident ~230 ms after movement onset. The early MRPs in this experiment were distributed over frontal electrode sites and maximal at site FC1. The late MRP was lateralized and maximal over electrode site FC1.

The latency of the late MRP was determined as the peak of negativity between +20 to +160 ms after the onset of movement (onset of movement occurred at time zero). For the early BP, amplitudes were quantified by calculating the mean amplitude from -1000 ms to -50 ms before movement onset. Late MRP amplitudes were taken as the peak-to-peak value from the mean amplitude value of the early BP to the peak negativity of the late BP between +20 to +160 ms after movement onset. The re-afferent potential (RAP) amplitude was taken as the peak-to-peak value from the peak negativity of the late BP (+20 to +160 ms after movement onset) to the peak of the RAP that occurred between +140 to +300 ms after movement onset.

Data analysis

Our first hypothesis was: 1) The early cue related MRP component would increase in amplitude for a similar unimanual task following cued inphase BMT and would be correlated with a decrease in reaction time despite a lack of mobility and imposed tonic load of the right wrist. To test this hypothesis we used repeated measures one-way ANOVAs comparing average amplitudes of the early MRPs from the post-training block to those from the pre-training block. The Pearson product moment correlation coefficient (r) was calculated between the post- minus pre-training difference in early MRP amplitude versus the post- minus pre-training difference in reaction time. Our second hypothesis was 2) the amplitude of the early cue related MRP component would increase in amplitude in

the later portion of cued inphase BMT (trial 2) as observed in previous studies (Smith & Staines, 2006). To test this hypothesis we used repeated measures one-way repeated measures ANOVAs comparing average amplitudes of the early MRPs from the last 40 repetitions to those from the 1st 40 repetitions of cued Inphase BMT (trial 2). The same analyses were applied to the late MRP and RAP following and during the cued inphase BMT paradigm. To measure possible differences in the amplitude of the contingent negative variation (CNV) a repeated measures one-way ANOVA comparing the average amplitudes of the CNV from the last 40 repetitions to those from the 1st 40 repetitions were measured (from electrode sites CZ and FCZ). To limit the number of comparisons, statistical tests were performed over specific electrode positions, identified by visual inspection of the topographical distribution of the MRP. For the pre- versus post-training cued unimanual movement analysis frontocentral sites CZ, FCZ, C1, C3, FC1, FC3 were analyzed. For the cued inphase block (trial 2) CZ, FCZ, C1, C2, C3, C4, FC1, FC2, FC3 and FC4 were analyzed.

Results

Pre- versus post-training cued unimanual movement - group analysis

The early MRP was maximal over frontal electrode sites (FC1: $-3.46 \mu\text{V} \pm 0.79$) and had an onset latency of approximately 1830 ms prior to movement onset. The late BP peaked after movement onset at approximately 80 ms after movement onset. The scalp distribution of the late BP was lateralized to the left hemisphere and was maximal over FC1 ($-5.14 \mu\text{V} \pm 0.67$). The re-afferent potential (RAP) was maximal at FC1 ($9.74 \mu\text{V} \pm 1.25$) with latency of ~ 370 ms after movement onset.

A one-way repeated measures ANOVA revealed that the amplitude of the early MRP component significantly increased in the post-unimanual trial following cued inphase bimanual movement training (Figure 5-5; FCZ: $F_{1,9} = 6.36$, $p = 0.03$; CZ: $F_{1,9} = 4.27$, $p = \text{NS}$; C1: $F_{1,9} = 4.85$, $p = \text{NS}$; C3: $F_{1,9} = 6.89$, $p = 0.03$; FC1: $F_{1,9} = 9.6$, $p = 0.013$; FC3: $F_{1,9} = 8.63$, $p = 0.017$). The amplitude of either the late MRP component or RAP did not change in response to cued inphase BMT (Fig. 5-5A). The contingent negative variation (CNV) (Fig. 5-6) did not change in amplitude in the post-unimanual movement trial following cued inphase BMT (FCZ: $F_{1,9} = 2.38$, $p = \text{NS}$; CZ: $F_{1,9} = 1.4$, $p = \text{NS}$). These data replicate previous findings.

Pre- versus post-training cued unimanual movement - behavioural data

A one-way repeated measures ANOVA of the data shown in Fig. 5-7A revealed that reaction time (RT) significantly decreased in the post-unimanual movement trial following cued inphase BMT ($F_{1,9} = 16.67$, $p = 0.003$). There were no significant effects of training time (pre- vs post-training) on movement time (Fig. 5-7C) ($F_{1,9} = 0.13$, $p = \text{NS}$). Figure 5-7B shows the significant correlation between early MRP differences and RT following inphase BMT ($r = -0.63$, $p = 0.05$).

Cued bimanual training trial

The cued early MRP was maximal over frontocentral electrode sites (FC4: $3.08 \mu\text{V} \pm 1.5$) and had an onset latency of approximately 1814 ms prior to movement onset. The late BP peaked after movement onset at approximately 57 ms. The scalp distribution of the cued late MRP was lateralized to the left hemisphere and was maximal over FC1 ($6.29 \mu\text{V} \pm 0.72$). The cued re-afferent potential (RAP) was maximal at FC1 ($11.3 \mu\text{V} \pm 1.62$) with latency of approximately 208 ms after movement onset.

A one-way repeated measures ANOVA revealed that the cued early MRP significantly increased in amplitude in the last 40 repetitions compared to the first 40 repetitions of cued inphase bimanual movement training (Figure: 5-8: FCZ: $F_{1,9} = 5.016$, $p = 0.06$; C1: $F_{1,9} = 4.88$, $p = 0.05$; FC1 : $F_{1,9} = 4.9$, $p = 0.05$). This replicates previous findings. Task performance was not assessed due to task accuracy exhibiting a ceiling affect.

Discussion

Summary of results

The present study examined the amplitude of the cue-related movement-related potential (MRP), in the healthy population, preceding and following cued inphase bimanual movement training (BMT) with an imposed movement restriction and tonic muscle load placed upon the right wrist throughout the task. Three results can be summarized. 1) Despite an imposed mobility restriction and tonic muscle contraction of the right wrist, the amplitude of the cue-related early MRP elicited by right wrist flexion, denoting preparatory excitability, increased following a single session of cued inphase BMT (Fig. 5-5). 2) This increase in early MRP amplitude was also significantly associated with a decrease in reaction time (RT) (Fig. 5-7B). 3) The early MRP component also increased in amplitude during the last 40 repetitions of cued inphase BMT compared to the first 40 repetitions (Fig. 5-8). These results potentially indicate that learning-related cortical adaptations occurred during the bimanual training paradigm, which remained and transferred to the post unimanual task. Cortical excitability and behavioural modulations occurred despite a lack of mobility and tonic load placed upon the right wrist.

Agreement with previous work

We have previously reported an increase in the amplitude of the cue-related early MRP component in response to BMT (Smith & Staines, 2006), specifically inphase BMT (Chapter 2). The current study replicated previous findings and further adds that full range of motion of bilateral wrists is not required in order to observe training-related modulations of the cue-related MRP. Even if a tonic inertial load is placed upon the musculature of the forearm, training-related adaptations to the cue-related MRP will still be present. This is an important finding since future training-related studies will involve stroke patients who may suffer from limited mobility of the stroke affected limb with added tonic muscle contraction of the affected musculature.

Strengths and limitations

The rationale for the current study was to determine if the cue-related MRP 1) could be measured from a movement that was restricted and 2) used to assess cortical excitability modulations in response to inphase BMT despite an imposed movement restriction and tonic load upon the musculature. If the cue-related MRP is to be used in the stroke patient population it would be useful to determine if the cue-related MRP could be recorded in a healthy individual with a simulated motor deficit to determine if limited mobility restricts learning-related cortical adaptations induced by cued inphase BMT. Ultimately, it would be very beneficial to discover a measurement tool of central nervous system function that might inform rehabilitative strategies to enhance motor function following a stroke. A small number of studies have reported using fMRI to measure treatment effects during the first months of recovery after stroke and to predict behavioural gains (Cramer et al., 2007; Dong, Dobkin, Cen, Wu, & Winstein, 2006; Hodics, Cohen, &

Cramer, 2006). Stinear et al. (2007) reported that functional anisotropy of white matter integrity of the posterior limb of the internal capsule can predict motor gains during stroke recovery and Koski et al. (2004) has used TMS to measure cortical excitability modulations in the first two sessions of rehabilitation to predict response to subsequent motor therapy. Functional MRI and TMS are expensive tools to use in order to gauge responsiveness to a training regime. The cue-related MRP extracted from an EEG recording on the other hand is relatively less expensive and is more sensitive to detect within-session cortical excitability modulations compared with fMRI or TMS.

