Neurophysiological Mechanisms of Motor Cortical Modulation Associated with Bimanual Movement

By

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Author’s Declaration

Abstract

The neural correlates of bilateral upper limb movement are poorly understood. It has been proposed that interhemispheric pathways contribute to the modulation of motor cortical excitability during bimanual movements, possibly via direct connections between primary motor areas (M1), or via a central cortical structure, such as the supplementary motor area (SMA). The ability of one hemisphere to facilitate activation in the other presents a unique opportunity for motor rehabilitation programs using bilateral movements. The focus of this thesis was to investigate the mechanisms underlying bimanual movements in a group of healthy control participants using functional magnetic resonance imaging (fMRI), and subsequently to identify the types of movements that are most likely to maximize M1 activity. It was hypothesized first, that movements involving more proximal muscles, which are known to have a greater number of transcallosal connections, would produce a larger facilitation of M1 activity; and secondly, that the greatest facilitation would occur during those phases of movements where homologous muscles are active simultaneously (i.e. in-phase bilateral movements). The current results demonstrate that the M1 regions and the SMA work together to modulate motor cortical excitability, and that the greatest modulation of activity is seen during movements involving proximal muscles. The findings presented may have clinical relevance to motor rehabilitation programs involving bilateral movements.

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List of Abbreviations

APBT = Active-passive bimanual therapy
ANOVA = Analysis of variance
ACC = Anterior cingulate cortex
BATRAC = Bilateral arm training with rhythmic auditory cueing
BOLD = Blood oxygen level-dependent
CIT = Constraint-induced therapy
DTI = Diffusion tensor imaging
PMd = Dorsal premotor cortex
EMG = Electromyography
FOV = Field of view
FDI = First dorsal interosseus
FSR = Force sensitive resistor
FA = Fractional anisotropy
fMRI = Functional magnetic resonance imaging
GLM = General linear model
GMP = Generalized motor plan
IHI = Interhemispheric inhibition
LFP = Local field potential
MRI = Magnetic resonance imaging
MEP = Motor evoked potential
M1 = Primary motor cortex
NMS = Neuromuscular stimulation
RF = Radio-frequency
ROI = Region of interest
rTMS = Repetitive transcranial magnetic stimulation
SMA = Supplementary motor area
TMS = Transcranial magnetic stimulation

Introduction

The neural correlates of bilateral upper limb movements are incompletely understood. While many activities of daily living require one-handed movements, the brain appears to have a built-in coupling mechanism for the upper limbs. This is evidenced by the tendency of the brain to synchronize movement characteristics between the arms, whether in terms of amplitude, direction or frequency of movement. Furthermore, the observed inhibition of the ipsilateral hemisphere during unilateral movements has reinforced the view that motor systems are geared towards bilateral movements, and that this framework must be overcome to perform one-handed movements.

The observation of cross-facilitation between hemispheres has led to the development of hypotheses related to the representation and production of bimanual movements. One of the main challenges that remain is to determine the source of interhemispheric communication during bilateral movements, and in particular, the mechanism by which one hemisphere can modulate the other. While the existence of callosal pathways linking homologous motor representations in the two primary motor cortices (M1) lends support to theories proposing a direct interhemispheric facilitatory mechanism, the role of such connections during bimanual movements has not yet been established. As bilateral M1 activation is consistently observed during bilateral movement, establishing the contribution of such connections relative to the role of the supplementary motor area (SMA) and other cortical structures has been difficult. Although there is emerging evidence that M1 activity can be modulated by bimanual movements, the neural mechanisms underlying such changes have not been identified. A deeper understanding of the neural correlates of bilateral movements is required, particularly for the application to motor rehabilitation.

Chapter 1: Review of relevant literature

1.1 Motor irradiation

Traditional theories of movement have described motor control as a purely contralateral phenomenon, requiring little or no input from ipsilateral motor areas.[1] However, unilateral movements may be accompanied by ipsilateral activity that is not directly involved in motor control.[1-3] This phenomenon is known as "motor irradiation" and refers to an excitation of the ipsilateral motor pathway during the performance of a unimanual movement[1]. Such excitability does not often produce an overt movement and may only be detectable with electromyography (EMG). The cortical contribution to such facilitation has been confirmed by neuroimaging studies that correlate EMG activity to increased activity in the ipsilateral primary motor cortex (M1).[3-5]

It is unclear what the functional significance is of such an activation pattern. Ipsilateral activity may be related to movement intensity[2] or complexity[6], and is also seen when learning a new motor task.[7] Thus, the ipsilateral hemisphere may be recruited when performing unimanual movements that are particularly effortful.

One of the most significant implications of motor irradiation is that it provides a neurophysiological correlate of the brain's interlimb coupling mechanism. Activation of the ipsilateral motor cortex has been implicated as the neural basis of mirror movements[8], which presumably result from a failure to inhibit motor irradiation. Mirror movements refer to motor output from homologous muscles during intended unimanual movements. Such movements are often seen in young children, but tend to disappear around 9 years of age, a timepoint that corresponds to the myelination of the corpus callosum.[1] Indeed, mirror movements in adults are considered pathological, as their production is normally prevented by an interhemispheric inhibitory drive from the active hemisphere to the inactive.[9] In general, voluntary unilateral movements produce inhibition of the ipsilateral motor cortex, a process likely mediated by callosal connections.[9, 10] Inhibition of the ipsilateral hand is also seen at the level of the pyramidal decussation, indicating that while such communication may originate cortically, inhibition is transmitted at multiple points along descending tracts.[11]

Suppression of M1 activity using repetitive transcranial magnetic stimulation (rTMS) can improve the performance of motor tasks with the ipsilateral hand (e.g. rTMS over left M1 improves performance of the left hand) and increases excitability of the opposite M1, presumably due to a removal of transcallosal inhibition.[12] Indeed, the presence of ipsilateral activity appears to involve a decrease in inhibitory interneuron activity.[13]

1.2 Neural correlates of bimanual movement

There are several unanswered questions surrounding the representation of bimanual movement in the brain. It is not yet known how information is coordinated between the hemispheres, where the motor commands originate from, or which structures are responsible for interhemispheric communication. More uncertainty surrounds how the loss of one of these components, often seen following a stroke, can affect the system.

Bilateral movements are known to activate an extensive network that is not simply a superimposition of two unilateral movements. The established bilateral network includes the bilateral sensorimotor areas, the supplementary motor area (SMA), the cingulate motor area, the dorsal premotor cortex, and the posterior parietal cortex.[14, 15] However, the exact source of interhemispheric mediation has not yet been identified. While much evidence points to cross-facilitation originating from the motor cortex, there is evidence that other areas may be involved in this process. Various structures have been shown to play important modulatory roles in bimanual coordination, including the SMA, the cerebellum[16], and the basal ganglia.[17] In particular, the SMA has received much attention as a critical modulatory structure during the performance of bimanual movements. Spatial and temporal differences in ipsilateral and contralateral activity have been used to support the theory of the SMA, and not direct M1 connections, as the source of bimanual control. The ipsilateral motor cortical activity corresponding to unimanual movements was found by Cramer et al.[18] to be shifted relative to the location of contralateral activity on the opposite hemisphere, indicating that direct callosal connections between the motor cortices may not be the origin. In addition, the activation of both motor cortices prior to movement onset observed by Hoshiyama et al.[19] also casts doubt on the theory that the source of ipsilateral activity is the opposite hemisphere.

A recent study by Johansen-Berg and colleagues[20] using diffusion-weighted MRI identified a region of the SMA whose structural integrity appears to be correlated with bimanual coordination skills. In general, midline motor areas appear to play an important role in the performance of bimanual movements.[21, 22] Lesions of the SMA have been shown to produce deficits in bimanual coordination.[1] Furthermore, primate work indicates that extensive callosal connections exist between hand representations in the primate SMA, making them a likely source of communication.[23] Such findings are in support of the general motor plan (GMP) theory, which hypothesizes that a common motor command is specified for both limbs in order to perform coupled movements more efficiently.[24] The GMP theory requires the involvement of a central, cortical motor area that has extensive connections to both M1 regions, such as the SMA. The finding by Donchin et al.[25] of a group of neurons in the SMA that are specific for bilateral movements also lends support to the central command theory.

However, components of the bilateral network may display specialized activity during the performance of such movements that does not necessarily indicate a role in motor control.

1.3 The primary motor cortex and bimanual movements

In addition to its role in contralateral motor control, the primary motor cortex also appears to contribute to movements that are specifically bimanual in nature.[25] The upper limbs appear to have a preference for coupled movements that is evident in the attempt to synchronize characteristics such as the direction, frequency or amplitude of movements.[26] The attempt to coordinate different spatial and temporal parameters implies either a common source of motor control, or neural crosstalk between the hemispheres (or both). Such communication may occur at multiple levels throughout the system, including what is known as *high level crosstalk*, which refers to communication between hemispheres via cortical transcallosal connections.[26] Callosal connections between motor cortices would support the existence of a direct facilitatory relationship between the two hemispheres that may underlie the ease with which bilateral movements are performed. A study by Kuhn and colleagues[27] examined ipsilateral responses to TMS in patients with implanted deep brain stimulators and found that stimulation of one hemisphere resulted in bilateral motor responses, likely mediated by transcallosal connections between electrodes.

