

Cortical adaption influences excitability in the dominant and non-dominant hands following
complex novel motor training

by

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CORTICAL ADAPTION INFLUENCES EXCITABILITY IN THE DOMINANT AND NON-DOMINANT HANDS FOLLOWING COMPLEX NOVEL MOTOR TRAINING

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Abstract

The primary motor cortex (M1) can dynamically control the magnitude of motor refinement through motor plasticity. Plasticity can be investigated by looking at changes to motor excitability, which has been established to be stronger in the non-dominant hemisphere of right handed participants. However, it is unclear if these differences in excitability following a training task would still be present if participants performed a task that was equally as difficult for both the dominant and non-dominant hands. Thus, the first goal of this thesis was to develop and validate a novel motor training task designed to be equally challenging for both hands. Participants were required to trace a novel sinusoidal pattern, varying in both amplitude and frequency that was mirrored in both the right and left hand. The time course of learning was plotted over two separate training sessions. The second study then utilized this task to answer the question of which hemisphere has a greater plastic potential, determine by quantifying changes motor excitability, and the time-course over which these changes occur. Motor cortical excitability before and after learning was investigated using recruitment curves which evoke MEPs at 7 different stimulation intensities in order to better capture a more robust measure of hemispheric excitability for both the left and right hand.

The training task was indeed novel as it equally challenged both the dominant and non-dominant hands of a healthy right handed population and lead to remarkably similar learning curves over six blocks of learning and similar retention. In the second study, only the dominant hemisphere had significant decreases in excitability following the motor learning task. A secondary study indicated that the time-course over which these changes occurs suggests that when learning a novel training task which the participant is naïve to, motor training and increases to performance have a rapid onset as changes to excitability were only seen on the first day of training. This may indicate that even though the non-dominant hemisphere has greater initial excitability, the dominant hemisphere has a greater ability to modulate excitability levels showing a greater potential for plastic adaption.

Key Terms Primary Motor Cortex, Laterality, Handedness, Motor Training, Plasticity, Motor Excitability

Declaration of Original Work

I, Luc Holland, declare that all work contained in this thesis is of my own work unless otherwise referenced. None of the work composing this thesis has been previously submitted in either whole or in part at this, or any other, University. All research has been conducted in accordance with the University of Ontario Institute of Technology's Research Ethics Committee.

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I thank my supervisor Dr. Paul Yelder as well as Dr. Bernadette Murphy for their ongoing support. Your extensive knowledge in this field of literature has been irreplaceable to my own knowledge and foundation in research. Your ongoing encouragement and direction have greatly supported the development of my understanding in research concepts, writing fundamentals, and critical thinking skills.

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List of Abbreviations Used

ACH- Acetylcholine

Ag-Silver- Periodic Element

AgCl- Silver Chloride

ANOVA- Analysis of Variance

BG- Basal Ganglia

cAMP- Cyclic Adenosine Monophosphate

cMI- Contralateral Motor Cortex

CS- Conditioning Stimulus

CST- Cortical Spinal Tract

dMI- Dominant Motor Cortex

EMG- Electromyography

FA- Fractional Anisotropy

FDI- First Dorsal Interosseous

fMRI- Functional Magnetic Resonance Imaging

ISI- Interstimulus Interval

LICI- Long Interval Intracortical Inhibition

LI- Laterality Index

LTP- Long Term Potentiation

NdMI- Non-Dominant Motor Cortex

MEP- Motor Evoked Potential

MPF- Mean Power Frequency

MRI- Magnetic Resonance Imaging

MI- Primary Motor Cortex

SEPs- Somatosensory Evoked Potentials

SICF- Short Interval Intracortical Facilitation

SICI- Short Interval Intracortical Inhibition

SMA- Supplementary Motor Area

SI- Primary Sensory Cortex

TMS- Transcranial Magnetic Stimulation

TS- Test Stimulus

[1]

SECTION I: LITERATURE REVIEW

Chapter 1- Introduction Cortical and Functional Asymmetry

The use of the human hand is defined throughout every action of every day of our lives. These movements help shape and form the functional ability of our hands in that one may become more useful than the other. Handedness is composed of both manual dominance and preference (Guiard 1987). Cortical dominance suggests that a person's movement has a strong accuracy, as it would be selected for use during a gross movement that requires finesse, and is a function of pre-disposition. However, cortical preference suggests a much higher rate of hand usage, in that the limb is more likely to be selected for a given motion (Guiard 1987). This establishes a perceived dominance of a person to use one hand over the other. This phenomenon is known as *Hand Asymmetry* and becomes represented within the increased functional ability of one hemisphere over the other. The hemispheric asymmetry has a representation within the primary motor cortex of the brain, as the dominant hemisphere (dM1) has an increased amount of representation within the corresponding side (Ilic et al. 2004) compared to the non-dominant hemisphere (NdM1). In addition, the different hemispheric motor representation for different muscles is a dynamic system, that is, it can change depending on the amount of activation of a certain region within the motor hemisphere (Hammond et al. 2004) and provides the foundation for motor plasticity.

As the dominant hand has cortical origins within the contralateral cortex, an increase in usage causes an increase of representation within the primary motor cortex (M1). This increase in representation may lead to an increased ability to control motor evoked potentials (MEPs) which get sent to motor neurons and muscles causing movement (Volkman et al. 1998). Muscles that require increased refinement to modulate fine motor tasks result in an increased area of

representation in the M1. This motor refinement is substantiated through modulating the descending motor signals in order to increase accuracy in selected muscle by either increasing or decreasing the conditioned motor stimulus sent from the M1. Along the M1 lies the motor homunculus which, depending on the region, has different representations for different motor areas. These areas range from genital functioning on the medial border, to facial functioning on the lateral border (Fig. 1). Once a planned motor signal is received from pre-motor cortex, a motor command or action potential is produced causing a muscle movement. The control of these MEPs are dependent on inhibition and facilitation mechanisms that lie within the interneuronal circuitry of the hemispheres and ultimately help determine the level of excitability within the two hemispheres (Chen 2004; Chen et al. 1998).

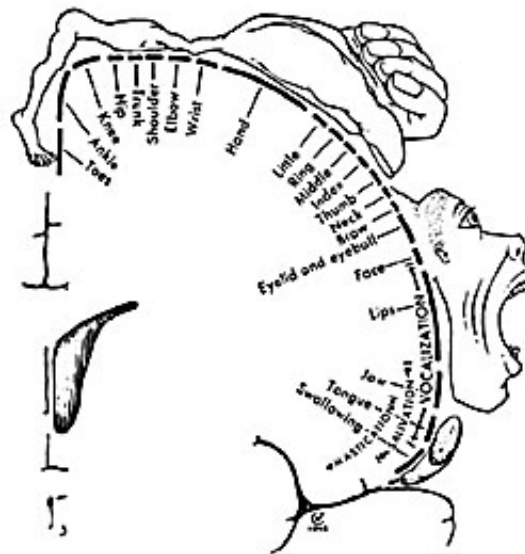


Figure 1. An image of the motor homunculus showing different motor areas control specific parts of the body (Penfield and Rasmussen 1950).

Whereas right handed individuals have the ability to complete most modern day actions with only their dominant hand, left handed people require the constant use of both their preferred and non-preferred hand to receive the same conveniences. Since there are different motor expressions between the dominant and non-dominant hands, we would expect there to be different levels of cortical representation and thus different levels of excitability within the interneuronal circuitry. The literature has been equivocal with regards to differences in cortical excitability between hemispheres. However recent work by Daligadu et al (2012) using cortical stimulus response curves found that the dominant hand was more excitable which is suggested to be a function of a greater potential for neuroplasticity. A challenge when studying cortical plasticity in response to training is finding a training task that is equally novel for both the right and left hands. Study One of this thesis set out to do this, specifically asking if a novel motor training task designed to be equally challenging for both hands will lead to differential changes in corticomotor excitability between the dominant and non-dominant hemispheres. The time-course over which these changes in corticomotor excitability take place is also investigated.