The central limitation of the current study is the generalization of the findings within healthy participants to those who have suffered a stroke. We do acknowledge that the mobility restriction used in the current study was an attempt to simulate spasticity of the wrist; however, preventing movement of the wrist and imposing a load upon the musculature is vastly different than an upper motor neuron lesion causing spasticity of stroke affected musculature. A stroke, particularly within premotor regions, can cause spasticity and concomitant flexion contracture (O'Dwyer, Ada, & Neilson, 1996). Spasticity is the result of disinhibited spinal reflexes that are usually controlled by descending pathways of supraspinal regions (Mayer & Esquenazi, 2003). Without descending control of the reflexes muscles become hypertonic leading to difficulty in moving the limb actively or passively (Mayer & Esquenazi, 2003). The findings of the current study cannot predict if the cue-related MRP can be elicited by a cued movement in the stroke population. Future study is required to assess the cue-related MRP in this population in terms of lesion location, stroke severity, concomitant diagnosis (e.g. depression), sex and age.

The Bereitschaftspotential and Stroke

A few studies have used the self-paced Bereitschaftspotential (BP) to measure cortical excitability in stroke patients (Honda et al., 1997; Kitamura, Shibasaki, & Takeuchi, 1996; Platz et al., 2000; Shibasaki, 1975; Tarkka, Kononen, Pitkanen, Sivenius, & Mervaala, 2008; Wiese, Stude, Sarge, Nebel, Diener, & Keidel, 2005b) and point to the potential to record the cue-related MRP in the stroke population. In a study by Wiese et al. (2005a) the self-paced BP was used to measure preparatory and executory excitability following a stroke sparing subcortical regions. Contrary to fMRI that has poor temporal resolution or TMS that only conveys information pertaining to the excitation of the muscles, the self-paced BP extracted from an EEG recording can clearly differentiate between preparatory and executory excitability with enhanced temporal resolution. By way of the self-paced BP, Wiese et al. (2005a) reported an intact early BP component, denoting preparatory excitability; however, the late component, representative of motor execution, was lateralized to the contralesional primary motor cortical region. Therefore, demonstrating a modulation of the localization of the BP components following a stroke.

Tarkka et al. (2008) has utilized the self-paced BP to measure cortical excitability modulations in response to constraint-induced training (CIT), a rehabilitative method whereby the unaffected limb is constrained to force a patient to use their stroke-affected limb. Following a two-week CIT regime, Tarkka et al. (2008) reported a reduction in the time to complete a movement test and a 15% improvement in functionality. The amplitude of the BP component did not change following CIT; however, a spectrum analysis of the preparatory component of the BP revealed a decrease in frequency over the region of the SMA.

Platz et al. (2000) has used the self-paced BP to assess cortical excitability patterns of stroke patients who present with hemiparesis, deafferentation and ideomotor apraxia. Platz et al. (2000) reported that the self-paced BP could be used to assess specific cortical excitability modulation underlying different clinical presentations. For example, hemiparetic patients exhibited a more lateralized early BP component to the lateral premotor region, opposed to a central activation pattern over the SMA region observed in healthy control subjects. The observation that the early BP component lateralized to the lateral premotor area indicated the possible importance of the lateral premotor cortex in motor generation following a stroke with subsequent hemiparesis.

Therefore, the above studies demonstrated that the self-paced BP can be used to measure cortical excitability modulations in response to cortical injury due to a stroke, during movement-related training and to assess cortical excitation patterns according to specific clinical outcomes. These data allude to the possibility of recording and using the cue-related MRP in the stroke population in the same manner.

Conclusion

Despite a decrease in mobility and tonic load placed upon the musculature of the right wrist, cued inphase BMT enhanced the amplitude of the early MRP associated with movement preparation. The increase in preparatory activity was also associated with a behavioural enhancement. These results point to the potential of utilizing the cue-related MRP as a measure of cortical excitability in the stroke patient population who may suffer from lack of mobility of the affected wrist. Previous research has recorded and used the self-paced BP to measure cortical excitability and training-related modulations in the stroke patient population. We hope to use the cue-related MRP in the same manner to gauge

within-session cortical excitability modulation in response to bimanual movement training in stroke patients.

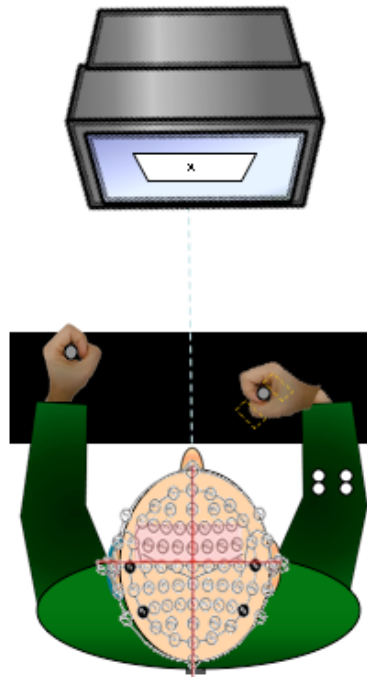
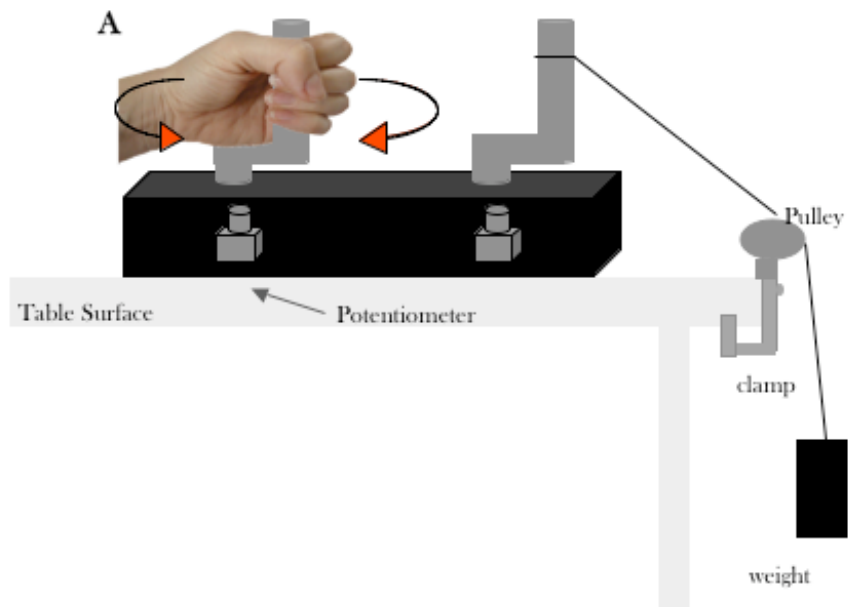


Figure 5-1 - (A) The custom-made wrist movement device consisting of two handles linked to two potentiometers. A weight linked via a pulley was attached to the right handle to impose a 3% tonic load upon the right wrist musculature. (B) The top view of the wrist movement device. Two blocks were attached to the device to restrict right wrist movement to the terminal 30° of flexion. Left wrist movement was not restricted.