In general, data from TMS studies provides strong support for the role for such direct callosal connections in cross-facilitation. TMS allows measurement of the effect of stimulating one motor cortex on the opposite motor pathway. Evidence that signals can be rapidly transmitted between the two M1 regions indicates a strong degree of connectivity. Even during unimanual movements, the ipsilateral motor cortex is thought to contribute to the timing of muscle recruitment, which likely occurs through direct transcallosal pathways to the opposite motor cortex.[28]

While it is often difficult to determine the level of the motor system where such communication is occurring, studies that have directly compared spinal and cortical responses seem to favour a transcallosal system of communication. Stedman and colleagues[3] report that contraction of the dominant first dorsal interosseus (FDI) muscle causes increased amplitude of motor evoked potentials (MEPs) elicited from the non-dominant FDI by contralateral TMS. Testing at the level of the spinal cord in the same study revealed largely attenuated responses to direct stimulation, indicating that such effects, particularly at lower-intensity contractions, are likely to be cortically mediated.[3] Additional findings from a similar study conducted by Stinear and colleagues[29] confirm that while MEP amplitude was facilitated by contraction of the homologous muscle, F-wave amplitude was unaffected. Since F-waves are known to represent motoneuron excitability, the authors conclude that such modulation is likely occurring at a supraspinal level.[29]

Much of the evidence relating to transcallosal connectivity has come from primate studies. Following injections of a radioactive tracer into the hand and arm area of the motor cortex, Goldman and Nauta[30] demonstrated projections to homotopic areas of the opposite M1 in young monkeys. Similarly, work by Jenny[31] revealed direct connections from the hand region to the contralateral M1. While Rouiller et al.[23] report that only sparse connections exist directly between hand representations in the primary motor cortices, the evidence generally supports the existence of callosal connections between homotopic areas of the motor cortex,[32, 33] including the hand and arm regions.[30, 31] However, it is generally agreed that limited connections exist between representations of distal musculature, particularly in the finger and hand[23, 34], while connections between more proximal muscles, such as those in the forearm, are more extensive.[34] Recent evidence indicates a somatotopic mapping of callosal connections between body representations in M1.[35]

There is increasing evidence that such transcallosal connectivity may underlie the stability of bilateral movements. A recent study by Carson et al.[36] reports that cross-excitability during bilateral forearm rotation depends on the postural context in which they are performed. Specifically, facilitation of the opposite M1 is greatest during those phases of movements that engage homologous muscles simultaneously. Indeed, Hess and colleagues[37] demonstrated early on that muscle action potentials obtained from active hand muscles are facilitated by contraction of the homologous muscle. Since then, TMS studies have provided further confirmation of this cross-excitability, and have demonstrated a facilitation of MEPs with activity of the opposite homologous muscle.[3, 13, 29, 36, 38] While Stinear et al.[29] report that such facilitation occurs to an equal degree between the dominant and non-dominant hemispheres, the findings of Aramaki et al.[39] indicate that activity in the non-dominant motor cortex appears to be suppressed during bimanual in-phase movements, indicating increased neural crosstalk and an increased contribution of the dominant motor cortex to the control of such movements.

Patterns of movement where homologous muscles are active concurrently (termed in-phase) are more stable than anti-phase patterns,[40] likely because the two muscles are sharing common movement parameters.[39] The work of Kelso et al.[41] established that at high frequencies, anti-phase patterns will shift to resemble in-phase patterns. There is a built-in tendency for the brain to favour movements that exhibit mirror symmetry.[24] Indeed, evidence indicates that motor activity may originate bilaterally, but is actively inhibited during the performance of unilateral actions. Consequently, the production of mirror movements is thought to be due to the recruitment of both motor cortices during intended unimanual movements.[38]

A recent study using diffusion tensor imaging (DTI) has linked measures of fractional anisotropy (FA) with interhemispheric inhibition in M1, revealing a linear correlation between FA of hand motor fibres and the inhibition as measured with paired-pulse TMS.[35] Furthermore, connections between hand representations appear to inhabit a defined section of the corpus callosum.[35]

In particular, transcallosal connections appear to be critical for continuous bilateral movements.[42] Interhemispheric connections between the two primary motor areas play an important role in the transfer of information during bimanual coordination tasks.[43] Indeed, experimental evidence has confirmed the presence of both excitatory[44] and inhibitory[4, 45] connections between the motor cortices.

1.4 Bilateral training and stroke rehabilitation

In recent years, several studies have sought to incorporate upper limb bilateral movements into a rehabilitation program, or have examined the effects of short-term bilateral movements on motor recovery, largely with positive outcomes. The control of bilateral movements following a stroke remains similar to that of healthy subjects.[46] Stinear and Byblow[47] report that following 4 weeks of active-passive bimanual therapy (APBT), greater than 50% of patients showed a decrease in the size of excitable motor maps as measured with TMS in the unaffected hemisphere, a change that was correlated with improved performance. Indeed, in stroke patients, bimanual therapy may help to increase excitability of the affected corticospinal tract.[48] Similarly, Mudie and Matyas[49] trained stroke patients on a series of functional bilateral tasks and reported significant improvements in performance of the hemiplegic arm over the course of 8 weeks, changes that appeared to be maintained 6 months later. Summers et al.[50] found improvements in movement time and functional ability of the affected arm following a bilateral training protocol in chronic stroke patients that involved repeated practice of a block placement task. Such improvements may be associated with a re-mapping of the target muscle in the unaffected hemisphere.[50] Short-term improvements in motor function due to bimanual therapy have also been reported. Harris-Love et al.[51] found that switching from unimanual to bimanual reaching results in increased peak velocity and acceleration of the paretic arm.

Bilateral movement has been reported to improve both movement quality[51, 52] and bimanual coordination skills[53, 54] in stroke patients. Even passive or simulated bilateral movements appear to improve functional reorganization as a result of sensory feedback.[55, 56] In addition, several studies have investigated the compounded benefits of coupling bilateral training to other protocols or feedback mechanisms. Luft and colleagues[57] combined bilateral upper limb movements with rhythmic auditory cueing (BATRAC), and compared the effects to dose-matched control exercises. Participants undergoing BATRAC showed significantly greater increases in the activation of motor areas in the unaffected hemisphere when compared to control subjects, indicating the reorganization of contralesional networks.[57] Following 6 months of BATRAC, chronic stroke patients showed improvements in several different measures of upper arm motor function, including the Fugl-Meyer and Wolf Motor Function Test, as well as increases in strength and active range of motion.[54] In another coupled protocol, Cauraugh and Kim[58] employed EMG-triggered neuromuscular stimulation (NMS) in addition to bilateral movements with chronic, hemiparetic stroke patients and reported significantly greater functional improvements than in patients performing unilateral movements while receiving NMS. Improved motor performance has even been reported with the use of a robotic arm trainer to assist hemiparetic patients to perform bilateral movements.[59]

Yet, studies employing bimanual therapy have not been unequivocally successful. Bimanual movement was found by Platz et al.[60] to produce no improvement in motor performance when compared to unimanual movement, although the authors were testing completely or near-completely recovered stroke patients. Similarly, Lewis and Byblow[61] found that concomitant use of the unaffected hand actually worsened motor performance; however, patients were tested using a complex circle drawing task that produced performance decrements even in healthy control subjects. Nonetheless, such divergent findings underlie the need to determine the characteristics of those patients most likely to benefit from a bilateral training protocol.

Aside from training parameters, several factors may influence the neural response to bilateral therapy, including lesion location and severity. Specifically, the integrity of corticospinal tracts may determine responses to motor rehabilitation. Feydy et al.[62] report that increased ipsilateral recruitment was seen in those patients who had suffered damage to the motor cortex, while those with an intact M1 appeared to return to a more contralateral pattern of activation. In addition, the side of stroke may influence motor reorganization,[63] with recent evidence indicating that the degree of interhemispheric inhibition is influenced by whether the affected side was previously also the dominant side.[64]

An encouraging sign is the success of bilateral studies that have employed a wide variety of movement types. Training studies involving everything from block placement, to APBT, to simple wrist or finger extension movements, have all reported positive results.[65] A key characteristic of bilateral movement training appears to be that both hands perform similar actions;[49] however, the impact of movement symmetry on training effectiveness has not yet been established. Bilateral training paradigms involving both alternating and simultaneous patterns of movement have been found to be effective.[65] Indeed, in-phase and anti-phase bilateral movements have been reported to activate distinct bimanual coordination networks.[66]

1.5 Opportunities for plasticity post-stroke

Studies investigating other forced-use paradigms, such as constraint-induced movement therapy, have also reported largely positive results.[67-69] The EXCITE clinical trial, which involved intense practice with the affected arm over a 2-week period, resulted in significant improvements in arm motor function among patients receiving the intervention, effects that persisted for at least one year following therapy.[68] Such changes are thought to result from reorganization or unmasking of functional motor pathways.

A key concept underlying the use of bilateral movements in stroke rehabilitation is that the brain is in some way hard-wired for such inter-limb coupling. This is hardly surprising given the number of tasks one performs on a daily basis requiring coordination of the hands. Consequently, it is possible that while the contralateral pathways involved in unilateral movement of the affected arm may be damaged following a stroke, alternate pathways involved in bilateral movement may still be intact. Indeed, evidence from fMRI studies in stroke patients has shown enhanced activity in the affected primary motor cortex (M1) with bilateral movements, compared to when subjects are moving with their affected hand alone.[70, 71] Over-activation of the unaffected sensorimotor cortex was found by Calautti et al.[72] to be part of an early recovery strategy. Following stroke, an enhancement of activity in the unaffected (ipsilateral) motor cortex with paretic hand movement is commonly reported.[70, 71, 73-76] Such ipsilateral activity is often seen during the course of stroke recovery, [6, 77] but is normally transient.[62, 78] While sustained ipsilateral activation has been reported to be indicative of poor motor recovery,[79-81] several studies have indicated an important role for the unaffected hemisphere in the beneficial functional reorganization of the cortex. [6, 57, 73, 75, 81-83] Foltys et al.[6] report that good recovery following stroke corresponds to an increased reliance on bilateral motor cortical activation. Ipsilateral motor activity has been suggested to be a part of a recovery mechanism,[83] as one motor cortex has the ability to functionally compensate following disruption of the other.[84] Thus, while the recruitment of the contralesional hemisphere may represent a beneficial compensatory strategy in the early phases of stroke recovery, a gradual return to a more balanced, contralateral pattern of activation is generally correlated with better outcomes.

Indeed, the basis of motor rehabilitation may be the recruitment of other brain regions in order to compensate for damaged components.[26] The brain's capacity for plastic change following stroke is well-established.[85] Significant changes in the motor maps representing hand regions have been reported following neurorehabilitation.[86, 87] The principle of neuroplasticity underlies techniques such as CIT, where the hope is that forcing use of the affected limb will encourage the brain to re-train motor pathways. It is unknown whether studies that have reported success using bilateral training are also due to the development, or unmasking, of new, compensatory cortical connections. The changes in arm function following bilateral training may represent plasticity in the affected hemisphere, including an unmasking of motor pathways, or may involve the reorganization of secondary or ipsilateral motor networks. It is also possible that bilateral movements represent an increased challenge to brains typically focused on regaining simple motor control. Additional activation may be due, in part, to an attempt to re-learn complex motor skills.