Chapter 2- Inclusion Criteria for Literature Review

Methods for quantifying and comparing focal excitability measures in the motor hemispheres have been done in the past, however few have used a more global approach in using recruitment curves. To our knowledge, no studies have coupled the use of a novel validated complex training task over two days along with a global motor excitability measure to determine hemispheric differences to neural plasticity. We suggest that these components will lead to a more robust effect of motor training than seen in previous training methodologies due to a higher exposure to the motor training task. In order to find relevant background material, key words such as

motor evoked potentials, motor training tasks, motor excitability, laterality, primary motor cortex, transcranial magnetic stimulation and motor plasticity were used to methodically review pertinent literature. The online library directory at the University of Ontario Institute of Technology, where the research was conducted, along with Google scholar were used as the primary database sources for which the literature was searched. In addition to these digital sources, hard copy resources were also used to review structural components of the motor system. With the exception of one paper, which was a seminal article that led to human trials, studies involving non-human primates were not included as well as papers which were not written in English. Studies that used somatosensory evoked potentials (SEPs), direct stimulation of the motor hemisphere, or any other means of cortical stimulation other than TMS were excluded from the review as they were outside the scope of the completed research. Studies involving fMRI were included in the literature search as it is a technique that demonstrates activation patterns relevant to motor training in a complimentary modality. The scope of the review includes commentary on the anatomy of the corticomotor system, a review of corticomotor plasticity, and further commentary on functional and anatomical differences between the dominant and non-dominant hemispheres as a result of use-dependant plasticity.

Chapter 3- Cortical Anatomy Related to the Motor System

3.1-Micro-Anatomy

In order to fully grasp movement changes with plasticity of the motor cortex, neural anatomy, and more specifically neural micro-anatomy, were explored. The cortex is composed of six different layers each with different microstructures (Fig. 2) (Kandel et al. 2000). These layers

differ in composition as well as function in movement. Layer I is primarily a buffer layer and is composed of dendrites, responsible for collecting incoming motor signals and transferring them to the cell bodies for processing. Layers II and III are the first networks of intracortical communication, as well as the location of the most superficial pyramidal cells. These connections are responsible for connecting several structures allowing for orchestration of motor commands. Pyramidal cells are one of the most plentiful neurons within the cortex and are responsible for the transmission of information between structures (Kandel et al. 2000). Layer IV of the cortical tissue is mainly concerned with afferent sensory input, as motor areas such as the primary motor cortex (M1) and supplementary motor area (SMA) have significantly smaller layer IVs than the somatosensory cortex (S1). Layer V is composed of the largest pyramidal cells and has the greatest horizontal dendritic connections resulting in the greatest between-structure communication of neural macrostructures. Layer VI is a mixed composition layer that begins the transition of cortical to subcortical tissue and is comprised of both grey and white matter.

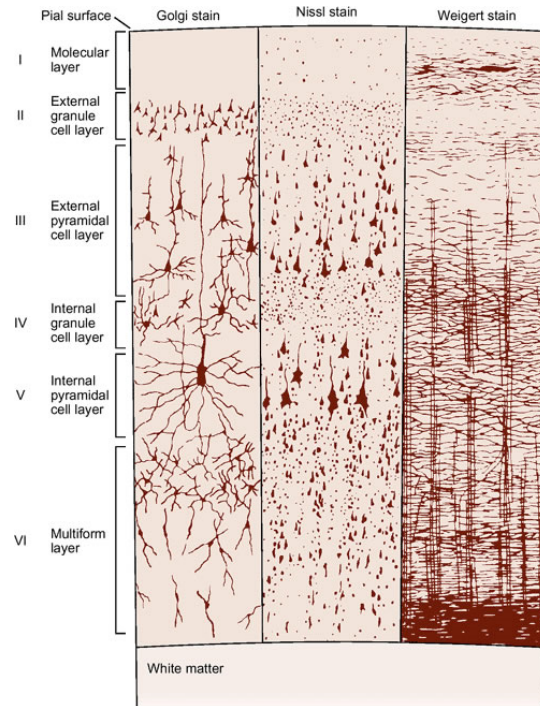


Figure 2- An illustration showing different layers that compose the primary motor cortex is displayed. Each layer is composed of different projects that have different roles in the modification and refinement of motor output, as well as communication with neighbouring structures through horizontal connections. Adapted from (Kandel et al. 2000).

The cerebral cortex is composed of both gray and white matter. The gray matter is heavily populated with cell bodies, allowing this tissue to perform the signal processing that is critical for motor control, and is composed of cells that are rich in cytoplasm (O'Brien and Sampson 1965). White matter however has few cells bodies, with dense amounts of myelination of nerve axons due to oligodendryte plasma membranes (O'Brien and Sampson 1965). This myelination allows for rapid transmission of nerve signals from the central nervous system (CNS) to the muscles throughout the body. Gray and white matter both decrease significantly in age as the CNS begins to deteriorate following the adolescent stages of young adulthood (Giorgio et al. 2010). In order for the myelinated axons to transmit signals from the cell bodies of the gray matter, signals must

synapse with dendrites of neighbouring neurons to further conduct the signal. Synapses take either electrical or chemical form and transmit highly specialized signals through similarly unique connections (Kandel et al. 2000). The electrical synapses are used for rapid signal transmission through depolarization of the post synaptic cleft while the chemical synapses can modulate the nerve transmission through the release (exocytosis) of synaptic neurotransmitters, such as acetylcholine (Ach), into the synaptic cleft.

The axonal tracts composed of white matter form vertical columns of which there are dorsal, lateral, and ventral sections constituting portions of the spinal cord. Descending motor tracts are responsible for maintaining muscle activation while the ascending tracts are responsible for relaying sensory information to the cerebral cortex and somatosensory areas. The descending motor tract responsible for the control of skeletal muscle is known as the corticospinal tract (CST). The CST originates in layer V of the primary motor cortex in addition to the supplementary and premotor areas of the brain, while terminating at distal synapses in the spinal interneurons as the descending motor signals are carried to the effector muscles (Fig. 3). These descending motor signals are heavily modified by a number of somatosensory inputs, such as visual and proprioceptive information, in order to fine tune the motor signal for the intended muscle activation or locomotive effect.