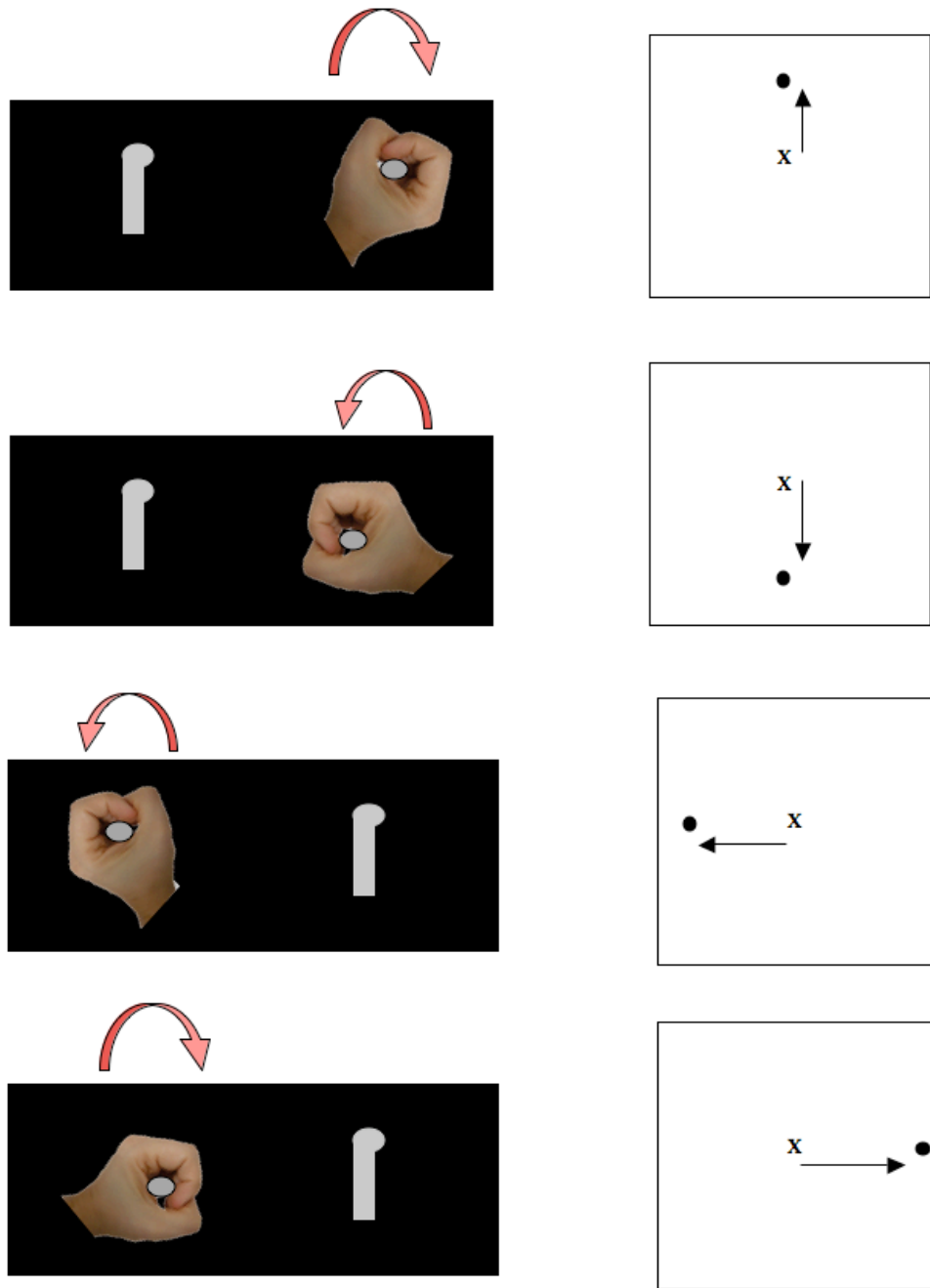


Figure 5-2 - (A) Unimanual wrist movement and corresponding cursor movement. (A) Right wrist extension controlled cursor displacement upward. (B) Right wrist flexion controlled downward movement of the cursor. (C) Left wrist extension controlled leftward movement of the cursor and (D) left wrist flexion controlled rightward movement of the cursor.

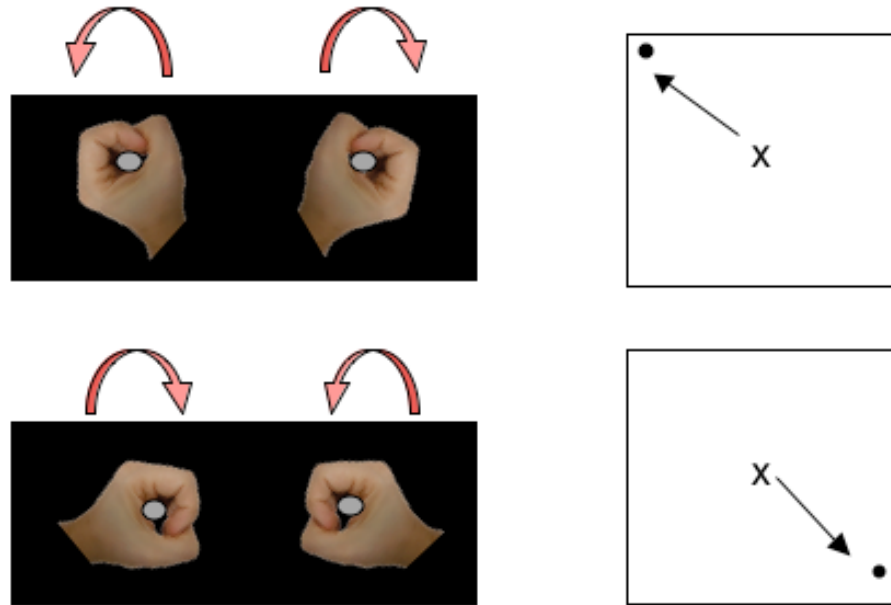


Figure 5-3 - Inphase bimanual movement patterns and corresponding cursor movement.

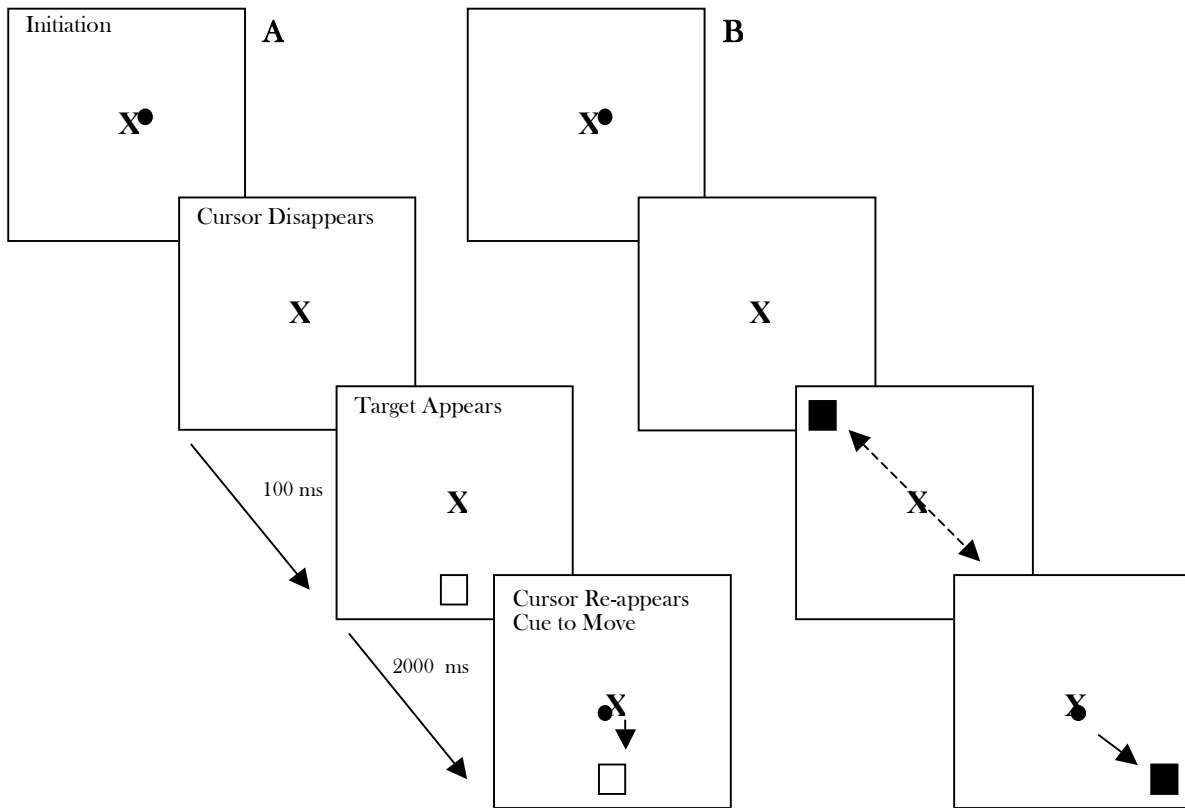


Figure 5-4 - (A) Steps to complete one repetition during the pre- and post-training unimanual movement task. (B) Steps to complete one repetition during the cued inphase bimanual movement training (black target).

| Subject | Maximum Force Production (g) | 3% MFP (g) |
|---------|------------------------------|------------|
| 1 | 9000 | 270 |
| 2 | 8000 | 240 |
| 3 | 15000 | 450 |
| 4 | 11000 | 330 |
| 5 | 7500 | 225 |
| 6 | 10050 | 300 |
| 7 | 5800 | 175 |
| 8 | 9000 | 270 |
| 9 | 5750 | 170 |
| 10 | 7000 | 210 |

Table 5-1 - Maximum force production and 3% of MFP in grams for each subject.