Alternatively, such changes may represent a release of inhibition coming from the unaffected hemisphere. Disinhibition would allow commands originating from the unaffected motor cortex to reach affected motor areas.[47] Indeed, one of the immediate effects of a stroke is to disrupt the delicate balance of excitation and inhibition that exists. An abnormally high inhibitory drive has been reported from the unaffected to the affected hemisphere during execution of unimanual movements with the paretic arm.[9, 88] Intracortical inhibition has been shown to decrease in both the affected and unaffected hemisphere following stroke.[89] Liepert et al.[90] demonstrated a decrease in inhibition of the affected M1 following stroke, likely as part of a compensatory strategy. Indeed, disinhibition may be an important mechanism underlying motor recovery.[47, 49, 57] In particular, the inhibitory transcallosal connections between hemispheres appear to be disrupted.[9, 88, 90, 91] Additionally, there is an increased excitability of the unaffected hemisphere, presumably due to a lack of inhibition coming from the affected hemisphere.[92] Bilateral training has been associated with cortical reorganization that moves toward a rebalancing of hemispheric activation patterns.[47] Bilateral movements are associated with a similar release of transcallosal inhibition that can increase interhemispheric interactions. Mudie and Matyas[49] suggest that the disinhibition that accompanies bilateral movement may allow the unaffected hemisphere to communicate a template for movement to the affected hemisphere. One of the few studies directly examining the effects of bilateral movement on interhemispheric interactions was conducted by Renner et al.,[48] who compared facilitation during bilateral and unilateral movements in control subjects and stroke patients. They report that concomitant movement of the unaffected or dominant hand increases excitability in the affected or non-dominant motor cortex in stroke patients, but not in control subjects, indicating changes in the inhibitory environment post-stroke.

1.6 Review of relevant methodology

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique commonly used in research studies. fMRI operates under the same principles as conventional structural MRI scans, which provide detailed, high-resolution anatomical images, but provide additional information about the function of neural networks. When co-registered to anatomical MR images, functional images can reveal which areas of the brain are active during the performance of a specific task, and thus can provide indirect information about neural circuits and functional networks.

In typical MR imaging, protons with different spins are aligned to the strong, uniform magnetic field supplied by the MRI scanner. The application of transverse radio-frequency (RF) pulses then disrupts this alignment. The rate at which protons return to their initial position and re-align their spin with the magnetic field is then measured and gives an indication as to the type of tissue the proton is found in. Only hydrogen ions are present in sufficient quantity to enable such a high-resolution contrast.[93] The two time constants, T1 and T2, reflect different properties of the tissue and thus produce different images. T2 is a measure of *transverse relaxation,* which indicates the length of time that protons remain in-phase following the application of the RF pulse, while T1 measures *longitudinal relaxation*, or the length of time required for the nuclei to realign their spins with the magnetic field after the RF pulse.

FMRI represents an extension of conventional MRI techniques that is used to infer neural activity by measuring blood flow in the brain. The basis of fMRI is the BOLD (blood oxygen level-dependent) signal, which is used as an indirect measure of neural activity. The assumption underlying the use of the BOLD signal is that the flow of information through a neuron requires energy, which produces increased metabolic demands in the tissue. Such demands for oxygen are coupled to an increase in blood flow that is measured as the BOLD signal. BOLD contrast is determined by the state of blood oxygenation, and thus, changes in blood flow are reflected in its signal.[94] The BOLD effect is generated by differences in the magnetic properties between oxygenated and de-oxygenated hemoglobin. Deoxygenated hemoglobin is a paramagnetic substance that alters the MR signal by the presence of high-spin iron.[94, 95] In contrast, oxygenated hemoglobin has zero electron spin[95].

Previous studies have established a link between neuronal activity, oxygen requirements, and blood flow.[93] As opposed to measuring action potentials directly, BOLD signal measurements appear to be closely correlated with the generation of local field potentials (LFPs), which reflect a gradual modulation of electrical potential that arises from the flow of neural information.[96, 97] Thus, it is the input and processing, and not the output, that is predominantly measured by fMRI.[96] Such signals are convolved with a hemodynamic response function in order to compensate for delays in blood flow dynamics.

Similar to anatomical images, functional images are acquired in a slice-by-slice manner, but with a lower resolution. As a result, images are co-registered to a T1-weighted anatomical scan so that the location of task-related activation can be accurately identified. The non-invasive nature of fMRI and the good spatial resolution produced by the images have made this technique a popular choice in neuroimaging studies.

Chapter 2: Research Questions and Hypotheses

One of the keys to achieving success with bilateral training is an understanding of the neural mechanisms underlying any change that results from bimanual movement. Presumably, any observable behavioural changes have as their basis a modulation of brain connectivity and/or excitability. However, the mechanisms underlying such modulation have not been determined. While primary motor areas and the supplementary motor area have been identified as candidate sources of such modulation, a detailed understanding of the method of interhemispheric communication is lacking. While the execution of bimanual movements likely relies on a strongly interconnected network, knowing how the components of that network interact represents the best chance to design training programs that can maximize excitability in the affected hemisphere. Observing the responses to bimanual movement in healthy control subjects presents an opportunity to study these interactions without the confounding factors that the altered post-stroke environment necessarily presents. It is essential to understand how the brain reorganizes itself after a stroke and what role bimanual movement may have in such reorganization in order to align rehabilitation strategies to these mechanisms.

Rehabilitation studies that employ bilateral movements are looking to exploit the brain's natural coupling tendencies to drive improvements of the paretic limb. If there is indeed a common neural drive to both hemispheres, or communication between the hemispheres themselves, activation of the unaffected motor cortex may be able to increase the excitability of affected motor areas. While such cross-facilitation would have to be actively inhibited or masked in a healthy system to prevent the regular occurrence of mirror movements, it may provide a unique opportunity for improved movement in stroke patients. Evidence of an increase in motor cortical activity with bilateral movement would provide a plausible mechanism for facilitation and may provide a neurophysiological explanation for the successful outcomes reported in earlier bilateral training studies.

In terms of specific training parameters, the most effective types of bilateral movements are likely to be those that maximize excitability in the affected motor cortex. Determining what these movements are requires a deeper understanding of how the hemispheres communicate. If, as previous studies have indicated, the degree of cross-facilitation depends not only on the bilateral nature of the task, but the timing and patterns of movement, the characteristics of what are likely to be the most effective bimanual movements can be identified. Currently, the neural mechanisms underlying the success of bilateral training programs remain similarly elusive. Once such mechanisms have been identified, rehabilitation programs can be designed to maximize neural crosstalk and thus the contribution of the unaffected hemisphere to motor recovery.

Thus, the aim of the current study is twofold; first, to identify the neural correlates of bilateral upper limb movement; and secondly, to identify the types of movements that will maximize the cross-facilitation between hemispheres. We will be investigating functional networks during the performance of simple bimanual motor tasks in healthy control subjects. We propose that the mechanisms underlying cross-facilitation of cortical motor areas in control subjects may underlie any changes seen in stroke patients undergoing bilateral training programs. Thus, we will attempt to identify the effect of bimanual movement on the modulation of M1 excitability, and will apply the data acquired from control subjects to a series of case studies in stroke patients. It is clear that not all stroke patients will derive identical, if any, benefits from the same training paradigm, and it will be essential in the future to identify the characteristics of those likely to benefit from a bilateral training program.

Given the recent evidence in support of the theory of transcallosal connections forming the basis of phenomena such as motor irradiation, we propose that the modulation of M1 excitability is a likely outcome of such crosstalk. If unilateral movements can cause a cross-facilitatory effect in the opposite hemisphere that is then obscured by the associated ipsilateral inhibition, coupling movements of the upper limbs together may remove such inhibition and facilitate the increased excitability of M1.

Identifying the source of this modulation remains a significant challenge. Given the large number of components in the bilateral network, and the established capacity of structures such as the SMA to communicate with both primary motor cortices, it will be difficult to attribute any changes in M1 excitability definitively to callosal connections. Increased activity in M1 will not confirm that such communication originates in M1, given the myriad of connections that exist between the primary, secondary, and central motor regions. Indeed, it is likely that any of the components of the bilateral network are capable of modulating excitability to a degree. While the strongest evidence exists for modulatory roles of either direct callosal connections or a central command structure, it is difficult to differentiate between these two. However, one possible method is to use the established differences in transcallosal connectivity between distal and more proximal muscles to test the source of the modulation. Presumably, muscles with a greater degree of callosal fibres connecting homologous regions of M1 will be more susceptible to cross-facilitation via these fibres during bilateral movements. Thus, movements with muscles of differing connectivity should result in differing degrees of facilitation if M1 connections are indeed the source of cross-excitability.

Specific hypotheses:

1. It is hypothesized that changes in the excitability of M1 may underlie the beneficial effects of bilateral training. An increase in contralateral M1 activity is expected to be seen when healthy subjects are moving bilaterally when compared to unimanual movements.
2. a) If communication is occurring via transcallosal connections, we expect to see a larger degree of facilitation during the performance of movements with more proximal muscles due to their larger numbers of direct interhemispheric connections.

   b) Recent evidence indicates that cross-facilitation is maximized during bimanual movement patterns that engage homologous muscles simultaneously. Thus, we expect to see a greater facilitation of M1 activity during in-phase movements as compared to anti-phase.

Chapter 3: Neurophysiological mechanisms associated with motor cortical modulation during bimanual movements

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Abstract: The neural correlates of bilateral upper limb movement are poorly understood. It has been proposed that interhemispheric pathways contribute to the modulation of motor cortical excitability during bimanual movements, possibly via direct connections between primary motor areas (M1), or via a central cortical structure, such as the supplementary motor area (SMA). The ability of one hemisphere to facilitate activation in the other presents a unique opportunity for motor rehabilitation programs using bilateral movements. In the current study, we investigated the mechanisms underlying bimanual movements in a group of healthy control participants using functional magnetic resonance imaging (fMRI). Our results indicate that the M1 and SMA work together to modulate motor cortical excitability, and that the facilitation of M1 activity under certain movement conditions has implications for motor recovery.