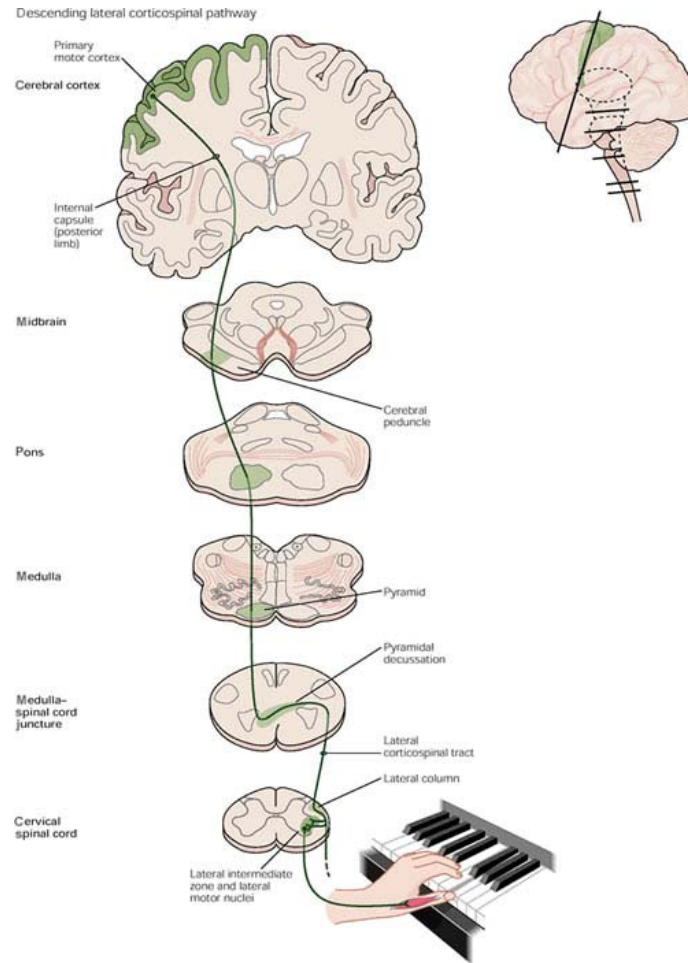


Figure 3. An image of the corticospinal tract presenting the path of signal transmission from the primary motor cortex, decussating at the medulla oblongata, and synapsing to the lower motor neuron in the ventral horn for elicitation in the target muscle. Adapted from (Kandel et al. 2000).

3.2-Micro Structure Plasticity

Through constant stimulation of cortical tissue, plastic changes in the microstructure of these tissues take place. This may lead to a so-called ‘conditioning effect’, which is the basis for the phenomenon of asymmetry in conditioned movement. The foundation of this asymmetry takes place in the plastic changes to the cortical microstructure (Amunts et al. 1996). The

microstructure is partly composed of neuropil, which is composed of dendrites, axons, and synapses. These cells are used to transfer messages across cortical structures making them more efficient. In the dominant (left) prefrontal gyrus of right handers, the neuropil population has an increased density when compared to the non-dominant side. In left handers however, there is little difference between population densities in both hemispheres (Amunts et al. 1996). This shows stronger anatomical laterality that occurs in right handers, which does not occur in the left handed population possibly due to pathway conditioning and a more bimanual usage of left handed individual's hands. Plastic changes also occur through the horizontal connections in the most densely populated cortical layer V (Sanes and Donoghue 2000), though these changes have been noted to take place in layers II and III. This neuronal layer has been suggested to be the substrate for neural plasticity as well (Rioult-Pedotti and Donoghue 2003; Rioult-Pedotti et al. 1998). Changes to the microstructure, or cortical synapses, occur through both intrinsic and extrinsic elicitation. In terms of intrinsic signals, rapid repetitive firing of neurons causes changes to the synapse to occur, enhancing the effect of signal transmission. In terms of extrinsic signal communication however, dendritic neuronal input from neighbouring cells transmit neural signals throughout neurons within close proximity, again enhancing the signal effect. The intrinsic and extrinsic neuronal changes, along with the resulting synaptic potential changes, cause synaptic plasticity (Kandel et al. 2000). When changes occur on the presynaptic terminal, the release of the neurotransmitter is potentiated. However, when there are changes that occur on the post synaptic cleft, there is signal modulation in the response to the neurotransmitter. These two events enhance the potency of the transmission of a signal through more efficient neurotransmitter release as well as more efficient re-uptake of the neurotransmitter on the post synaptic cleft. The release of this neurotransmitter is modulated by flow of Ca^{+2} via action

potentials, residual Ca^{+2} from an increase in synaptic transmission, and by the cAMP pathway which is responsible for increasing proteins that aid in the formation of new synapses (Kandel et al. 2000).

Synaptic plasticity has a highly regarded role in modulating learning at a microscopic level, in inducing changes to the neuronal synapse. The signal strength from a synaptic spike of one neuron near another can increase its metabolic efficiency if the strength of the spike is large enough (Hebb 1968). The ability of this synaptic effect may be dependent on activity and thus may be suspect to modification through task dependant activation (Rabinovich et al. 2006). Such task-dependant activations may come through long term potentiation via a repetitive complex task as proposed within the current research.

3.3-Macro Anatomy

Plastic re-modeling in response to stimulation of cortical tissue, specifically the primary motor cortex, can occur at both the micro- and macro- level. Other than the M1, a primary macro-structure involved in conditioned movement is the supplementary motor area (SMA), which receives sensory information with the M1 from the S1 and connects the dorsal and ventral premotor areas (Kandel et al. 2000). Along with the SMA, the dorsal/ventral premotor areas receive sensory information and integrate spatial constraints relative to the movement goal, determined by the pre-dorsal premotor area, and pre-supplementary motor area. These structures are composed of, and interconnected by, the microstructure that composes layer I-VI of the cortical tissue, with layer V being the main between-structure communication pathway. This organized signal then gets sent to the M1, where an efferent motor signal is sent to the respective effector site following spatial and temporal processing in the supporting neural structures

previously outlined (Carey et al. 2006). While the movement is taking place, the cerebellum, which is composed of 3 subsections, is responsible for keeping balance based on sensory information from the spinal cord regarding environmental interaction (Kandel et al. 2000). Past research has suggested that repetitive, learned movements get ‘recorded’ in the Basal Ganglia (BG) for future activation during required motion, as cortically originated motor learning travels to sub-cortical structures (Shah 2008). When the task again needs to be completed, the BG is activated before the supporting motor-planning structures to recall past movement patterns that have already been adapted (Shah 2008). Together this connection pathway receives sensory input, plans the most effective motor response via the pre-frontal cortices, and elicits a motor response through processing at the M1. It is this pathway that becomes modified through stimuli activation of neural connections through dendritic synapses

The M1 of the dominant and non-dominant hemisphere lies at the precentral gyrus which has connections to the supplementary motor area, among other structures (Tortora and Derrickson 2009). The premotor area which lies anterior-lateral to the M1 and the supplementary area, which lies anterior to the M1, are responsible for motor planning and propagates a signal to the M1 with directions of how to elicit a motor response from a specific muscle that requires activation. The activation of the M1 occurs in a contralateral fashion, as the right hemisphere controls movements on the left side of the body and vice versa for the opposing hemisphere. As mentioned throughout the introduction, the preferred usage of one hand over the other in right handers, with the more consistent bi-manual usage in left handers, causes asymmetries in the representations of different muscles within the M1 as well as their ability to control fine movement. These patterns of usage in daily cortical elicitation cause anatomical differences that can have effects on the macrostructure ‘map organization’ of the M1 anatomy.

3.4-Macro Structural Plasticity

There are structural differences between the white and gray matter that compose the neural tissue in the cranial vault. Specifically, there is a difference between the hemispheres of both right and left handers in terms of white matter depth (Büchel et al. 2004). Büchel et al. (2004) identified that there was a significant difference in fractional anisotropy (FA) within the dominant hemisphere of right and left handed participants, in addition to concluding that the specific area that had a significant increase in FA was the precentral gyrus of the dominant hemisphere. The depth of the precentral gyrus has shown to be different between the hemispheres of right handers, which classically have much more unilateral hemispheric activation. The prefrontal gyrus is deeper in the dominant hemisphere of right handers, with a much more shallow depth within the non-dominant hemisphere (Amunts et al. 1996; Foundas et al. 1998). This difference is represented morphologically by an anatomical laterality that may occur as a result of lifelong motor conditioning. However, the difference in comparative depth in the cortical hemispheres in left handed individuals apparently not so pronounced as the dominant hemisphere does not consistently present with a deeper prefrontal gyrus when compared to the non-dominant hemisphere (Foundas et al. 1998). This may be attributed to patterns of hand use and related behavioural adaptations.