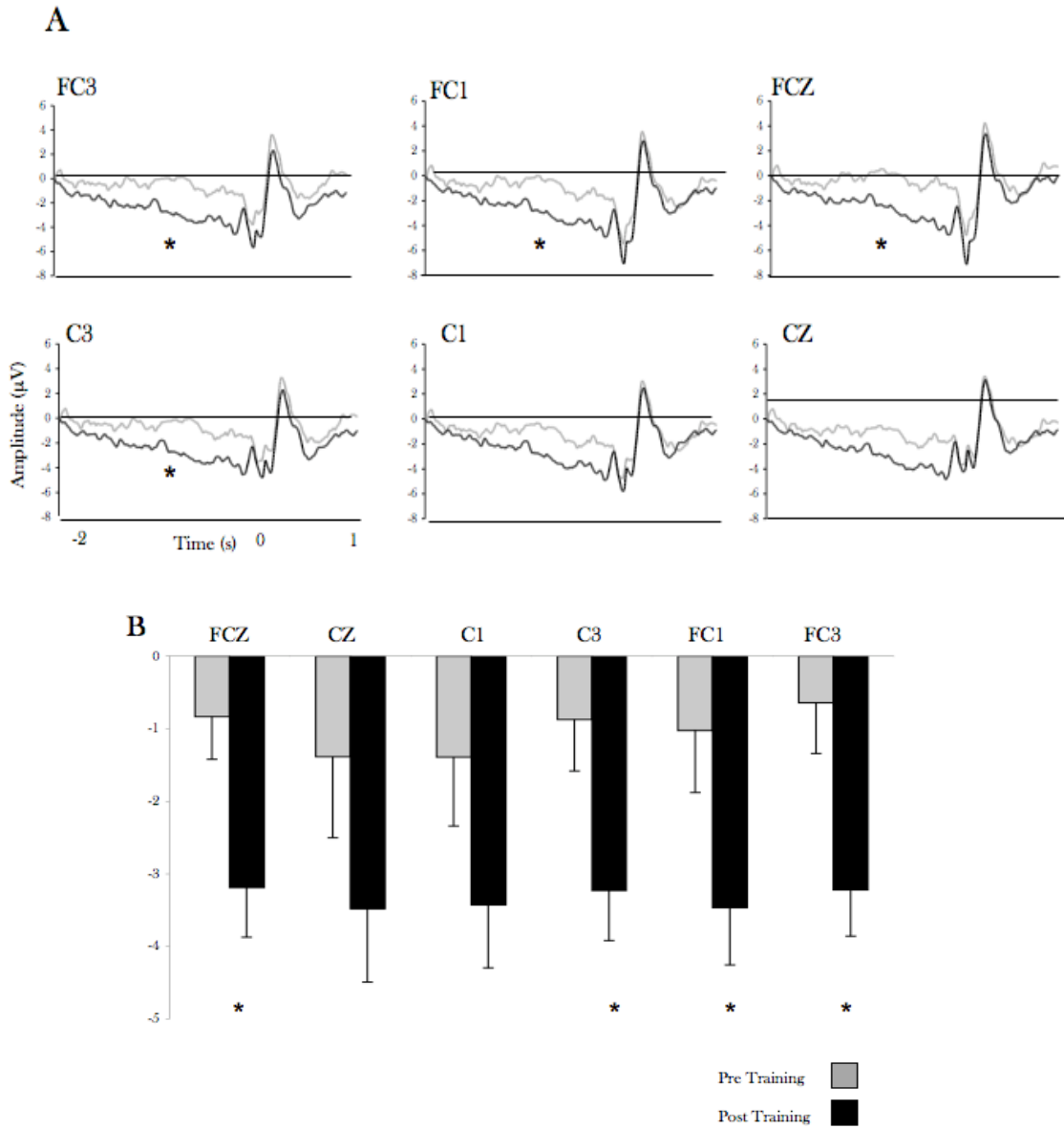


Figure 5-5 - (A) Grand average MRPs ($n=10$) time-locked to cued movement onset of the right wrist prior to (pre-training grey trace) and following (post-training black trace) practice of the cued inphase bimanual visuomotor training task at 6 electrode sites (FCZ, CZ, C1, C3, FC1 and FC3). (B) Group mean (\pm SE, $n=10$) early MRP amplitudes in the pre-training (grey bars) and post-training (black bars) conditions. * Indicates $p < 0.05$.

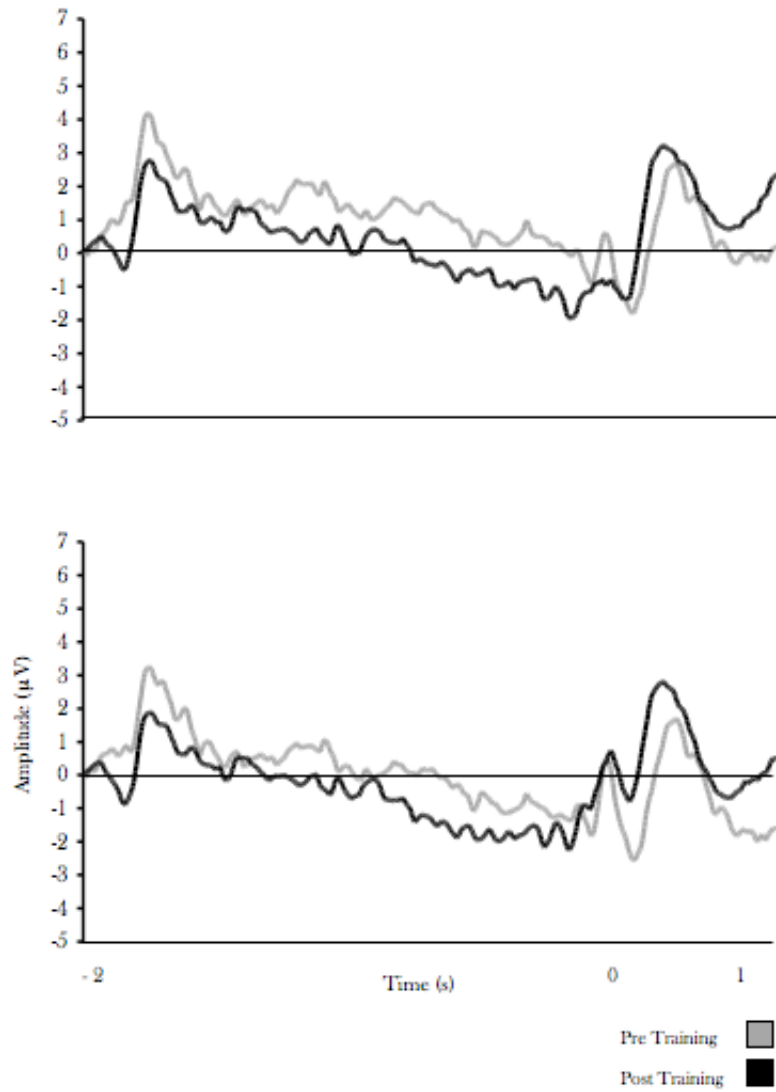


Figure 5-6 - Grand average CNVs (n=10) time-locked to the cue to move before (pre-training grey trace) and following (post-training black trace) practice of the cued inphase bimanual training in 2 electrode sites (FCZ, CZ).