3.1 Introduction

The substrates mediating interactions between the upper limbs are incompletely understood. In humans, bilateral movements are known to activate an extensive neural network, including the bilateral primary motor cortices (M1), the supplementary motor area (SMA), the anterior cingulate cortex (ACC), the dorsal premotor cortex (PMd), and the cerebellum.[14, 15] However, the way in which these structures interact and communicate to produce bilateral movements is not yet known. It has been established that unimanual movements are associated with a concomitant inhibition of the non-active hemisphere;[1, 11, 45] such observations have reinforced the view that the default setup of the human motor system is geared towards bilateral movement, and that this framework must be overcome in order to perform a unilateral action.

A neurophysiological correlate of this view is seen in the phenomenon of motor irradiation, which refers to an increase in excitability of the homologous motor pathway during the performance of a unimanual movement. Such excitability does not often produce an overt movement and may only be detectable with electromyography (EMG). The cortical contribution to such facilitation has been confirmed by neuroimaging studies that correlate EMG activity to increased activity in the ipsilateral M1.[3-5]

The observation of cross-excitability between hemispheres underscores the potential benefit of performing movements bilaterally when attempting to rehabilitate the brain following hemispheric injury. An understanding of the neurophysiological correlates of bimanual movements has important implications for motor recovery programs, particularly following stroke. To date, several studies have successfully integrated bilateral movements into stroke rehabilitation programs, with the majority resulting in improvements in motor function (see Stewart et al.[65] for review). As an extension of the forced-use theory of stroke rehabilitation, these studies have investigated whether any additional benefit can be derived from performing bilateral actions. Such an approach attempts to utilize existing interhemispheric communication pathways, with the expectation that the intact hemisphere may be able to facilitate activity in damaged motor areas. However, despite the encouraging findings presented in these studies, the neurophysiological mechanisms underlying such behavioural changes have not been identified, nor have the characteristics that may determine which patients will benefit from such an intervention.

The use of bilateral movement paradigms in stroke rehabilitation underscores the need for an understanding of how the brain responds to bilateral movements and the potential benefits of such movements at the cortical level. While several potential sources of bilateral interaction have been identified, the origin of interhemispheric communication is not yet known. Several studies investigating motor irradiation have observed that cross-facilitation appears to be maximized during those phases of movements where homologous muscles are active simultaneously[3, 13, 29, 36, 38] (i.e. in-phase or mirror movements). Such observations lend support to the theory that transcallosal connections between homologous motor representations may be the driving source of M1 modulation. However, strong evidence is also found for the role of more central structures, particularly the SMA, in the generation of bimanual movements.[1, 20-22, 24] While the role of the SMA in bimanual coordination is well-established, the contribution of central cortical structures to observed motor irradiation is unknown. A limited number of connections are known to exist between representations of distal musculature in M1, particularly in the finger and hand, whereas connections between more proximal muscles are more extensive.[23, 30-33] In contrast, both proximal and distal musculature are known to have extensive interhemispheric connections in the SMA.[23] These differing degrees of connectivity may have implications for determining the success of bilateral training programs. The investigation of responses to bimanual movement in healthy control subjects presents an opportunity to study these interactions without the confounding factors that the altered post-stroke environment necessarily presents. It is essential to understand what role bimanual movement may have in cortical reorganization following a stroke in order to align rehabilitation strategies to these mechanisms. In particular, understanding the mechanisms of communication is key to maximizing cross-facilitation and, it is hoped, activity in the affected hemisphere post-stroke.

Thus, the aims of the current study were twofold: first, to identify the neural correlates of bilateral upper limb movement; and secondly, to identify the types of movements that may maximize the cross-facilitation between hemispheres. Given the facilitation of M1 activity observed in unimanual movements, it was hypothesized that bilateral movements may modulate M1 excitability, a mechanism that may underlie the success of bilateral-structured rehabilitation programs. Additionally, the role of transcallosal M1 communication in such a system presumes that muscles with a greater degree of connectivity between homologous regions of M1 will have an increased susceptibility to cross-facilitation via these fibres during bilateral movements. Thus, it was expected that movement involving more proximal muscles would result in a larger degree of cross-facilitation due to their larger numbers of direct interhemispheric connections. Lastly, it was hypothesized that a greater degree of M1 facilitation would be seen during in-phase movements as compared to anti-phase, based on previous literature indicating that cross-facilitation is maximized during bimanual movement patterns that engage homologous muscles simultaneously.

3.2 Materials and Methods

3.2.1 Subjects

Ten healthy volunteers were tested (6 women, 4 men; age range 22 to 40 years; median age 26 years). Seven were right-handed, 1 was left-handed and 2 were ambidextrous according to the Edinburgh Handedness Inventory. Exclusion criteria were any contraindications for magnetic resonance imaging (MRI), or the presence of any neurological diseases. All subjects gave their informed consent to participate in the study and the experimental procedures were approved by the Sunnybrook Health Sciences Centre Ethics Review Board and by the Office of Research Ethics at the University of Waterloo.

3.2.2 Experimental Procedure

Participants underwent a single fMRI testing session consisting of a high-resolution 3D T1 structural scan followed by four to six functional runs. In the distal condition, subjects performed single-event index finger abduction-adduction movements. A custom-built wooden hand rest isolated the index finger on each hand, allowing it to apply force to a pressure-sensitive bulb, while immobilizing the thumb and remaining fingers. The force sensitivity of the bulbs was calibrated to the strength of each subject. Each run consisted of alternating periods of rest and activity (2 sec on/18 sec off) for approximately 5 minutes (15 repetitions). Subjects were visually cued to move by the appearance of a stimulus on a screen projected into the scanner. Custom-built devices transmitted subjects' movements to a computer program that allowed them to control the position of a bar on the screen with their wrist and/or finger movements. Every 20 seconds, subjects received a cue to move their bar to a second (target) bar on the screen and were instructed to maintain the position until the target bar dropped (2 sec). In the proximal movement condition, participants performed a single rapid pronation-supination movement of the wrist while gripping a long wooden dowel between the fingers. The visual stimulus remained the same. FMRI was performed during six different movement conditions: a) in-phase wrist pronation/supination; b) anti-phase pronation/supination; c) unilateral pronation/supination; d) in-phase index finger abduction/adduction; e) anti-phase finger abduction/adduction; and f) unilateral finger abduction/adduction. All unilateral tasks were performed with the left hand, regardless of hand dominance, in order to standardize laterality effects. Task order was randomized across all subjects. Due to time constraints, the unilateral condition was only performed by 7 of the 10 subjects.

3.2.3 Data Acquisition

Functional and anatomical imaging was performed at Sunnybrook Health Sciences Centre on a 3T whole body GE MRI scanner. Each participant underwent a high-resolution 3D anatomical scan (acquired axially, FOV=20, 124 slices, 1.4 mm slice thickness) prior to the collection of functional images. BOLD images were acquired axially using gradient echo imaging with single-shot spiral in-out readout (TR=2000 ms, TE=30 ms, theta= 70, FOV=20, 26 slices, 154 timepoints).

3.2.4 Data Analysis

Structural and functional MR images were processed using Brain Voyager QX (Brain Innovation, Maastricht, Netherlands). 3D images were transformed into standardized Talairach space prior to coregistration of functional data. Pre-processing of functional scans consisted 3D motion correction using trilinear interpolation, and temporal filtering including linear trend removal and a high-pass filter set at 3 cycles/time course. Functional scans were convolved with a standard hemodynamic response function prior to running single and multi-study general linear models (GLMs) on individual and group data. Activated clusters passing an uncorrected threshold of $p<0.001$ were considered significant. Region-of-interest (ROI) analysis was conducted on the right M1 and the SMA. ROIs representing the hand region of the primary motor cortex were drawn on each anatomical scan, and were defined by the following borders: anterior, by the posterior 2/3 of the precentral gyrus; posterior, by the central sulcus; medially by 50% of the distance from the medial border of the hand knob to the midline; and laterally by the lateral aspect of the hand knob. For the SMA, the anterior border was defined by the line ascending from the anterior commisure; the posterior border from the precentral sulcus; the superior border by the surface of the cortex; the inferior border by the most inferior aspect of the superior frontal sulcus; the medial border by the longitudinal fissure; and the lateral border by the extension from the superior frontal sulcus that separated the superior and middle frontal gyri. The level of activity was determined by the number of activated voxels passing an uncorrected threshold of $p<0.001$ and through measurement of the average blood oxygenation level-dependent (BOLD) signal change across conditions. The number of voxels activated in each condition was calculated and expressed as a percentage of the total ROI volume. In addition, a 2 x 2 analysis of variance (ANOVA) using effector (proximal/distal) and symmetry (in-phase/anti-phase) was performed to determine the effect of movement characteristics on activity in both the M1 and SMA.

3.3. Results

3.3.1 Activation in primary motor cortex—effects of muscle group and movement symmetry

As seen in Figure 3.1, group-level contrast maps between bilateral in-phase and unilateral conditions confirmed the differing effects of proximal and distal arm movements on M1 activity observed in individual data. The large activated regions in the left M1 and SMA are the result of contrasting a left-handed task with a bilateral task; however, activation in the right M1 was also notably distinct between the two conditions. A significant upregulation of right M1 activity was observed with bilateral movement relative to unilateral movement in the pronation/supination task ($p<0.05$, Fig.3.2a). While a similar trend was observed in the finger abduction task, this difference was not statistically significant ($p=0.15$, Fig.3.2a).