In order to consolidate motor learning, the activation of the pathways composing the motor system changes following a motor learning task. There is an increase in the activation of the premotor cortex, posterior parietal and cerebellar cortices that occurs several hours following a motor learning task (Shadmehr and Holcomb 1997). It is thought that this period of increased post training activation decreases the instability of motor learning and consolidates motor memory, thus decreasing 'behavioural interference' on learning a new motor training skill

(Shadmehr and Holcomb 1997). Following training of both skilled and non-skilled participants, it was noted by Koeneke et al. (2006) that the participants who were considered to have a strong ability of the selected performance prior to the motor task had a lower amount of activation in the primary and secondary motor areas than the naïve group. This indicates that naïve; non-skilled participants demonstrate up regulated cortical activation following a motor training task and may be a better suited population for identifying magnitudes of neuronal excitability between hemispheres, such as in the current proposed work.

It is thought that these anatomical differences will give rise to functional differences that can be studied using modern imaging and testing techniques. Such studies have been completed using fMRI techniques in order to showing incidental and developmental pathways following repetitive movements over weeks of training (Ungerleider et al. 2002). Consequently transcranial magnetic stimulation as well as magnetic resonance imaging techniques can be used to identify levels of cortical excitability. It seems therefore that the mechanism /s of changes to cortical excitability between right and left-handed participants following complex training are not clearly established. However the issue of anatomical asymmetries as presented in this thesis is argued to be relevant to the overall question and therefore warrants further research.

Chapter 4-Asymmetry in Plastic Potential

The basis of motor asymmetry occurs through repetitive activation of guided movement pathways. The resulting conditioning effect was previously thought to be the origin of motor asymmetry, however humans may be born with a predisposition (Sun and Walsh 2006). Hepper et al. (2005) found that increased right handed development can be seen in embryos as early as 8

weeks old, in addition to babies sucking on their preferential thumb which led to a largely retained handedness profile as the children aged. Shifting of the dominant hemisphere, which in most babies is the right hemisphere between ages 1-3, occurs after the child is 3 years old and shifts to a left hemisphere dominance (Chiron et al. 1997). Together these suggest that, as children, humans have predisposed genetic coding that results in a handedness profile to be pre-selected. It is then the constant usage of this motor pathway, over the opposing, that preferentially strengthens the motor pathway resulting in asymmetry. However, it is possible to change the preference of the handedness profile through repetitive movement of the non-preferred hand, over a significant period of time (Teixeira and Okazaki 2007). This asymmetry of motor pathways continue to manifest in the increased ability of one hand over the other, and may develop differently in right, compared to left, handed individuals. Right handers have shown no difference between the activation profiles in the motor hemispheres during simple tasks with a greater lateralized activation profile while completing sequential tasks (Solodkin et al. 2001). Left handers have a similar profile of activation between the hemispheres during simple tasks however with more complex sequential tasks this trend decreases with one side having increased activation (Solodkin et al. 2001). This suggests that left-handers have more bilateral activation as tasks become more complex while right-handers stay highly lateralized regardless of task requirements. As with the upper limbs, the lower limbs show differential lateralization that is dependent on cortical activation. For example, the cortical activation patterns between the knee, ankle, and toes are different. This is postulated to be due to the varying amount of muscle refinement in the knee compared to the ankle and toes during similar flexion/extension movements, resulting in larger cortical representation and resulting motor control in the more active muscles (Kaprili et al. 2006). This gives rise to an increase in asymmetry between

muscles that are refined more robustly. As humans get older, this lateralized ability in motor function changes. The asymmetry in motor ability decreases between the dominant and non-dominant hemispheres, while the performance of those hemispheres with the respective muscle activations, decreases (Raw et al. 2012). Due to this decreased motor performance, there is a resulting increase in bilateral activation to increase stability in the movement patterns.

Chapter 5-Functional Hemispheric Differences with Laterality

Transcranial magnetic stimulation (TMS) is a non-invasive tool that stimulates discrete neuronal populations within the M1 in order to elicit a motor response (Hallett 2000). This tool activates specific neuronal cells within the cortex and can give reliable information regarding the composition and function of neuronal systems (Rothwell et al. 1991). A paired-pulse technique uses two different controlled stimulations separated by a defined time period. When using a paired-pulse, the neuronal populations responsible for the fine-tuning of these descending motor signals can be selected based on manipulating the intensities of the conditioning stimulus (CS), test stimulus (TS) and interstimulus interval (ISI). When using a single pulse configuration however, stimulus-response curves can be collected which allow researchers to quantify the excitability of a motor hemisphere in a certain moment in time (Daligadu et al. 2013). Both of these pulse configurations, and the relevance of their findings, will be explored in the following section. This tool has been used heavily in the area of M1 hemispheric laterality literature (Bäumer et al. 2007; Büchel et al. 2004; McGinley et al. 2010; Pearce and Kidgell 2009; Peurala et al. 2008).

Through the discussion of the preceding section the neurophysiological basis of hand asymmetry was explored. This current section focuses on the manifestation of these neurophysiological changes in the ability of the motor hemispheres to fine-tune motor output resulting in functional movement. In order to study functional hemispheric differences and possible mechanisms of laterality, intracortical neural populations can be studied. When these neuron pools are activated the resulting motor response is collected using surface electrodes depending on the effector muscle targeted over the motor homunculus. The use of TMS allows different populations of interneurons to be activated by manipulating the timing and intensity of the stimulator outputs. In addition to the excitation of intracortical neurons that refine the descending motor signals, magnetic resonance imaging (MRI) has been used to identify changes of cortical excitability levels. Dassonville et al. (1997) found that with increasing degrees of handedness, there was a correlation with the asymmetry and activation of the contralateral hemisphere, with the more lateralized hand having a higher amount of activation on the contralateral side. This provides evidence for the concept that increased degrees of handedness increases the lateralization in the recruitment of hemispheric input for modulation of these movement pathways.

5.1-Functional differences with Laterality: Paired Pulse TMS

A benefit to paired pulse configurations with TMS is that specific neuronal populations that govern the effects of inhibition and facilitation of MEPs can be consistently activated in order to study functional differences between the motor signal processing in different hemispheres and handedness populations. Civardi et al. (2000) investigated the functional differences between left and right handers while manipulating the interstimulus interval (ISI) between stimuli using

paired pulse TMS. It was determined that right-handers had a significantly stronger ability to demonstrate implicit functional use of their dominant M1 as compared to their non-dominant M1 (Fig. 4a) that was not seen with left handers (Fig. 4b).

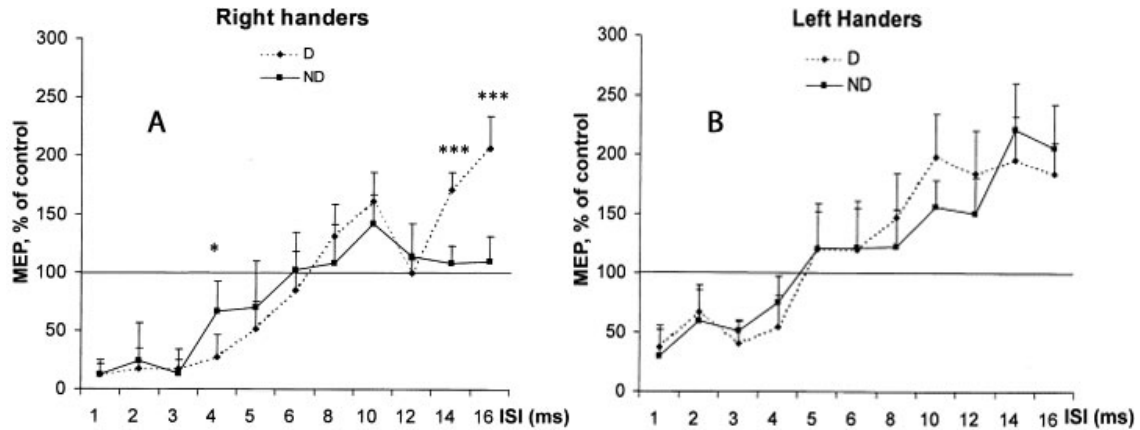


Figure 4. Differences in MEP amplitude between the hemispheres of right handed (A) and left handed (B) individuals at rest. ‘*’ indicates a $p < 0.05$ and ‘***’ indicates a $p < 0.001$. Figure is adapted from (Civardi et al. 2000).