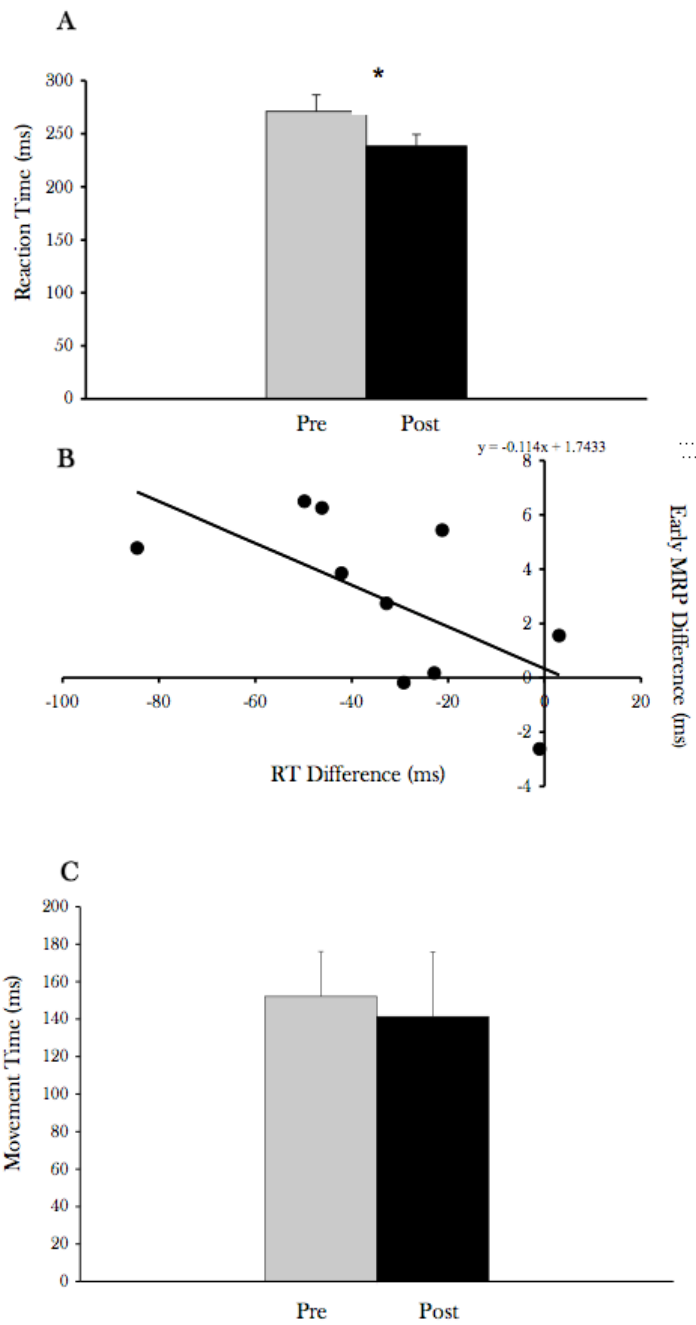


Figure 5.7 - (A) Grand average reaction time (n=10) in pre-training grey bar and post-training black bar. (B) Correlation analysis between the post-training minus pre-training difference in early MRP amplitude and reaction time in response to the inphase visuomotor training paradigm. MRPs were measured from CZ (n=10). (C) Grand average movement time (n=10) in pre-training grey bar and post-training black bar. * Indicates $p < 0.05$.

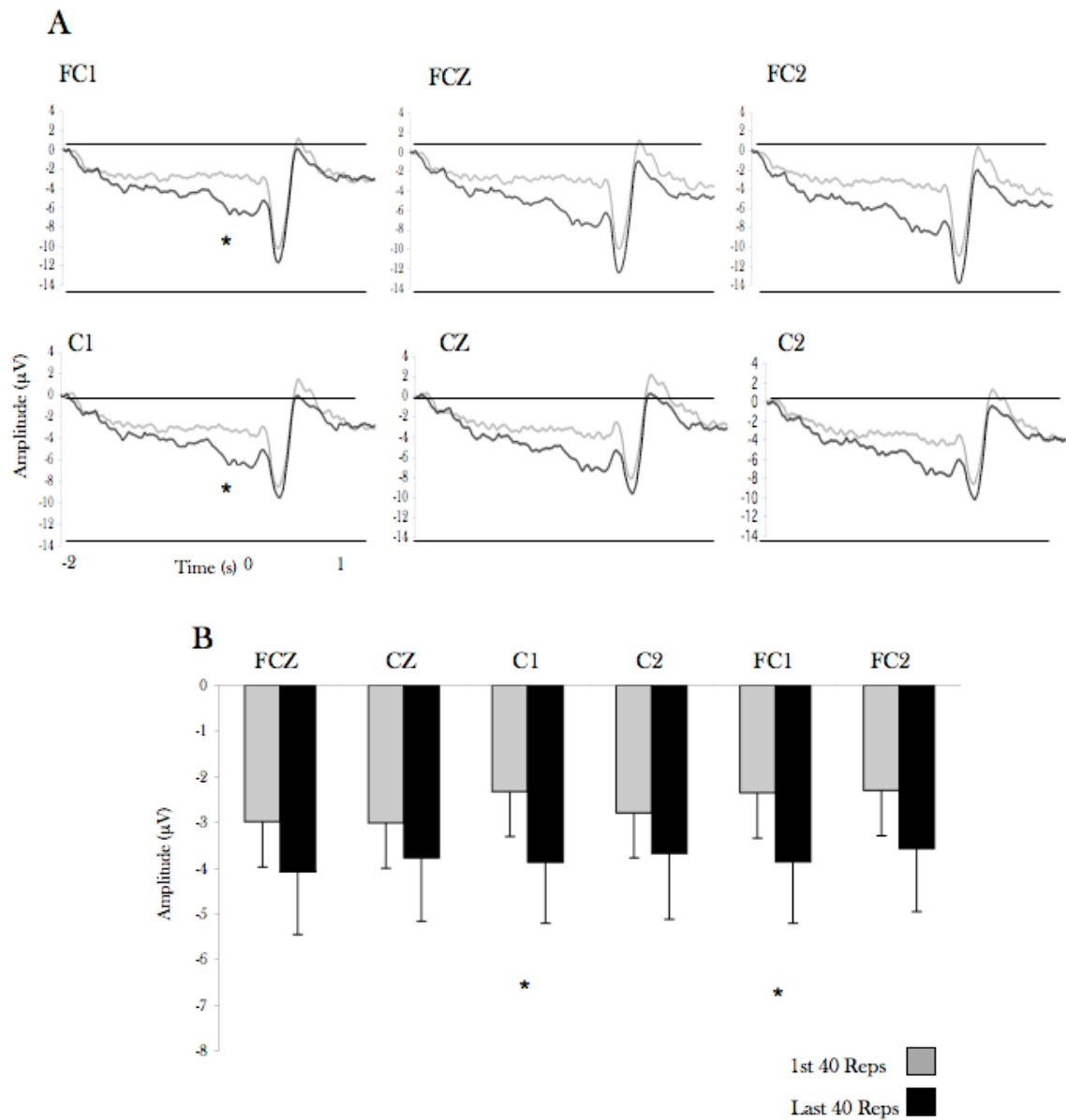


Figure 5-8 - (A) Grand average MRPs ($n=10$) time-locked to cued movement onset of the right wrist in the first 40 repetitions (grey trace) versus the last 40 repetitions (black trace) of the inphase bimanual visuomotor training task (trial 2) at 6 electrode sites (FCZ, CZ, C1, C2, FC1 and FC2). (B) Group mean (\pm SE, $n=10$) early MRP amplitudes in the 1st 40 repetitions (grey bars) and last 40 repetitions (black bars) for inphase BMT at 6 electrode sites (FCZ, CZ, C1, C2, FC1 and FC2). * Indicates $p < 0.05$.

Chapter Six - General Discussion & Future Directions

General Discussion

This thesis encompassed an investigation of the cue-related MRP, a measure of preparatory and executory excitability in response to a visually cued movement, in terms of: (1) its application to the measurement of learning-related cortical adaptations in response to bimanual movement training (BMT) (Chapters 2, 3 and 5), (2) cortical localization (Chapter 3), (3) influential kinematic parameters (Chapter 4) and (4) for future applicability to stroke related research (Chapter 5).

Cortical excitability and cued inphase BMT

In Chapter 2 we demonstrated that cued inphase BMT more so than cued antiphase BMT or repetitive unimanual training enhanced preparatory excitability, determined by an increase in the amplitude of the early MRP, in the last forty repetitions of cued inphase BMT. This same effect was demonstrated in Chapter 3, experiment one, trial 2. The bimanual training task of Chapters 2 and 3 involved wrist movements utilizing full range of motion and of equal amplitudes. However, Chapter 5 demonstrated that movement of equal amplitudes of the wrists was not a prerequisite to cued inphase BMT effects upon preparatory excitability during the last 40 repetitions of cued inphase BMT and in turn the post-unimanual task. Chapters 2, 3 and 5 (in addition to our previous work - Smith and Staines, 2006) are the first series of experiments to utilize the cue-related MRP as a measure of cortical excitability modulation in response to bimanual movement learning in the healthy population. We originally hypothesized that bimanual movement training would enhance primary motor cortical (M1) excitability; however, to our surprise M1 excitability was not affected by cued BMT. Instead, we have consistently observed an

increase in the amplitude of the early MRP associated with movement preparation following inphase BMT in particular (Chapters 2, 3 and 5). In Chapter 3, experiment one; we demonstrated that the cued inphase BMT paradigm did not modulate the amplitude of the self-paced early BP component, representative of SMA activation. This result demonstrated that cued inphase BMT of Chapters 2, 3 (trial 2) and 5 did not primarily modulate SMA excitability; therefore, exemplifying a differential locus of cortical modulation in response to this type of training. A source localization method (sLORETA) demonstrated that the cue-related MRP and self-paced BP differed in cortical localization only when considering the early component. The primary generators of the cue-related MRP were determined to be the lateral premotor cortex, M1 and S1. Whereas the self-paced BP was primarily generated by the SMA, M1 and S1, replicating previous investigations of the self-paced BP (Deecke, 1987; Deecke & Lang, 1996; Shibasaki et al., 1980; Shibasaki & Hallett, 2006). Therefore, the question is; how did inphase BMT drive an increase in lateral premotor cortical excitability? We propose two models: 1) disinhibition within the lateral premotor cortical regions via interhemispheric communication in response to homologous muscle activation, and 2) a subcortical network comprising the cerebellum, in addition to the lateral premotor cortex.