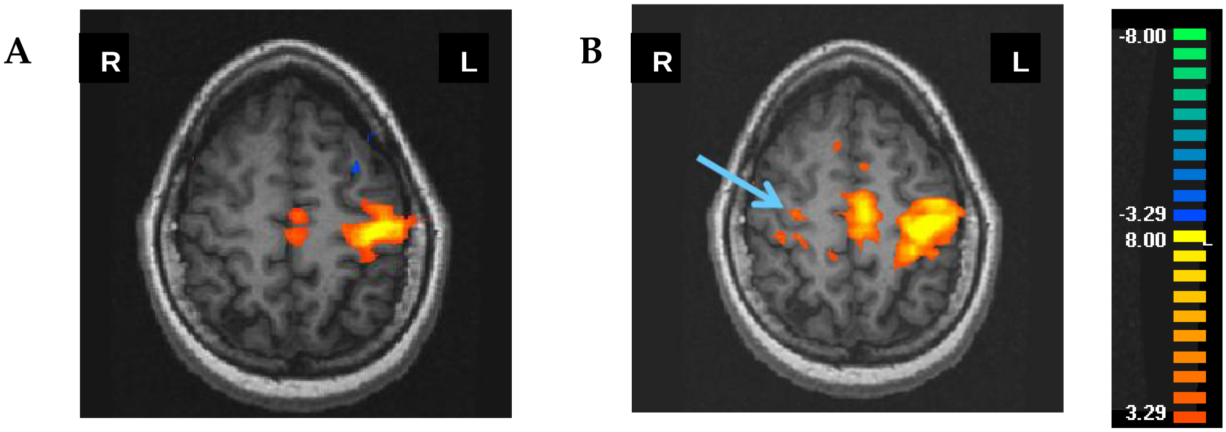

Figure 3.1: Group-level contrast maps showing regions differentially activated between bilateral in-phase and unilateral conditions during distal (A) and proximal (B) movements. Red areas indicate regions of increased activity during bilateral movements; blue represents increased activity during unilateral movements. Arrow indicates facilitatory activity in right M1 during bilateral pronation/supination when compared to unilateral movement (n=7, $p<0.001$). Colour scale indicates t-values.

Measures of the percent BOLD signal change in right M1 showed a similar trend as the volume measures in the proximal movement condition (Figs. 3.2a and 3.2c). The peak BOLD signal increased with bilateral movement compared to unilateral, although this difference was not significant. In the distal movement condition, the trend seen in volume measures was reversed, with unilateral finger abduction showing a slight increase in BOLD signal compared to bilateral movement. Again, this difference was not statistically significant.

Volume measures showed no significant effect of movement symmetry for either the proximal or distal movement conditions (Fig. 3.2b). In both the finger abduction and wrist pronation tasks, peak percent signal change measures were higher in the anti-phase condition than for the in-phase condition, but there were no statistical differences (Fig. 3.2d). Results from a 2x2 ANOVA revealed a main effect of effector for BOLD signal change in right M1 [$F(1,9) = 8.49$, $p < 0.017$].

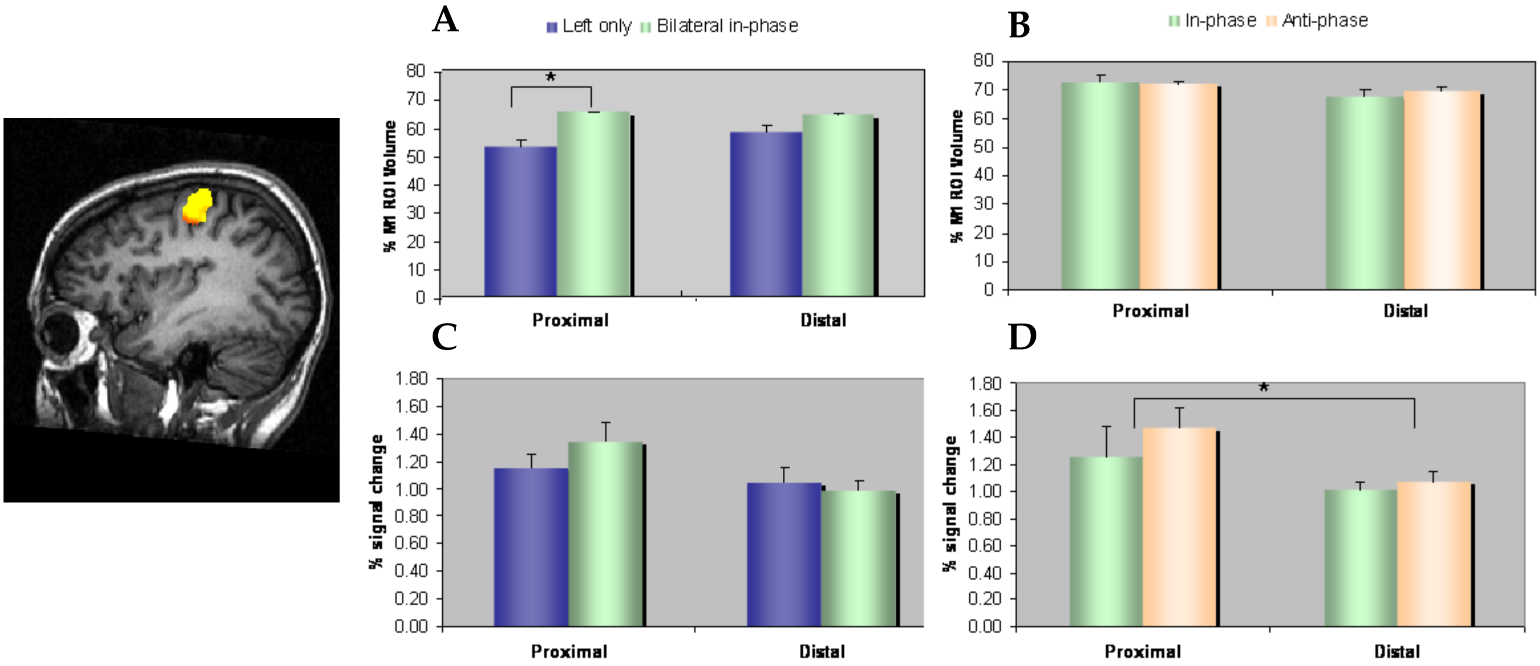

Figure 3.2. Effect of movement type and movement symmetry on right M1 activity during unilateral and bilateral movement. Graphs display volume of activity (top row) and BOLD signal change (bottom row) during unilateral and bilateral movements (A and C), and during in-phase vs. anti-phase bilateral movements (B and D). (* = $p<0.05$)

3.3.2 Activation in supplementary motor area

A significant increase in the volume of SMA activity was observed during bilateral pronation/supination relative to unilateral movement ($p<0.05$, Fig. 3.3a). No such increase was seen during the finger abduction/adduction task ($p=0.5$). Measures of BOLD signal change showed a similar trend, with a greater increase seen in the proximal movement condition than the distal; however, in this case the difference was not statistically significant. No significant differences were found between the bilateral in-phase and anti-phase conditions as measured by volume or BOLD signal changes. Results from a 2x2 ANOVA revealed a main effect of effector for BOLD signal change in the SMA [$F(1,9) = 15.33$, $p < 0.004$].

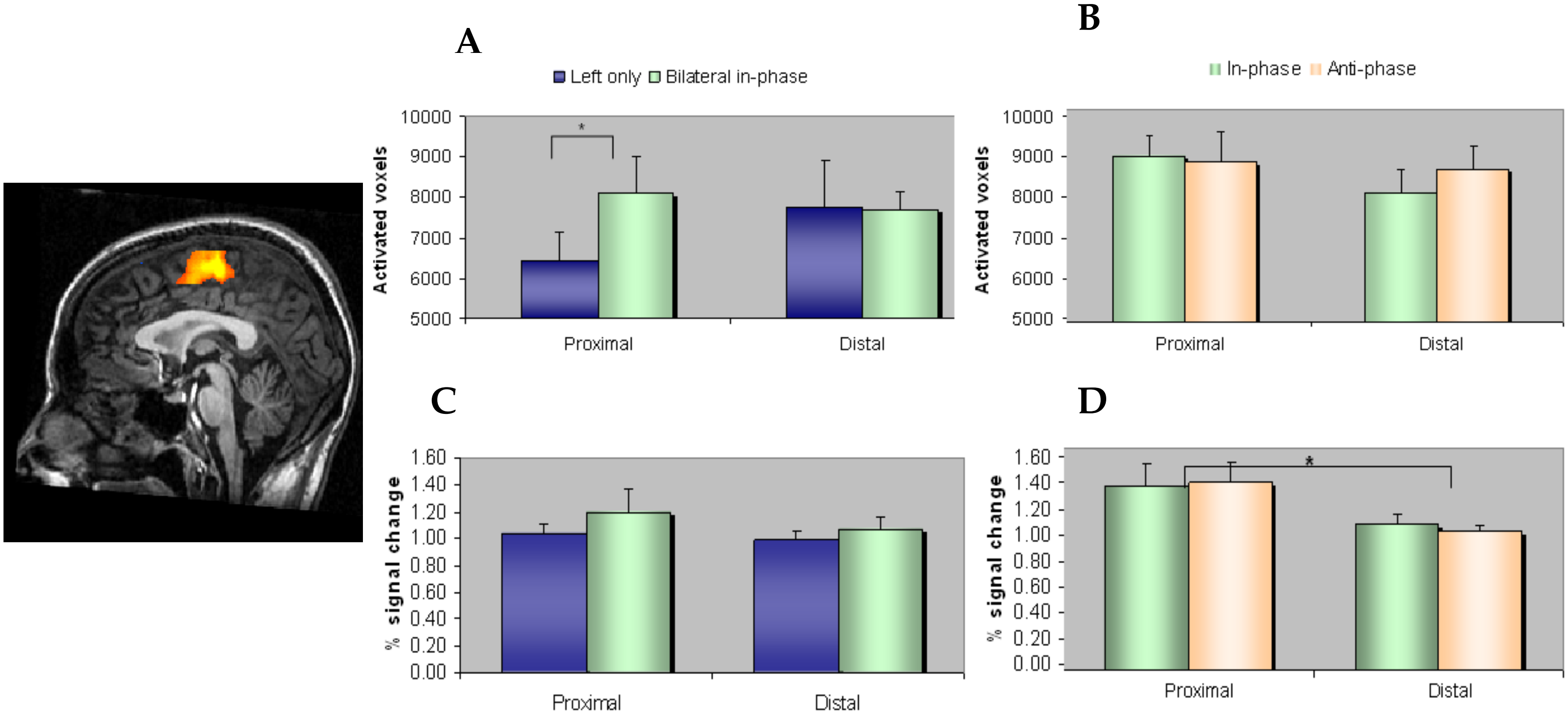

Fig. 3.3. Effect of movement type and movement symmetry on SMA activity during unilateral and bilateral movement. Graphs display number of activated voxels (top row) and BOLD signal change (bottom row) during unilateral and bilateral movements (A and C), and during in-phase vs. anti-phase bilateral movements (B and D). (* = $p<0.05$)

3.4. Discussion

The current study attempted to investigate whether bilateral movements can modulate M1 excitability. The findings presented indicate that bilateral movement can increase the level of M1 activity above that seen in unilateral movements, and that this effect is most prominent in movements involving more proximal muscles. A significant upregulation of both M1 and SMA activity was observed during bilateral movement with proximal muscles, indicating that the degree of transcallosal connectivity influences the response to bimanual movement. In addition, results from a 2x2 ANOVA revealed a main effect of effector muscles for BOLD signal change in both the right M1 and the SMA.