In right handers, the dominant hemisphere had significantly stronger inhibition and facilitation, however in left handers there was no significant difference between each hemispheres. It was also noted that when comparing the hemispheres between handedness groups, the dM1 of the right handers have significantly stronger inhibition while the dM1 of the left handers had significantly stronger facilitation as seen in Fig. 5a (Civardi et al. 2000). This relationship was mirrored in the comparison of handedness populations’ NdM1 (Fig. 5b).

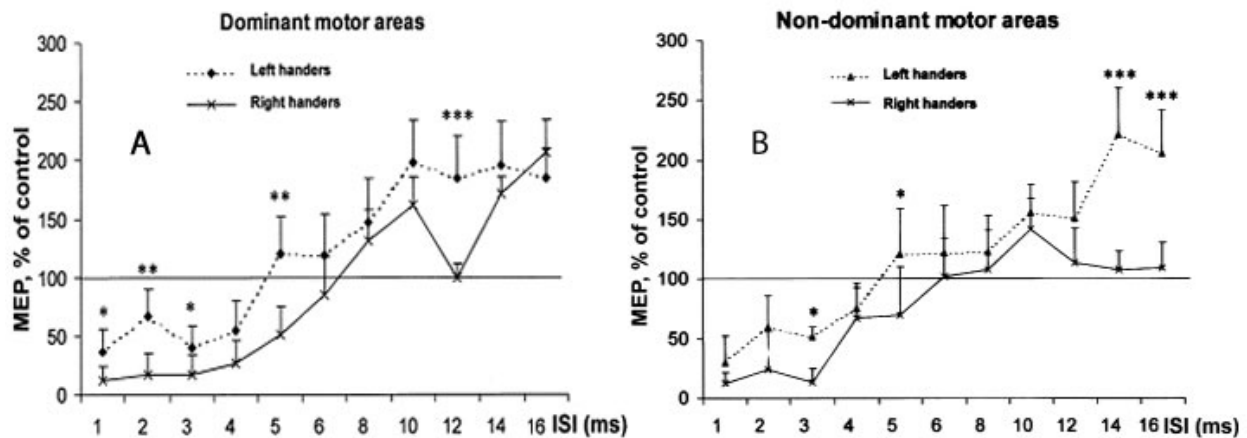


Figure 5. (A &B) Differences in MEP amplitude between the handed populations of the dominant (A) and non-dominant (B) hemispheres at rest are shown. ‘*’ indicates a $p < 0.05$ and ‘***’ indicates a $p < 0.001$. Figure is adapted from (Civardi et al. 2000).

This suggests that the inhibition pathways may require greater conditioning in order to increase inhibitive strength as right handers had a significantly stronger inhibition in their dominant hemispheres. This finding is limited in the literature, however, as few other studies have directly compared motor refinement differences between right and left handers while comparing hemispheres between groups. Hammond et al. (2004) investigated different strengths of inhibition and facilitation between the hemispheres of right handers. They found that facilitation was significantly stronger in the dM1 (Fig. 6). They also found that inhibition was significantly stronger in the dM1 as well, in addition to the dM1 having significant inhibition with a quicker onset of activation than the NdM1 (Fig. 7).

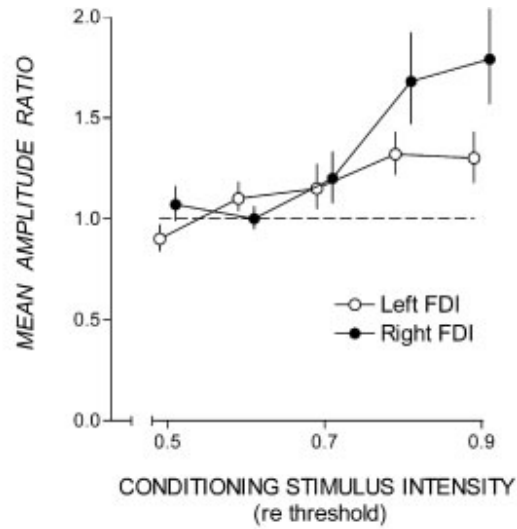


Figure 6. Differences in MEP amplitude showing effects of facilitation between the left and right hands of right handed participants. Figure is adapted from (Hammond et al. 2004).

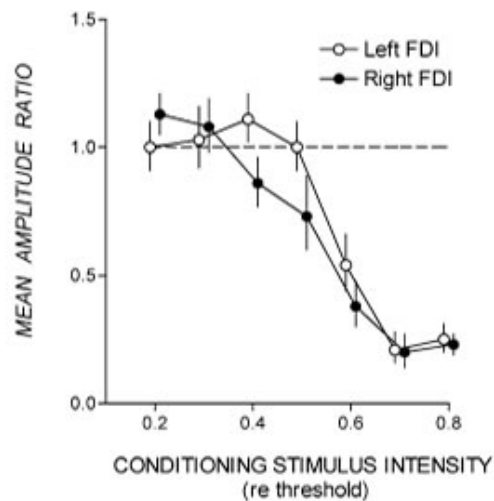


Figure 7. Effects of inhibition mechanism of motor control on MEP amplitude are shown between the left and right hand of right handed participants. Figure is adapted from (Hammond et al. 2004).

This indicates that the inhibitory mechanisms in the dM1 of right handers have greater threshold sensitivity as well as a stronger inhibition compared to the NdM1. However, the threshold sensitivity that was seen with inhibition was not seen with excitation, again suggesting that the inhibition control may require more conditioning to greatly increase its potency. These findings were mirrored in another study by Hammond and Garvey (2006), who were looking at the mechanism of LICl in right handers. They found that LICl had significantly stronger levels of inhibition in the dM1 in addition to having an inhibitive effect faster than the NdM1 (Fig. 8). While mainly focusing on the functional abilities of the limbs, Przybyla et al. (2012) were looking at asymmetries between handedness groups while completing a reaching task with varying pattern requirements. They found that in their right handed population there was a greater difference between the number of errors the dominant and non-dominant hands had. However, their left handed population had a much smaller difference between the errors that each limb had in successfully completing the reaching task. They suggested that the larger laterality that was seen in the right handers, and which was absent in the left handed samples, was evidence of life long conditioning that resulted in an increase in cortical dominance with right handers.