How preparatory excitability increased in response to cued inphase BMT is most likely attributable to the nature of the current training task itself. Studies of non-human primates (Hoshi & Tanji, 2006; Riehle & Requin, 1989) and humans (Jancke et al., 2000; Koch et al., 2006; Sugiura et al., 2001) have reported that activation of the lateral premotor cortex, specifically the dorsal portion (PMd), increased in response to visually or acoustically triggered movement. Conversely, self-generated movement predominantly

increased cortical excitability of the SMA, a cortical region primarily associated with bimanual movement mediation. The first potential model that could represent preparatory excitability modulation in response to cued inphase BMT could involve interhemispheric communication via cortico-cortical connections between bilateral lateral premotor regions and corresponding homologous muscle representations by way of the corpus callosum. The lateral premotor cortex is predominantly activated during externally cued movement; therefore, it may have been possible that the cued inphase BMT task, activating homologous muscle representations, released inhibitory effects within the lateral premotor region, which translated into an enhancement of the early MRP. Bilateral lateral premotor regions, specifically the dorsal portion (PMd), are highly connected interhemispherically (Boussaoud, Tanne-Gariepy, Wannier, & Rouiller, 2005b). In a repetitive TMS (rTMS) study by Bestmann et al. (2008) disruption of left PMd excitability decreased excitation of the contralateral PMd and M1; however, this effect was observed only during movement opposed to rest. Therefore, the left PMd region modulated interhemispheric activation of the right PMd and M1 only during a motor task. There is no evidence indicating that cued inphase bimanual movement increased activation within the lateral premotor cortex in an interhemispheric manner. Stinear and Byblow (2002) have demonstrated in healthy subjects, using paired-pulse TMS, that inphase bimanual movement caused disinhibition within homologous muscle representations of the M1, whereas antiphase bimanual movement enhanced an inhibitory effect within the same regions. At present effects of inphase bimanual movement upon lateral premotor cortical excitability has not been investigated. Additionally, if inphase bimanual movement training caused a disinhibition of homologous muscle representations within the lateral premotor cortex due to

interhemispheric communication, then the same effects should have occurred within the M1. However, we have never observed a change in the late MRP, likely indicative of M1 excitability, in response to short-term (approximately 45 minutes) cued inphase BMT (Chapters 2, 3 and 5, in addition to Smith and Staines, 2006). But, we cannot definitively assert that the cue-related MRP is sensitive enough to measure M1 excitability modulations in response to cued inphase BMT. Overall, the effect of cued inphase BMT may involve a subcortical loop engaging the cerebellum in addition to the lateral premotor cortex more so than interhemispheric interaction.

In a study of split-brain patients (Kennerley et al., 2002), who no longer exhibited communication between the two hemispheres, it has been shown that these patients cannot execute a discrete antiphase bimanual movement or an inphase or antiphase continuous bimanual task. However, split-brain patients could execute a discrete self-paced inphase bimanual movement. This phenomena has been termed the “bimanual advantage” (Ivry & Richardson, 2002). This study (Kennerley et al., 2002) demonstrated that the corpus callosum is required for spatial coupling of complex bimanual movements (for example, bimanual circle drawing) and for mediating interhemispheric communication between regions executing a continuous bimanual task (for example continuous bimanual flexion and extension of the index fingers). On the other hand, the split-brain patients could execute a task that was discrete and inphase indicating a differential locus of bimanual control for this type of movement.

A “bimanual advantage” in motor performance is also evident in the literature on finger tapping. A certain level of intertap variability characterizes simple externally cued unimanual tapping movements with the index finger. However, inphase bimanual tapping

movements reduce the intertap variability (Ivry & Richardson, 2002), alluding to a “bimanual advantage” of separate timing signals during the preparatory stage of movement (Helmuth & Ivry, 1996; Ivry & Hazeltine, 1999). The cerebellum has been linked to the timing function of externally cued movement (Ivry & Richardson, 2002), particularly the lateral portion of the cerebellum (Ivry et al., 1988). Investigations of patients with cerebellar lesions present with heightened temporal variability of the ipsilesional hand (Franz et al., 1996; Ivry et al., 1988), which is improved with inphase bimanual movement (Franz et al., 1996). Using MEG and a coherence analysis, a previous study by Pollok et al. (2005) linked the “bimanual advantage” to functional connectivity between the cerebellar hemispheres. Functional coupling between the cerebellar hemispheres was not observed when subjects executed an externally triggered unimanual movement or antiphase bimanual movement (Pollok et al., 2007).

Furthermore, In an fMRI study by Seitz et al. (2004) a patient with an infarction within the corpus callosum could not execute a self-generated antiphase or inphase bimanual movement; however, with a visual cue the patient regained the ability to execute the inphase bimanual task, consisting of bilateral thumb and index finger opposition. The inphase bimanual task was associated with an increase in the bilateral lateral occipital-premotor-cerebellar circuit. Therefore, the visual stimulus engaged two identical networks in each hemisphere, which allowed the patient to regain the ability to perform discrete inphase bimanual movement with an external cue. Results of healthy control subjects also revealed that bimanual inphase movement with an external cue increased activation of bilateral lateral premotor regions. Seitz et al. (2000; 2004) proposed that the SMA in addition to the cingulate motor area play a critical but different role in bimanual

coordination. Particularly in patients with callosal damage, Seitz et al. (2004) proposed the cerebellum as the locus of bimanual recoupling. Whilst the activation of the lateral occipital cortex was most likely due to the increased visual attention and dorsal premotor cortical activation with the external guidance of the movement.

In an fMRI study by Doyon et al. (2002) investigating unimanual training consisting of a sequence of button presses contingent upon a visual cue demonstrated that an increase in excitability within the lateral premotor cortex was related to increased excitability within the cerebellum, when cerebellar activity shifted from preliminary activation within the cerebellar cortex to the dentate nucleus (one of the deep cerebellar nuclei). Therefore, this study found evidence of an experience-dependent shift in activation within the cerebellum that increased excitability within the lateral PM cortex.

These investigations detailed above (Doyon et al., 2002; Kennerley et al., 2002; Pollok et al., 2005; Pollok et al., 2007; Seitz et al., 2004) lend support to the idea that the visually cued inphase bimanual movement paradigm of Chapters 2, 3 and 5 was possibly mediated by cerebellar coupling in addition to lateral premotor activation to prepare the visually cued task. Learning related modulation of lateral premotor excitability was then observed in the early MRP.

Bimanual training transfer to a unimanual movement

A few studies have investigated bimanual training transfer effects upon a unimanual movement (Burgess, Bareither, & Patton, 2007; Schulze, Luders, & Jancke, 2002; Vangheluwe, Puttemans, Wenderoth, Van Baelen, & Swinnen, 2004; Zanone et al., 1992 & 1997); however, these investigations have primarily measured behavioural responses during motor execution. For example, how well a subject could perform a unimanual

movement following a bimanual pegboard task (Schulze et al., 2002) or an asymmetrical bimanual task involving line drawing with one hand and star drawing with the other (Vangheluwe et al., 2004). Overall, the above mentioned studies demonstrated a positive behavioural transfer effect of bimanual movement training to a unimanual task; however, did not investigate the underlying cortical modulations that occurred. Schulze et al. (2002) speculated that the visually mediated bimanual pegboard task of inphase nature upregulated dorsal premotor cortical excitation, since this area is primarily implicated in visuosomotor association; however, the study did not provided direct evidence of this.

Chapters 2, 3 and 5, in addition to our previous work (Smith and Staines, 2006) are the first series of experiments to measure cortical excitability transfer effects from a bimanual movement to a similar unimanual movement. We observed that the preparatory element of the bimanual task transferred to the unimanual movement and corresponded to a behavioural enhancement (Chapters 2 and 5). We believe the increase in preparatory excitability is linked to an increase in lateral premotor cortical excitation (Chapter 3, experiment two). Studies by Maslovat et al. (2008; 2009) have reported similar results of increased motor preparatory efficiency following asymmetrical and asynchronous bimanual movement practice.

The transfer effects (decrease in RT) that we report for a similar unimanual movement in response to cued inphase BMT unfortunately do not lend insight into the generalizability of such training to other bimanual or unimanual movement patterns. Therefore, it is unclear whether the cued bimanual training effects are only present during the cued paradigm. If cued inphase BMT is used as a strategy to enhance motor recovery following a stroke then generalizability is important. Several stroke related studies using

inphase BMT have demonstrated a positive effect of training upon mobility of the affected limb (Luft et al., 2004; McCombe-Waller & Whittall, 2004; Mudie & Matyas, 2000; Whittall et al., 2000); therefore, generalizability has been demonstrated in the past, however further study is certainly required.