Cross-facilitation between motor cortices as a result of unilateral movements has been consistently observed.[2, 4-7] Motor commands executed in one hemisphere have been reliably shown to increase excitability of the opposite motor cortex; however, the mechanisms underlying interhemispheric communication are not well understood. Bilateral movements are known to activate a consistent neural network, within which the M1 and the SMA have emerged as likely candidates for cross-excitability changes (see review by Carson[1]). Indeed, the current results are in agreement with recent findings that bilateral movements increase connectivity not only between the right and left M1 areas, but also between M1 and the SMA[95, 98].

In the present study, the role of direct M1 connections was probed by using established differences in transcallosal connectivity between proximal and distal musculature. While current evidence supports the existence of callosal connections between homotopic areas of the motor cortex,[32, 33] it is generally agreed that very sparse connections exist between representations of distal musculature, particularly in the finger and hand,[23, 34] while connections between more proximal muscles, such as those in the forearm, are more extensive.[34] The observation of significant facilitation as a result of bilateral movement in the proximal, but not distal, condition lends support to the theory that transcallosal connections between homologous M1 regions may be modulating cortical excitability. This is supported by evidence from transcranial magnetic stimulation (TMS) studies that have indicated a role for such direct callosal connections in cross-facilitation.[29, 36] Transcallosal fibres linking M1 regions are thought to be predominantly inhibitory connections whose primary role is to suppress activation of the ipsilateral M1 during voluntary unilateral movements. Thus, coupling movements of the upper limbs together during bilateral movement may serve to remove this larger, surround inhibition and permit the direct facilitation of homologous regions that is normally suppressed.[45] Although sparse, connections between proximal muscles are not non-existent,[30, 31, 35] which may account for the slight increase in M1 activity with bilateral movement in the distal task.

Alternatively, the SMA may be the driving force behind the observed M1 modulation. Similar to the observed results in M1, increased SMA activity was detected only in the proximal movement condition. The finding that increases in SMA activity mirror those seen in M1 indicates that one or more components of the bilateral network may work together to increase activity in M1. Spatial and temporal differences in ipsilateral and contralateral M1 activity have been used to support the theory of the SMA, and not direct M1 connections, as the driving force of bimanual control. The ipsilateral motor cortical activity corresponding to unimanual movements was found by Cramer et al.[18] to be shifted relative to the location of contralateral activity on the opposite hemisphere, indicating that direct callosal connections between the motor cortices may not be the origin. In addition, the activation of both motor cortices prior to movement onset that was reported by Hoshiyama et al.[19] casts doubt on the theory that the source of ipsilateral activity is the opposite hemisphere. A recent study by Johansen-Berg and colleagues[20] using diffusion-weighted MRI identified a region of the SMA whose integrity appears to be correlated with bimanual coordination skills. In general, midline motor areas appear to play an important role in the performance of bimanual movements,[20, 21, 25] and lesions of the SMA have been shown to produce deficits in bimanual coordination.[99] Indeed, Grefkes et al[95, 98] report that SMA activity is a driving force behind M1 activation and interhemispheric coupling during bimanual movements. Furthermore, primate work indicates that extensive callosal connections exist between hand representations in the SMA, making them a likely source of interhemispheric communication.[23] However, the finding that SMA activity was not affected by bilateral movements involving distal muscles indicates that the contribution of the SMA to such movements may be minimal.

There is increasing evidence that M1 transcallosal connectivity may underlie the stability of bilateral movements. Recent work by Carson et al.[36] reports that cross-excitability during bilateral forearm rotation depends on the postural context in which they are performed. Specifically, facilitation of the opposite M1 is greatest during those phases of movements that engage homologous muscles simultaneously. Indeed, Hess and colleagues[37] demonstrated early on that muscle action potentials obtained from active hand muscles are facilitated by contraction of the homologous muscle. Since then, TMS studies have provided further confirmation of this cross-excitability, and have demonstrated a facilitation of MEPs with activity of the opposite homologous muscle.[3, 13, 29, 36, 38]

Furthermore, patterns of movement where homologous muscles are active concurrently are also more stable than anti-phase patterns,[40] likely because the two muscles are sharing common movement parameters.[39] The work of Kelso et al.[41] established that at high frequencies, anti-phase patterns will shift to resemble in-phase patterns. Thus, the brain's coupling mechanisms appear to favour movements that exhibit mirror symmetry.[24] Given these observations, it was hypothesized that a greater degree of facilitation would occur during bilateral in-phase movements.

However, in the current study, no significant modulation of M1 activity was detected as a result of movement symmetry. This discrepancy is likely due to the decreased sensitivity of fMRI to changes in the excitability of specific muscle representations. While it is possible that in-phase movements produced a greater facilitation of homologous muscle representations than anti-phase movements, such effects may have been overwhelmed in the generalized measurement of M1 activation. Nonetheless, when considering the modulation of overall M1 excitability, it appears that both types of bilateral movements are equally effective in this context.

Similarly, the results presented indicate that the SMA is not differentially activated during in-phase and anti-phase movements. This is in contrast to several studies that have shown the SMA to be preferentially active during anti-phase movement conditions.[21, 100, 101] However, it is possible that the simplistic nature of the task and the limited number of muscles involved may not have been sufficient to resolve a difference in SMA activity. In addition, while two of the studies referenced above involved finger movements similar to the ones performed in the current study , the protocol used by Steyvers et al.[100] required movement at near-maximal frequencies, which would require an increased SMA contribution, and Sadato et al.[21] report changes specifically in the SMA proper, which we did not distinguish from the pre-SMA.

A potential confound in the investigation of cross-facilitation between hemispheres is the influence of hand dominance. While Stinear et al.[29] report that such facilitation occurs to an equal degree between the dominant and non-dominant hemispheres, the findings of Aramaki et al.[39] suggest that activity in the non-dominant motor cortex is suppressed during bimanual in-phase movements, indicating increased neural crosstalk and an increased contribution of the dominant motor cortex to the control of such movements. Specifically, there may be an asymmetry in the direction of interhemispheric inhibition, with the dominant hemisphere exerting a stronger inhibitory influence on the non-dominant hemisphere.[102, 103] Viviani et al.[103] reported a timing delay between hemispheres that corresponded to the delay between hand movements, suggesting that the dominant hemisphere was originating and communicating motor commands to the non-dominant hemisphere. However, few other studies have consistently observed this delay with bimanual movements. While the current study does not address handedness, this may be an important factor for future bilateral studies to consider.

An important clinical application of the above findings is related to motor recovery programs. Rehabilitation studies that employ bimanual movements are looking to exploit the brain's bilateral networks to drive improvements of the paretic limb. If there is indeed a common neural drive to both hemispheres, or communication between the hemispheres themselves, activation of the unaffected motor cortex may be able to increase the excitability of affected motor areas. While such cross-facilitation would have to be actively inhibited or masked in a healthy system to prevent the regular occurrence of mirror movements, it may provide a unique opportunity for improved movement in stroke patients. Indeed, rehabilitation programs focused on bilateral movements have reported improved motor function in the paretic arm, including enhancements in movement quality and velocity, range of motion, strength, and bimanual coordination skills.[49-54, 58, 59] Bilateral training has also been associated with beneficial functional reorganization in both the damaged and intact hemispheres.[47, 48, 55-57] Given that functional motor recovery following stroke appears to be correlated with re-establishing normal, contralateral recruitment of motor areas,[72] movements that will maximize activity in the affected M1 will likely provide the best opportunity for such plasticity. The absence of a significant increase in either M1 or SMA activity during bilateral movements involving distal finger muscles indicates that movements with distal muscles (i.e. finger tapping) are not ideal for maximizing activity in the affected M1. One of the few studies directly examining the effects of bilateral movement on interhemispheric interactions was conducted by Renner et al.,[48] who compared facilitation during bilateral and unilateral movements in control subjects and stroke patients. They report that concomitant movement of the unaffected hand (or dominant hand in healthy subjects) increases excitability in the affected (or non-dominant) motor cortex in stroke patients, but not in control subjects, indicating changes in the inhibitory environment post-stroke that may favour a bilateral approach to training.

In conclusion, the major finding of the present study is that bilateral movements are able to facilitate activity in the primary motor cortex to a greater extent than unimanual movements, and that this effect is most prominent when performing movements involving more proximal muscles. Thus, while these results also suggest a significant role of the SMA, it appears that transcallosal M1 connections are involved in cross-facilitation. Consequently, bilateral movements involving muscles with a greater degree of transcallosal connectivity (i.e. more proximal muscles) are likely to provide the best opportunity to maximize activity in the motor cortex.

Acknowledgments

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Chapter 4: Brief Communication: Modulation of motor cortical excitability during bilateral upper limb movements in hemiparetic stroke patients

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Abstract Bilateral training has emerged as a potential therapeutic modality to treat post-stroke hemiparesis. However, the mechanisms underlying any behavioural changes resulting from such programs have not been identified. We investigated the response to unilateral and bilateral gripping movements in a sample of sub-acute, hemiparetic stroke patients. Region of interest (ROI) analysis was conducted on the primary motor cortex (M1) in the affected hemisphere to determine whether bilateral movements can modulate cortical excitability. Here, we show that in a subset of stroke patients, bimanual movements can facilitate activity in the affected M1, indicating that when a patient-specific approach is used, such techniques may have clinical applications for motor recovery.