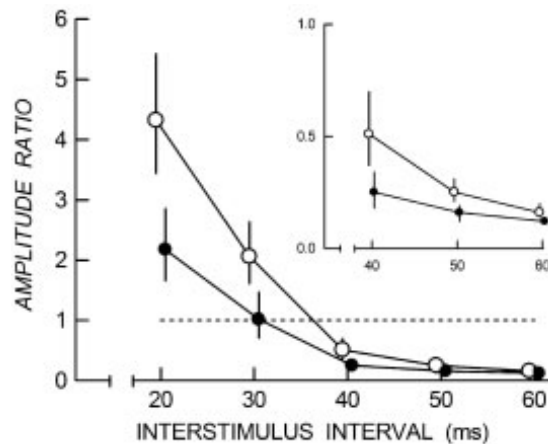


Figure 8. Effects of facilitation and inhibition on MEP amplitude. Points above the dotted line show facilitation while points below show inhibition. Solid dots are the dominant (right) hand and open dots are the non-dominant (left) hand. The inset graph shows greater detail on the range of 40-60 ms of ‘Interstimulus Interval’. The figure is adapted from (Hammond and Garvey 2006).

The findings of studies adopting the paired pulse technique have had contradictory findings (Civardi et al. 2000; Triggs et al. 1999) and thus may not be the most appropriate methodology to use in future studies. These findings, however, further develop background information showing different aspects of laterality among handedness groups. They also show fundamental differences of neuronal populations governing motor refinement between the dM1 and NdM1 of right and left handed individuals.

5.2-Functional differences with Laterality: Single Pulse TMS

A drawback to the use of paired pulse configurations is that this technique only captures the excitability of the motor hemispheres at a single intensity, and does not measure the response to increasing stimulus intensities. Another technique known as stimulus-response curves (Input-

output curves) is the systematic stimulation of the motor hemisphere with pseudo-randomized blocks of increasing stimulator intensity. The slope of the resulting curve has been suggested to be a measure of hemispheric excitability (Siebner and Rothwell 2003) as it is indicative of the motor hemisphere's response to increasing intensities and thus may be a more robust measure of global cortical excitability. Daligadu et al. (2013) found the left handed participants have a significantly increased excitability in both the dominant and non-dominant hemispheres (Fig. 9a) compared to right handed participants (Fig. 9b), at rest. In both handedness samples the non-dominant hemisphere had increased excitability.

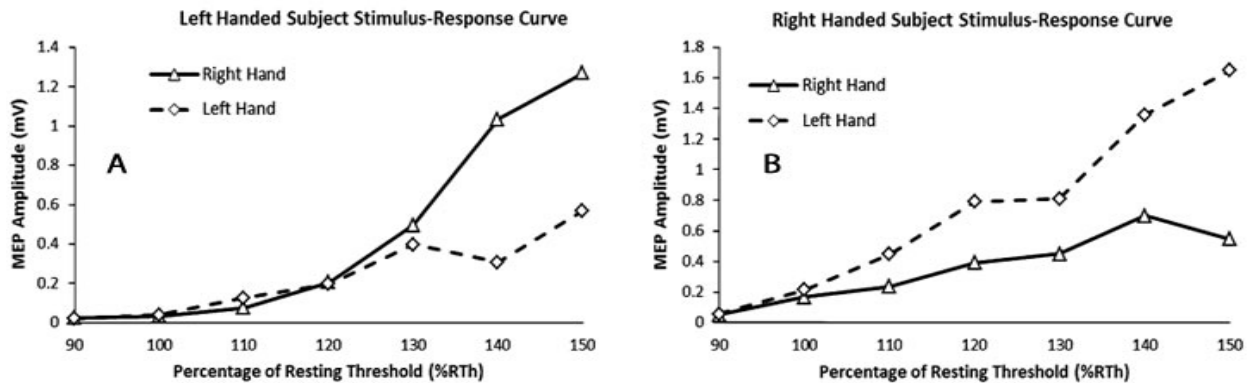


Figure 9. An illustration of the dominant and non-dominant hands for the right (A) and left (B) handed participants is shown. The slope of the created line is a function of corticomotor excitability. Adopted from (Daligadu et al. 2013).

Few studies have used the SR-curve technique to directly identify differences between the two motor hemispheres (Cirillo et al. 2009; Daligadu et al. 2013) and to our knowledge few have been completed while incorporating a training task (Cirillo et al. 2009; Lotze 2003; Perez et al. 2004). However, these studies use training tasks which we argue are not novel enough to equally tax both hemispheres and thus are not substantially robust to identify differences in excitability

between the dM1 and NdM1 following skilled training. These motor training tasks will be discussed further in the following sections.

Chapter 6-Motor Training

Throughout the process of skill acquisition following a motor training task, there are different levels of learning. More specifically, the increase in motor ability through completion of a training task occurs through slow and fast learning (Kleim et al. 2004; Rioult-Pedotti et al. 1998; Rosenkranz et al. 2007). Fast learning is characterised as the quick increase in motor performance during task completion. It is thought that this level of motor training primarily involves long-term potentiation (LTP) and changes to pre-existing synapses (Rosenkranz et al. 2007; Ziemann et al. 2004). Slow learning is characterised by the smaller, incremental increases in performance that occurs throughout days and weeks of motor task repetition. These changes may have influence on the neural composition of the motor hemispheres, as well as synaptogenesis as the motor cortices re-model in order to better and more efficiently perform the required task (Kleim et al. 2004; Monfils et al. 2005; Rosenkranz et al. 2007). The resulting increase in activation patterns can come after as little as 5-10 minutes of motor movement (Classen et al. 1998) and can be more pronounced if the task is 'novel' meaning the participants are naive to the required level of performance and accuracy in the task (Sanes and Donoghue 2000) resulting in similar performance adaption with the onset of training.

6.1-Training Tasks

Learning tasks can be implemented before, during, or after taking measures of cortical excitability. The use of a learning task in a pre-post design provides insight into the ability of intracortical excitability to change while completing a movement pattern. While identifying a task that is appropriate to include in such a research design, there are certain aspects the task should have. For example, the task should be novel in design (Sanes and Donoghue 2000), as this is imperative to create significant changes to the M1. When both hemispheres are tested, this means that the task does not favour the abilities of one hand more than the other, and that participants are naïve to the requirements of the task and associated movement. As the task should be equally difficult for each hand, the amount of cortical strain and modulation would theoretically be the same for both motor hemispheres. Gallasch et al. (2009) used a novel index-finger abduction task while looking at changes to motor excitability through looking at changes to MEP amplitude at a single intensity. To our knowledge this is the only example in the literature of a study involving a fine motor task coupled with a methodology for measuring cortical excitability. This approach though unique is not in our view well matched for determining global excitability levels as measures of global excitability likely require stimulation at more than one intensity with excitability parameters data reported as recruitment curves (Gallasch et al. 2009).

The degree of motor learning, or increase in skilled motor performance, may be based on the type of learning task that is used. Continuous and discrete motor tracing tasks have been used to identify hemispheric activation differences. Both have been found to actively stimulate the sensory motor, premotor and parietal cortices, as well as the cerebellum with varying degrees of similarity (Gowen and Miall 2007; Spencer et al. 2007). Continuous motor traces involve tracing

an object with undefined velocity and start/end points, such as drawing a circle, while discrete tracing tasks involve defined areas of a required increase in trace velocity with a more ordered sequential movement profile (Habas and Cabanis 2008). Habas and Cabanis (2008) found widespread recruitment of the M1 and somatosensory cortex with a continuous learning task. Increased activation of the right prefrontal cortex as well as the lateral hemispheric regions was noted. The prefrontal cortex is a significant area of elicitation as higher order thinking has been shown to induce learning in the M1, which is the main physiological cortical structure in this research. The use of drawing tasks, such as Japanese Kanji letters, has been used in the past as a training task (Hoshiyama and Kakigi 1999) however the approach typically uses elicited somatosensory evoked potentials (SEPs), rather than MEPs to identify cortical adaptation. An advantage of drawing tasks is that they can range from simple to complex in design; however they may require the activation of several muscles at once in addition to wrist and elbow deviation. In order to identify the changes of a single area of motor control within the M1 associated with learning we suggest that a task focusing on the activation of a single intrinsic hand muscle would be more appropriate to use. This approach limits the number of confounding variables that may influence the outcome, and the identified changes can be more confidently associated with the controlled parameters with recruitment of the single intrinsic hand muscle. Varying the amount of feedback the participants receive may be an important variable as well. Smyth et al. (2010) used two different groups that received varying levels of two different kinds of performance feedback during a skilled movement task to see changes in cortical excitability, with a wrist flexion/extension task. It was noted that feedback was an important factor to the increase in performance, with focus and attention being a possible variable. Pegboard tasks have been used as performance measures as well, as the number of successful pegs placed in a board