Training response and interindividual variability

Exhibited in the correlation analyses of the difference in early MRP component amplitude and reaction time following cued inphase BMT of Chapters 2 and 5, it was evident that some subjects did not respond to the training paradigm in terms of cortical excitability modulation or behavioural enhancement. Perhaps these subjects may have produced maximal early MRP amplitude or had an optimal reaction time (RT) in the pre-training trial. However, when looking at the data these subjects presented with an averaged RT of approximately 280 ms in the pre-training task, whereas the averaged RT for the group as a whole was approximately 270 ms and early MRP amplitude was marginal in some non-responders and robust in others. Therefore, the non-responders were not particularly more efficient at the task in the pre-training trial or showed modulation of the early MRP. Perhaps it is more to do with the individual's cortical recruitment strategy. Ball et al. (1999) have reported interindividual variability of cortical recruitment during a self-paced movement likely linked to differential performance strategy. When observing the cortical localization of the early MRP in Chapter 3, there are clear individual differences in the cortical focus of the early MRP where some individuals do not primarily recruit the lateral premotor area during an externally cued task but recruit primarily the SMA region. Perhaps these subjects have a different performance strategy; therefore, recruit different cortical regions to complete the task.

Three subjects, who participated in experiment two of Chapter 3, also participated in the cued inphase BMT paradigm with restricted range of motion (Chapter 5). These individuals were responders in the training study of Chapter 5, and primarily activated the lateral premotor region in the source localization study (Chapter 3, experiment two). It will require further study; however, it seems likely that one could predict a responder to cued inphase BMT by the primary activation of the lateral premotor region during externally triggered movement.

Antiphase BMT and cortical excitability modulation

Unlike cued inphase BMT, antiphase BMT did not modulate the cue-related early MRP component (Chapter 2). We do not wish to discount antiphase BMT as a valid training strategy to enhance cortical excitability. We propose that the cue-related MRP may not be an efficient tool to measure excitability modulations in response to antiphase BMT. Studies using rTMS (Serrien, Strens, Oliviero, & Brown, 2002) or investigations of Parkinson's disease patients (Almeida et al., 2002; Almeida et al., 2003; Johnson et al., 1998; Swinnen et al., 1997) indicate that disruption of SMA activity leads to a disruption in the execution of antiphase bimanual movement opposed to inphase bimanual movement with an external cue. Therefore, the SMA is evidently important for antiphase bimanual movement, even with an external cue. The lateral premotor cortex may still be involved in the preparation of a cued antiphase movement, but the SMA is required to temporally and spatially control an antiphase movement by mediating interhemispheric communication between its contralateral homologue and M1 (Serrien et al., 2002). Therefore, we hypothesize that the cue-related MRP representing predominant excitation of the lateral premotor cortex, in addition to the M1 and S1 (Chapter 3, experiment two) is not an

efficient tool to measure preparatory excitability modulations within the SMA. A future training-related study is proposed in the future directions section.

Thesis limitations

The first limitation of the current thesis pertains to the behavioural measure employed throughout each study. We were originally interested in exploring cortical excitability modulations induced by bimanual movement training and not behaviour specifically; however, during analysis we decided to implement a measure of behaviour and chose reaction time (RT) subsequently. We do acknowledge that RT is not the only behavioural measure that could have been utilized; time to peak velocity, time to peak acceleration, movement accuracy or EMG characteristics could have been viable options as well. We predict that accuracy measured by initial displacement of the cursor during the training trial would have revealed an accuracy enhancement in initial cursor movement direction in the later portion of the training trial in comparison to the initial portion of training. Since the late MRP is not shown to modulate in response to short duration cued inphase BMT (Chapters 2, 3 & 5) we hypothesize that behavioural measures associated with the execution of the movement would not exhibit modulations. We do predict that with a longer training duration, behavioural modulations associated with movement execution would become more evident.

A second limitation of the current thesis relates to Chapter 3, experiment two and the use of sLORETA for source localization of the components of the cue-related MRP and self-paced BP. Estimation of source localization of averaged EEG data inevitably is limited by the forward and inverse problems despite co-registration with a realistic individual head model. Explained by Plummer et al. (2008) the forward model is the set of

parameters specified within the analysis on which the source localization(s) are projected. Parameters include: compartments, surfaces and conductivities of the head model, also called the volume conductor or forward model. Based upon the specified parameters, the forward model will give a “unique solution”. The inverse problem by contrast has no unique solution; therefore, relies upon an inverse model or specific mathematical constraints. The inverse problem is defined as the computation of images of cortical activation based upon extracranial measurements (Pascual-Marquis, 2002). There are two major types of inverse modeling methods: dipole and current source density reconstruction (CDR). With the dipole method investigators select the number of dipoles to apply to the inverse algorithm. Conversely, the CDR makes no assumption about the number of cortical sources; therefore, CDR analysis requires a complex mathematical model. The sLORETA CDR mathematical model is based upon the idea that “neighbouring neuronal populations are more likely to undergo synchronous depolarization during a spontaneous discharge” (Pascual-Marqui et al., 1994; Plummer et al., 2008). Therefore, the sLORETA method will assume similar activation strengths of neighbouring regions. However, this assumption may not be appropriate for the data.

Some of the major issues with CDR analysis have been improved with the use of realistic head models, which predict the impact of the volume conductor on the EEG signal. In comparison, older spherical models created large errors in source localization. Another major issue is related to the conductivities of the tissue compartments of the human head used in the realistic head model. Are the conductivity values appropriate? Taken together, limitations of CDR analyses can occur due to the mathematical model chosen to represent the data. In Chapter 3, experiment two we used the sLORETA model

in addition to the digitized electrode positions and subject's structural MR image in order to create a realistic head model. sLORETA was selected because it is reported to have low localization error (Pascual-Marquis, 2002). However, it would have been a benefit to the current thesis to have localization results confirmed through fMRI investigation.

Stroke application

Chapter 5 demonstrated the potential to record the cue-related MRP in the healthy population despite a restriction of range of motion and a tonic load placed upon the musculature. The results of this study point to the potential to record the cue-related MRP in stroke patients who have decreased range of motion and tonic muscle contraction of the affected limb; however, until further study is conducted in this population we will not know for certain, since the mechanism underlying spasticity is entirely different than the imposition of a movement restriction and tonic load place upon the musculature of a healthy wrist. Previous studies have recorded the self-paced BP in stroke patients (Wiese, Stude, Sarge, Nebel, Diener, & Keidel, 2005b) and have used the BP as a measure of training-related cortical modulation (Tarkka et al., 2008) and clinical presentation (Platz et al., 2000). Therefore, it is most likely that the cue-related MRP can be recorded in the stroke population since the self-paced BP is quite similar to the cue-related MRP.

Patients who might benefit from cued inphase BMT protocol is beyond the scope of the present thesis; however, some speculations can be made. Ward et al. (2007) reported that stroke patients who have greater corticospinal damage exhibit greater excitation of the PMd during hand grip tasks with progressively increased force production requirements. When a cortical region exhibits increased excitation in response to a novel training task, early plasticity could occur leading to representational modulation and

behavioural improvements. Perhaps cued inphase BMT could optimize an increase in cortical excitability within the PMd of stroke patients that already present with increased PMd activation. It is probable that if the cue-related MRP can be recorded within a stroke patient, one session of cued inphase BMT could be used to assess whether the patient responded to the training type. If a response is detected than the type of training may be useful to enhance functional recovery in that patient. Specific studies regarding lesion location and effects upon the cue-related MRP would have to be assessed first. But, we hypothesize that patients who have sparing of the lateral premotor cortex, cerebellum, parietal cortex, M1 and S1 might benefit from cued inphase BMT.

Future Directions

There are many different studies that could evolve from the current thesis. Four potential experiments will be presented.

Chapters 2, 3 (trial 2) and 5 demonstrated that the cue-related early MRP component was an efficient measurement tool of training-related adaptations within preparatory regions in response to visually cued inphase BMT. In Chapter 2, modulatory effects upon the cue-related early MRP were not observed in response to cued antiphase BMT. Discussed in the general discussion, authors report that the SMA primarily mediates antiphase bimanual movement; therefore, the cue-related MRP is most likely not an efficient tool to measure modulations in response to cued antiphase BMT. We hypothesize that the amplitude of the self-paced early BP component would increase in the post-unimanual trial in response to cued antiphase BMT. A study such as this would be important to discern if varying modes of bimanual training variably effect differing event-related potentials. This type of research could highly benefit stroke related research, in that

these electrophysiological markers could be used to assess whether training-related cortical adaptations occur in response to specific modes of training within a single-session.

The second proposed study pertains to the nature of the cued inphase BMT paradigm. Would the increase in early MRP component amplitude remain if the task were acoustically cued? It is important to fully understand the task constraints required to enhance lateral premotor cortical excitability during a cued inphase BMT task.