Introduction

Stroke is a leading cause of neurological disability in North America, affecting more than 50,000 Canadians and 700,000 Americans annually.[104, 105] Of those individuals suffering a stroke, only 10% will recover fully.[104] Thus, while advances in neuroimaging and pharmacotherapy have significantly reduced the number of acute stroke-related deaths, the majority of stroke survivors are left with residual impairments. Post-stroke hemiparesis remains a leading cause of disability, affecting 50% of stroke survivors.[106] As a result, numerous attempts are being made to develop new and effective motor rehabilitation techniques, particularly in the acute and sub-acute phases of recovery, when damaged cortical regions are most amenable to plastic changes. In the past, modalities such as constraint-induced therapy (CIT) have been employed to encourage neural plasticity. Such forced-use paradigms involve actively constraining the unaffected limb in an attempt to increase usage of the affected arm, and have generally been shown to improve arm function. Another promising therapeutic strategy involves the simultaneous use of both the affected and unaffected limbs together, in an attempt to exploit existing interhemispheric pathways to promote the function of the affected arm. Previous research from our lab in healthy control subjects has indicated that bilateral movement can facilitate activity in the primary motor cortex (M1) to greater levels than those seen in unilateral movement. In the present study, we attempt to investigate whether bilateral upper limb movement can similarly modulate activity in the affected hemisphere, and in particular, the affected M1, in stroke patients. It was hypothesized that bilateral upper limb movement would result in increased activity in the affected M1, compared to moving the paretic arm alone.

Methods

Subjects

Ten right-handed, sub-acute patients were recruited from admissions to Sunnybrook Health Sciences Centre (8 males, 2 females; average age 64.9 years). Inclusion criteria were a first-ever, unilateral stroke with residual upper limb hemiparesis. Participants were screened for any contraindications to magnetic resonance imaging (MRI) prior to being tested. Measures of maximum grip strength were made using hand dynamometers. Functional impairments were assessed using the Chedoke-McMaster Stroke Assessment hand and arm scale. Patient characteristics are shown in Table 4.1.

PATIENT ID	AGE	SEX	LESION SIDE	CORTICAL/ SUBCORTICAL	LESION LOCATION	LESION VOLUME (mm^3)	CMSA ARM SCORE	GRIP STRENGTH (KG)		HANDEDNESS
								Affected	*Unaffected*	
1	51	M	R	C/SC	BA1-4, 6, 9, 11, 22, 34, 43-45, 47	70033	4	29	43	R
2	59	M	R	C/SC	BA11, 25, 34, 38, 47, basal ganglia	14389	1	0	22.6	R
3	66	M	R	n/a	n/a	n/a	6	27.3	49.8	R
4	67	M	R	C/SC	BA4, 6, basal ganglia, thalamus	2440	3	22.5	46.5	R
5	58	M	R	SC	Thalamus	390	3	11	26.5	R
6	37	F	L	C/SC	BA6, 8, 9, 32, 44-47	24549	N/A	25	24	R
7	99	M	L	C/SC	BA1-4, 6, 7, 40, 43, basal ganglia, thalamus	20130	5	42	37	R
8	64	F	L	SC	Basal ganglia	1301	5	18	23	R
9	78	M	L	C/SC	BA3, 4, 6, 18, 19, 44, basal ganglia	5655	4	16.5	41	R
10	70	M	L	C/SC	BA6, basal ganglia	1779	3	11	30	R

Table 4.1: Clinical patient information. Patient 3 had an acute parieto-frontal lesion that was absent on the subsequent, sub-acute MRI scan, although motor deficits remained. The Chedoke-McMaster Stroke Assessment score represents the level of impairment of the affected arm, with 1=no impairment and 7=severely impaired.

Experimental procedure

Patients performed a series of brief, isometric grip and release movements while undergoing functional MRI (fMRI). Gripping tasks were performed under three conditions: right hand only, left hand only, and both hands simultaneously. A block design was used, with either 30s of gripping alternating with 30s of rest for 5 cycles, or with 10s of gripping alternating with 20s of rest for 10 cycles. All scans were 5 minutes in length. Task order was randomized across all patients.

During the performance of gripping tasks, patients held a rigid plastic tube enclosed by a force sensitive resistor (FSR) in each hand that recorded the movement characteristics. The resistance changes of the FSR's were proportional to the force applied. Values were converted to a voltage and digitized at a rate of 100 Hz (National Instruments, DAQ6070) before being analyzed for rate of gripping and amount of force applied. Prior to each scanning session, subjects were trained to perform the motor tasks at a self-paced rate of approximately 0.5 Hz and with low amplitude. The maintenance of contraction rate both within and across scans was confirmed from the FSR data.

Data acquisition

Structural and functional imaging was performed on a 1.5 Tesla whole-body GE MRI scanner. Sagittal scout images were first obtained with a T1-weighted inversion recovery acquisition (echo time TE=20 ms; repetition time

TR=2000 ms; inversion time TI=800 ms; field-of-view FOV = 22 cm; acquisition matrix 256x192; half k-space acquisition; 17 slices; 5 mm thick). These images were used to localise 26 contiguous slices, 5 mm thick, beginning approximately at the superior margin of the cerebral cortex, for the subsequent functional scans. Functional images were acquired axially using gradient echo imaging with single-shot spiral in/out readout, offline gridding and reconstruction, and first-order correction for spatial magnetic field inhomogeneity (TE=40 ms; TR=1500 ms; flip angle $\theta=80^{o}$; acquisition matrix=64x64; FOV=20 cm, 210 timepoints). This resulted in voxels with dimensions of 3.125mm x 3.125mm x 5mm and a volume of 48.8 µl. Conventional T1-weighted three-dimensional fast spoiled gradient echo anatomical images (TE=3.4 ms; $\theta=35^{o}$; acquisition matrix-256x256; 124 slices; 1.2 mm thick; FOV=22x16 cm) were also acquired for use in co-registration of functional maps. Total scan time for each subject was approximately 40 minutes.

Data analysis

Images were processed using Analysis of Functional Neuroimaging (AFNI, version 2.25) software. Functional images were motion-corrected by aligning each image to the 11th acquired image in individual fMRI scans. Structural scans were transformed into standardized Talairach space prior to the co-registration of functional data. Statistical analyses of time course data were performed on a voxel-by-voxel basis using the orthogonalized correlation method to yield crosscorrelation images with respect to a reference square-wave function matching the time course of the experimental design and signal intensity fluctuations. The reference square-wave function was shifted 6 seconds to account for the hemodynamic response. Voxels were deemed significant if the correlation coefficient exceeded 0.35 ($p < 3.0x10^{-6}$ uncorrected) and if they formed a cluster with a volume greater than three contiguous voxels. The minimum cluster size and a threshold of 0.35 corresponds to a corrected value of $p<0.01$.

A region of interest (ROI) was defined for the primary motor cortex (M1) in the stroke-affected hemisphere on individual anatomical scans. This region was subsequently used to compute the number of voxels and the average % signal change comprising the activated clusters in the unilateral and bilateral tasks.

Results

Individual patient data reflecting changes in volume (Fig.4.1) and BOLD signal change (Fig.4.2) in the affected M1 are shown below. Data across the ten patients was variable, with 50% of patients showing a facilitation of M1 volume with bilateral movement and 50% showing larger volumes during unilateral movement (Fig.4.1). Of those patients displaying facilitation during bilateral movement, 4 of 5 also revealed a corresponding increase in peak BOLD signal (Fig. 4.2). Individual characteristics were variable across patients demonstrating a positive effect of bilateral movement. However, three right-hemisphere patients (P1, P3, and P5) displayed the largest facilitation of M1 activity as a result of bilateral movement (Fig.4.1). Although two of the left hemisphere patients (P8 and P10) also showed a similar trend, the changes were of a much smaller magnitude (Fig.4.1). Overall, volume and signal change measures were generally consistent with each other, although two patients (P7 and P10) showed opposite trends for the two measures.

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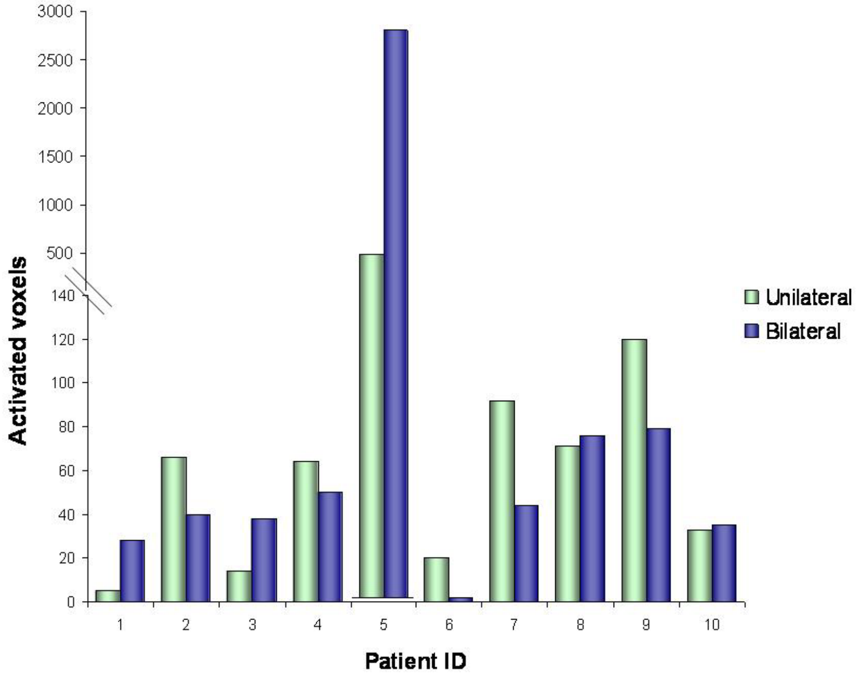

Figure 4.1: Individual data displaying differences in volume of affected M1 activity between unilateral (affected) and bilateral hand movements (n=10)