during a 30s trial is associated with accuracy and efficiency in ability (Garry et al. 2004). The authors noted that while sampling for ICI, there was a decrease with inhibition for ~20 minutes following the task in only the dominant hemisphere of the right handed participants, and that this had a correlation with motor learning. A number of studies have used non-skilled ballistic thumb abductions/adductions to study M1 activation (Cirillo et al. 2009; Classen et al. 1998), though this movement lacks skilled performance associated with a task involving dynamic changes to target requirements. As well, 'retention' training sessions, which is the completion of an identical protocol following short or long periods after the initial session, may be important for determining consolidation effects with degrees of incremental learning between trials (Adams 1987; Hauptmann and Karni 2002). A drawback to most of the motor tasks reviewed is that they lack 'complexity' with a limit on the difficulty of the training task, they do not include a skill performance measure, or they do not equally task both the dominant and non-dominant hand.

6.2-Changes in Plasticity with Learning Tasks

The primary motor cortex is not only involved in the acquisition of skilled motor performance but is also involved in the early phases of skill consolidation (Nitsche et al. 2003). Motor skill performance is attained through several stages, consisting of fast rapid learning of a skill set, a consolidation phase, and slow learning which has smaller incremental gains in motor ability (Karni et al. 1998; Kleim et al. 2004). Priming effects are the gains of fast learning that occurs after only a few trials of a motor task, and does not require much of a 'consolidation' phase in order to show skill acquisition has taken place (Hauptmann and Karni 2002; Karni et al. 1994). Skill learning however requires time to evolve, and may require repeated sessions in order to

show that a significant amount of skill acquisition has taken place (Hauptmann and Karni 2002; Karni et al. 1994). This time and sleep dependant process occurs several hours after the learning task has taken place, and may show an incremental effect with the participant having better slow-learning during the completion of several other learning sessions, with little cross over with the associated cortical motor areas on the contralateral side (Hauptmann and Karni 2002; Karni et al. 1998; Karni et al. 1994). During this time the brain has alternating activation patterns, which are motor task dependant, that result in the recruitment of different cortical areas depending on the ability of the participant as well as the complexity of the task (Nudo et al. 1996; Petersen et al. 1998). This process consolidates the skill that had been learned through the motor task and stores it as a motor memory which can be altered with further task completion (Brashers-Krug et al. 1996; Shadmehr and Holcomb 1997). Fast learning constitutes gains in motor performance during training sessions (Karni et al. 1998), while most learning occurs during the consolidation phase several hours following a motor task and has been shown to be influential with tasks that have visual and perceptive characteristics (Karni et al. 1998; Polat and Sagi 1994; Schoups et al. 1995; Karni et al. 1994). These activity-dependant changes in skill training take place in the M1, may cause changes to neighbouring motor neurons (Adkins et al. 2006) and are not due to changes in the corticospinal tract (Adkins et al. 2006; Muellbacher et al. 2001).

Plasticity in microstructure, as mentioned in prior sections, can enhance the phenomenon of motor asymmetry. The basis of this mechanism is repetitive activity-dependant neuronal recruitment that allows strengthening of neural populations within the M1 that govern muscle activation. In order for plastic changes to these neural populations to occur, the movement pattern must be voluntary and repetitive. Garry et al. (2004) found an increase in MEP

facilitation with decreased inhibition following a single peg-board task training session. Facilitation increased equally in both the contralateral and ipsilateral M1 however, while the decreased inhibition occurred only in the dominant hand suggesting a relationship between inhibition and hand used. Lotze (2003) determined that during a wrist flexion-extension exercise, movement that was voluntary had a significantly higher amount of contralateral M1 (cM1) activation than non-voluntary movement, as well as larger intracortical facilitation and cortical excitability compared to passive movement. These findings were extended in the work of Perez et al. (2004) who compared the voluntary and non-voluntary flexion-extension of the ankle. Voluntary movement again had significantly increased excitability when compared to non-voluntary passive movement, as well as having a decrease in errors throughout the protocol. This suggests a greater amount of increased motor performance take place during active movement and that these relationships occur throughout the bodies' movement range. The resulting change to cortical activation is dependent on mental focus and voluntary, rather than passive, movement tasks. Though there may be similarities between these limb's segments, it has been suggested that in order to have potentiation of an increased muscle response, a conditioning effect must be established through ballistic, rather than slow dynamic, movements (Muellbacher et al. 2001). It has been shown that significant changes to cortical representation in the motor hemispheres can occur with movements involving only one muscle rather than a group of muscles involved in larger gross tasks (Classen et al. 1998). Neuron recruitment in the M1 that controls the mechanisms of inhibition and facilitation has inversed relationships when applied to tasks involving one or many muscles. Tinazzi et al. (2003) found that inhibition is increased when there are numerous co-activations of hand muscles with a whole hand grip, while facilitation occurs with much more individualized movements such as index finger abduction.

This suggests that these mechanisms act inversely with respect to muscle activation even though they are both activated in the cM1, however it is unknown the impact that this change has on the global corticomotor excitability of the motor hemispheres.

Chapter 7-Measures of Muscle Fatigue

When characterising and quantifying muscle fatigue there are several different components that should be considered. Electromyography signals are used to analyze muscle contractions from a summation of several muscle fibres firing at the same time. These EMG signals can be collected using surface electrodes in order to non-invasively collect electromyographic signals from the desired muscle. These surface EMG electrodes are most optimally placed on the midline of the muscle belly in order to obtain the largest signals of muscle contraction power and frequency (De Luca 1997). When a muscle is fatigued, usually after repetitive activation or a sustained contraction, there is a decrease in power and frequency of firing of the muscle. Fatigue can be defined as a decline in the ability to constantly perform at a certain level, and to have a decreased ability to maintain or generate a certain force or power output (De Luca 1983; Vøllestad 1997). It can be caused by decreased internal motivation, or on a more physiological basis due to decreased excitation of motoneurons, excitation of muscle fibres, changes in Ca^{2+} concentration, or changes to the function of actin-myosin cross bridge formation (Vøllestad 1997). One of the most efficient and commonly used techniques to measure fatigue is by using the force or power or frequency measurements that are recorded using surface EMG technology (Vøllestad 1997). The mean power frequency (MPF) method, which uses the spectrum changes and frequency shift, have been used in several studies (De Luca 1983; De Luca 1997; Lindstrom et al. 1970; Öberg et al. 1990; Petrofsky and Lind 1980; Vøllestad 1997) and is beneficial over other

techniques as it is not dependent on muscle temperature or the amount of contraction in the muscles. Significant fatigue is characterized by a 8% drop in MPF, as a participant is not considered fatigue unless there MPF drops by 8% or more after the muscle has been strained (Öberg et al. 1990). Based on these findings the training task should maintain a level of muscle activation that is sub-fatigue in order to ensure that changes to cortical excitability measures are due to changes in the cortical neural-anatomy and not the physiology of decreased activation due to onset of muscle fatigue.