Investigations of the dorsal premotor cortex reveal that visual feedback is required for on-line error correction (Lee & van Donkelaar, 2006), and enhanced activation (Vaillancourt, Mayka, & Corcos, 2006). We hypothesize that visual feedback is required during the cued inphase BMT paradigm; therefore, cued inphase BMT with acoustic cuing will not affect the amplitude of the early MRP components.

The third proposed study uses fMRI to investigate the cortical localization of the cue-related MRP and self-paced BP and involves cued inphase BMT implemented across several days. This study would be used to confirm the localization results of Chapter 3, experiment two and would support the use of the cue-related MRP to measure cortical excitability and potential modulations within the lateral premotor cortex, M1 and S1. It is plausible that within session changes in cortical excitability would not be evident using fMRI therefore several training days would be required.

The fourth and final proposed study would be within the stroke patient population. The first component of the study would be to assess patients who exhibit a cue-related MRP. The data would be assessed according to lesion location, stroke severity, time since stroke, different function motor testing, sex and age. Those patients who exhibit a cue-related MRP would then participate in cued inphase BMT. To perform the training task,

patients would require a certain range of motion to participate. Within training-related modulations of the cue-related MRP would be assessed following the training intervention. If within session changes are evident in some stroke patients within the cue-related MRP, a more longitudinal study could be implemented to measure probable movement related performance enhancements.

Conclusion

The current thesis points to the advantageous use of the cue-related MRP as a measure of preparatory excitability modulation in response to cued inphase BMT. We are the first to use the cue-related MRP as a measure of learning-related cortical adaptation in response to BMT, and it is a novel and surprising result to observe specific modulations of the cued MRP in response to a specific mode of training. This result demonstrates the potential to use specific ERPs to measure cortical adaptations in response to specific modes of training, which would be a very advantageous tool to use within future stroke related research. Overall, the results of the current thesis provide needed understanding of the training requirements that ultimately modulate the MRP and illustrate the kinematic parameters that may influence the presentation of the MRP. Therefore, studies utilizing the MRP should be controlled accordingly. These data will inform future training-related studies in the healthy and stroke patient populations that use the cue-related MRP as a measure of learning-related cortical adaptation and open the door to a vast array of research endeavours.

Appendix One: EMG output when using the wrist movement device versus goniometric sensors

Introduction

Two goniometric sensors placed upon the posterior aspect of the subject's hands and wrists accomplished cursor control during the task in Chapter 2. In subsequent Chapters 3, 4 and 5, cursor control was mediated by a custom made wrist movement device, consisting of two hands that rotated in clockwise and counter-clockwise directions so that wrist flexion and extension occurred in the horizontal plane. Subjects were required to grasp the handles of the device to rotate the handles and in turn control the cursor of the computer screen; therefore, with the advent of the device increased tonic load upon the musculature could occur and confound future cue-related MRP results making interpretation more difficult when comparing the investigation using the goniometric sensors (Chapter 2) versus the wrist movement device (Chapters 3, 4 and 5). Therefore, this methodological study investigated averaged EMG output of the Flexor digitorum superficialis (FDS) and extensor digitorum (ED) muscles during two conditions: 1) right wrist flexion and extension while gripping the handle of the wrist movement device and 2) right wrist flexion and extension without gripping the handle of the device. We hypothesized that EMG amplitude would be comparable when gripping versus non-gripping of the wrist movement device.

Materials & Methods

Subjects

Five healthy subjects. All subjects will give their written consent to participate in the study that has been approved by the Office of Research Ethics at the University of Waterloo.

EMG Recording Procedure

EMG will be recorded from the flexor digitorum superficialis (FDS) and extensor digitorum (ED) of the right forearm. EMG will be sampled at a rate of 1000 Hz.

Behavioural Tasks

Subjects performed 10 cued right wrist flexion movements followed by extension movements while gripping the device handles, and 10 cued right wrist flexion then extension movements while not gripping the handles. For the non-gripping task the fingers were relaxed at 0-5° flexion (therefore, not gripping the handles) and the hand was strapped to the handles along the proximal metacarpal phalangeal joints of digits 2-5. The order of flexion and extension movements of the right and left wrists were randomized.

Data Analysis

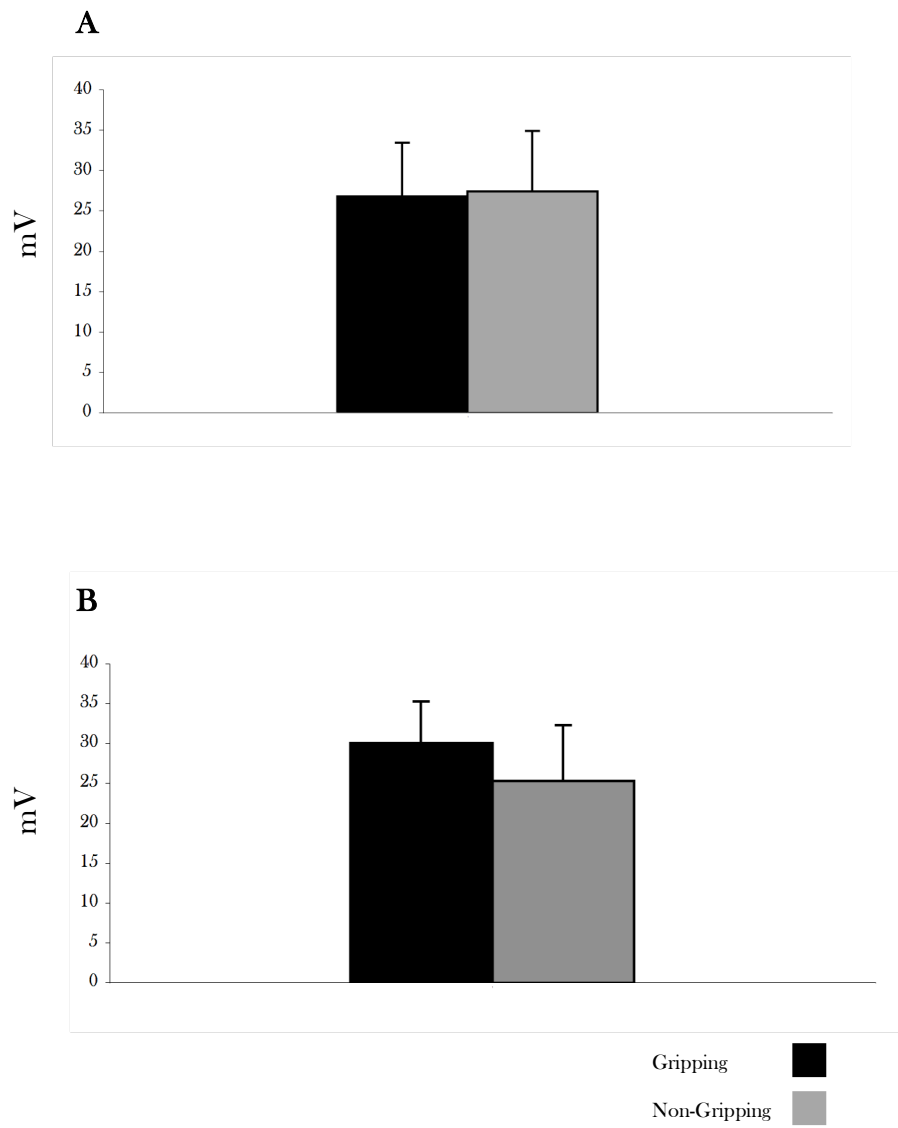
All analyses were conducted using Noraxon (U.S.A. Inc). EMG onset and termination was marked manually in the continuous data file. EMG data was full wave rectified and the amplitude was quantified over the mean duration as the area under the curve. Mean EMG amplitude was compared using a 2 (gripping/non-gripping) X 2 (FDS/ED) repeated measures ANOVA.

Results

Shown in appendix Fig. 1, the averaged EMG activation measured as area under the curve was no different during gripping versus non-gripping conditions for the FDS or ED muscles ($F_{3,12} = 0.16$, $p = 0.92$).

Discussion

EMG output is no different during gripping of the wrist movement device handle versus non-gripping, in either the FDS or ED muscles. This result indicated that the use of the wrist movement device does not introduce a possible confound to the interpretation of training-related modulations by the measurement of the cue-related MRP (Chapters 3, 4 and 5), or when comparing results utilizing gonimetric sensors (Chapter 2).



Appendix Figure 1 - Group mean (\pm SE, n=5) average EMG of flexor digitorum superficialis and (B) extensor digitorum muscles during gripping (black bar) versus non-gripping (grey bar) of the wrist movement device handle.

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