B

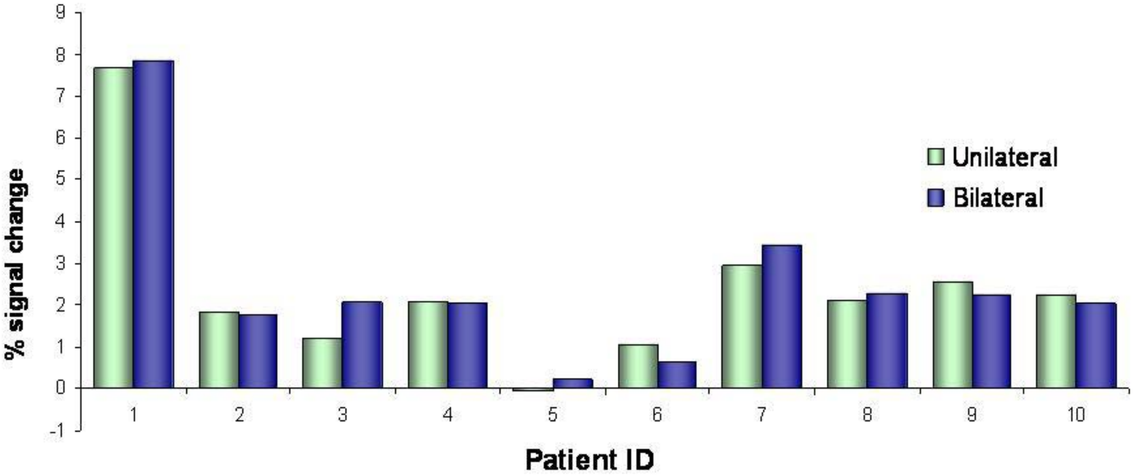

Figure 4.2: Individual data displaying % signal change across activated voxels. Values represent changes in peak BOLD signal during unilateral and bilateral movements in the affected M1 (n=10)

Discussion

The results presented indicate that a subset of stroke patients show the potential to facilitate M1 activity in the affected hemisphere with bilateral movement. While this effect was observed in less than 50% of patients, the degree of upregulation in those patients showing the effect may have important clinical significance. The wide range of responses observed in M1 emphasizes the patient-specific approach that should be used in determining suitability for a bilateral training program. Furthermore, these results suggest that treating patients as individual cases is essential in studies investigating the potential benefits of such techniques.

Previous work from our lab has indicated that bilateral movement has the ability to modulate M1 activity, even in young healthy subjects. This is thought to be partially attributable to cross-facilitation from the active motor cortex, possibly via transcallosal pathways connecting homologous M1 regions. However, changes of the magnitude seen here are greater than those typically reported in the healthy population as a result of direct facilitation between hemispheres. Thus, an additional factor is likely influencing the modulation of excitability. It has been reported that following a stroke, unusually high levels of interhemispheric inhibition (IHI) are imposed on the affected hemisphere from the unaffected.[9, 64, 88, 107] This may be particularly prominent during the generation of voluntary movements with the paretic arm.[88, 107] Consistent with this, of the three patients demonstrating the largest changes in M1 activity, two displayed unusually low levels of activity during performance of the unilateral task. While preliminary, this finding supports the theory that high resting levels of inhibition may impede motor activity. The subsequent increases with bilateral movement suggest that the underlying motor network may be intact, but that motor cortical excitability in the affected hemisphere is being impeded during unilateral movements, possibly via transcallosal inhibitory connections. Consequently, it is hypothesized that a release of inhibition may underlie the large increases seen here. Even in healthy subjects, unimanual movements are typically associated with inhibition of the ipsilateral hemisphere, presumably to prevent the occurrence of mirror movements.[9] Following a stroke, however, the balance of interhemispheric inhibition and excitation may be altered, and in particular, the inhibitory transcallosal connections between hemispheres are often disrupted.[9, 88, 90, 91] Furthermore, over-excitability of the unaffected hemisphere can exert an excessive inhibitory influence on the damaged hemisphere, which in turn, is unable to activate its own inhibitory connections, causing a cycle that results in consistently reduced activity in the ipsilesional hemisphere. However, the generation of bimanual movements is not subjected to cross-inhibitory influences and in fact is associated with a release of inhibition.[49, 53, 98, 108] A reduction in IHI has a direct role in allowing motor commands to be executed in the affected hemisphere, and may also serve to make the brain more responsive to plastic changes resulting from structured rehabilitation.

While preliminary, right-hemisphere patients appear to be more responsive to modulation resulting from bilateral movements. However, a potential confound exists in using only right-handed patients. Several studies have reported a hemispheric asymmetry during the performance of bimanual tasks, with the dominant hemisphere exerting a stronger influence over bimanual control.[39, 102, 103] Accordingly, it is possible that some of the observed facilitation may be attributed to an increased involvement of the dominant, intact hemisphere during bimanual movements. However, further research is needed to explore this issue. In addition, in the context of stroke, numerous sources of variability must be taken into account, including the effect of lesion location and volume. Furthermore, factors such as age, severity, and integrity of existing corticospinal tracts will likely influence the response to bimanual movements.

In conclusion, these results demonstrate that, for a subset of stroke patients, bilateral movements may have beneficial effects on motor cortical excitability in the affected hemisphere. It is clear that not all patients will benefit from such an approach; thus, a patient-specific approach to treatment is recommended. However, given the changes observed in the current study, bilateral training can be considered a suitable and indeed a beneficial approach to motor rehabilitation following stroke.

Chapter 5: General discussion

The overall aim of this work was to establish a link between the neural correlates of bimanual movement and the potential for neuroplasticity following stroke. Taken together, the findings presented indicate that the modulation of corticomotor excitability may provide a substrate for behavioural changes resulting from bilateral training.

The pathology of stroke necessitates a further understanding of the compensatory processes that are activated following injury. While the underlying mechanisms are not completely understood, it is generally believed that recovery is related to functional reorganization. Thus, an important goal of motor rehabilitation programs is to maximize opportunities for plasticity. The results of the brief communication indicate that the removal of transcallosal inhibition may be an important feature of bilateral movements. While such disinhibition has a direct role in allowing motor commands to be executed in the affected hemisphere, an indirect advantage is the induction of plastic changes via rehabilitation. As plasticity-dependent changes in primary sensorimotor cortex likely underlie improvements following rehabilitation,[65] it is crucial to release excessive inhibitory influences on the affected hemisphere to allow cortical reorganization and motor learning to occur. Disinhibition has been identified as an important mechanism underlying motor recovery,[47, 49, 57] and may induce reorganization in both the affected and intact hemispheres.[57] It has been suggested that the disinhibition that accompanies bilateral movement may allow the unaffected hemisphere to communicate a template for movement to the affected hemisphere.[49] Bilateral training has been associated with reorganization in contralesional networks, which may promote the recruitment of intact brain regions as part of a compensatory strategy.[57] However, bilateral training has also been associated with cortical reorganization that shifts toward a rebalancing of hemispheric activation patterns.[47] Stinear and Byblow[47] report that following 4 weeks of bimanual therapy, more than half of patients showed a decrease in the size of excitable motor maps as measured with TMS in the unaffected hemisphere, a change that was correlated with improved performance. Similarly, Summers et al.[50] report a similar decrease in motor representation in the intact hemisphere in bilaterally trained patients showing improved motor function.

The seminal work by Nudo et al.[86] demonstrated the ability of the motor cortex to adapt following injury. However, it is clear that not all patients will respond identically to the same intervention. A further benefit of bilateral training, through the release of inhibitory influences on the affected hemisphere, may be to essentially “prime” the brain for rehabilitation, making patients more responsive to training interventions. Thus, in patients with a large imbalance in interhemispheric inhibition, bilateral movements can serve as a precursor to more targeted training programs.

Limitations and future directions

Both of the studies presented used functional magnetic resonance imaging (fMRI) as a neuroimaging technique. While fMRI generally provides excellent spatial resolution, there is also significant smoothing of activated regions across a particular time series. Thus, the inability to distinguish changes in the activity of specific muscle representations remains a weakness of fMRI. Furthermore, the relatively poor temporal resolution of fMRI (2000 msec), makes it difficult to determine the sequence of activation within the bilateral network; specifically, whether SMA activity drives M1 activation, or whether they are simultaneously activated. Similarly, the timing onsets of ipsilateral and contralateral M1 activation could not be distinguished. Future studies using techniques such as positron emission tomography (PET) or electroencephalography (EEG) may be able to shed some light on these issues. A further limitation is that due to the risk of head motion, participants did not perform movements recruiting the most proximal arm and shoulder muscles, which would have provided a stronger contrast to the movement of distal finger muscles.

One of the major considerations in a study involving relatively few stroke patients is the many confounds present in such a heterogeneous population. Numerous sources of sources of variability, including lesion location and volume, handedness, age, motor impairment, and the integrity of existing corticospinal tracts make the interpretation of training responses difficult. In addition, when attempting to identify the ideal parameters for a motor rehabilitation program, it is important to note that factors such as the movement task, duration, frequency, and intensity can all affect the outcome. Another question surrounding the use of bilateral training is whether such treatments are best suited for acute, sub-acute, or chronic stroke patients. There may be fundamental differences in the response to training depending on the phase of recovery. For example, increased involvement of the ipsilateral, unaffected hemisphere is generally considered to be a beneficial compensatory mechanism immediately following a stroke,[6, 72, 77] but in later stages, persistent recruitment of intact motor areas is correlated with poor motor recovery.[72]

Given the variety of factors that can influence the response to training, it is important to be able to identify which patients will benefit from bilateral training. The ultimate aim of such an endeavour will be the development of patient-specific treatments to ensure that each individual receives rehabilitation that will result in the best chance for motor recovery.

In addition to establishing criteria for the use of bilateral training, the link between behavioural changes and the underlying neurophysiology has yet to be made. The current study takes the first step by showing a plausible link between changes in motor behaviour and changes in motor cortical excitability that occur as a response to bilateral training. However, whether such M1 modulation has any direct effect on movement generation, or can improve factors such as strength, movement quality, flexibility, or range of motion has yet to be determined.

5.1 Conclusions

Overall, the results of this thesis provide evidence that motor cortical excitability can be modulated by bilateral upper limb movement, in both the healthy and stroke patient populations. These findings elucidate the possible mechanisms underlying such modulation, and provide a rationale for continued investigation into the beneficial effects of bilateral training as a potential therapeutic intervention.

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