Chapter 8-Summary of Literature Review and Research Focus

Laterality that develops due to lifelong conditioning, through constant usage of either a person's dominant or non-dominant hands, has developed through anatomical and functional cortical asymmetries. In terms of the anatomical difference the pre-central gyrus, which is responsible for the control of descending motor signals, is deeper in the dominant hemisphere of right handers (Amunts et al. 1996; Foundas et al. 1998). While in left handers, there is a much more random distribution of motor hemispheric activation. Functionally, there is a difference between the two hemispheres ability to control fine movement that is seen in the laterality of errors and their analysis while completing several different grasping tasks with varying movement patterns ranging from pinching to whole hand gripping (Przybyla et al. 2012). These findings show different characteristics of refinement that lateralization can effect, as it has changes that are both anatomical and functional in nature.

Training tasks have been used to a small degree to study cortical excitability levels, as it has been found that cortical activation increases with task difficulty as complexity increases (Dassonville

et al. 1997). Using the slope of recruitment curves rather than recording changes to MEP amplitudes may be a more beneficial methodology of defining the global motor-excitability and has rarely been used in combination with a motor training task (Lotze 2003; Perez et al. 2004). Motor training tasks have been used in past work to elicit changes to the composition of the motor cortices, however drawbacks to these tasks have been outlined. We suggest a task of sufficient novelty be used in concert with recruitment curves in order to not only define the amount of cortical excitability in the dM1/NdM1 but also to determine which hemisphere has the greater potential for motor plasticity. A repetitive tracing task incorporating varying amounts of feedback, activation, and with sufficient levels of difficulty is suggested here to be most appropriate for this research, and a task of this sort has only been used in one study to our knowledge (Gallasch et al. 2009). Though several studies have attempted to quantify motor excitability in the two hemispheres using a training task (Gallasch et al. 2009; Garry et al. 2004; Smyth et al. 2010), none to our knowledge have used a task such as the one proposed in combination with recruitment curves to measure corticomotor excitability across two days of training. This approach will help identify which hemisphere has a greater potential for strength of refinement modulation as well as when these changes take place as a function of a time-course following a motor training protocol. Thus, this manuscript includes a research design which encompasses a pre-post structure that identifies changes to cortical activation/recruitment patterns of the FDI, a monosynaptic muscle, following a customized complex tracing task. Tracing tasks have been noted to result in better accuracy as well as increased shape retention when compared to simple copying tasks (Gonzalez et al. 2011). This tracing task will incorporate characteristics of past literature (Civardi et al. 2000; Daskalakis et al. 2002; Lotze 2003; Raw et al. 2012) however will include a more thorough procedure with specific focus on the between-

hemisphere differences of activation/recruitment patterns following a complex tracing task. Due to the current gap in the literature regarding this emphasis, the tracing task needs to be a customized tracing task that can be performed by both the right and left hands with the FDI as the prime mover (Hausmann et al. 2004).

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SECTION II: MANUSCRIPTS

Manuscript #1

Levels of Motor Skill Acquisition in the Dominant and Non-Dominant Hand Following a Novel Discrete Complex Training Task

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Abstract A novel complex motor training task was used to validate a new protocol for use in motor excitability studies. Typically motor training tasks such as reaching or other gross movements are used to elicit changes to neuronal pools that govern motor refinement in the dominant (dM1) and non-dominant (NdM1) motor hemispheres (Garry et al. 2004; Lotze 2003; Przybyla et al. 2012). Here we investigate a dynamic discrete complex tracing task using the index finger to attempt to validate a novel training methodology. The progression of decreasing motor error was measured in the dominant and non-dominant hands of 12 right-handed males (Laterality Index (LI) of 81.25 SD=5.22). Each participant completed 3 different training blocks for each hand during two separate training sessions separated by 24 hours, with the hand that “learned first” counter-balanced between left and right in a pseudo-random order. We found no significant difference between the progression of increased motor performance across two days of training between the dominant and non-dominant hands of right handed males (40% and 41% decrease in error , respectively) confirming that the task was equally difficult for both hands. The time-course changes to motor performance as a function of the tracing task may provide insight into mechanisms of motor learning that cause changes to micro/macro neural structures. We conclude that the proposed training task was indeed novel and did not lead to fatigue, indicating that it is sufficient to be used in a larger study looking at excitability changes following a complex motor training task.

Key Terms *Motor Training Task, Handedness, Motor Performance, Motor Training, Primary Motor Cortex*

Introduction

The primary motor cortex (M1) is not a static motor structure but rather has a dynamic composition, with the capability of ongoing modification, through use dependant plasticity, of neural connections that form the M1's neural components. These use-dependant changes can be caused by skilled and non-skilled repetitive movements and tasks found throughout many examples in the literature (Cirillo et al. 2011; Classen et al. 1998; Garry et al. 2004; Koeneke et al. 2006; Lotze 2003). Motor skill acquisition through motor training has been characterised through fast and slow processes, with fast training occurring through long-term potentiation (LTP) like changes while slow training occurs in the hours of consolidation following motor training as well as additional sessions over days of continued trials (Muellbacher et al. 2001; Rosenkranz et al. 2007; Ziemann et al. 2004). It is thought that the early phase of learning, with LTP like changes to existing neural synapses, is the origin for cortical plasticity of the motor cortices (Gallasch et al. 2009; Muellbacher et al. 2001; Ziemann et al. 2004). The use-dependant plasticity in the motor cortices is reliant on active rather than passive movement (Lotze 2003; Perez et al. 2004) as participant attention and focus may be important factors to learning. Repetitive motor hemisphere elicitation through movement tasks induces reorganization of the M1 cortical map with increased areas of representation (Adkins et al. 2006; Butefisch et al. 2000) and increased functional ability (Liepert et al. 2000). This map reorganization can occur with as little as 5-10 minutes of motor training from a single session (Sanes and Donoghue 2000).

The motor cortices composing the dominant and non-dominant cortices are use-dependant in the development of their motor refinement ability. This process can be divided into hand preference and hand dominance, as hand preference suggests an *a priori* origin while hand

dominance is developed through life long usage (Guiard 1987). Motor training tasks can be used in research to quantify the difference between the two hemispheres' ability to refine descending motor signals. Many studies adopt training methodologies that do not equally tax both the dominant and non-dominant hands, with one hand having a significant advantage at training onset such as with pegboard and other reaching tasks (Garry et al. 2004; Przybyla et al. 2012). We argue that a more appropriate training task would equally challenge both the dominant and non-dominant hands with a novel movement pattern not typically performed by either hand in order to eliminate bias in movements more commonly practiced and expressed by the dominant hand and/or limb.

Most studies involve training tasks that are either gross movements such as reaching tasks and large joint flexion/extension (Garry et al. 2004; Lotze 2003; Perez et al. 2004), or movements focusing on the fingers (Cirillo et al. 2011; Classen et al. 1998; Koeneke et al. 2006), in combination with studying varying characteristics of cortical refinement. However few studies have targeted a novel approach to motor skill training with discrete finger movements, with only one to our knowledge (Gallasch et al. 2009). Novel tasks, such that the participant is naïve to the movement and skill required, will create a tool that can be used to identify differences in cortical excitability measures between the dominant and non-dominant M1.

We sought to validate a motor training task measuring levels of motor performance increase and ensuring that the task did not lead to muscle fatigue. Motor training in this case refers to the decrease in percent error throughout the completion of repetitive index finger abduction/adduction during a novel tracing task. The current study involved one experiment, consisting of two days of training, in order to identify the level of motor skill acquisition for both the dominant and non-dominant hemispheres of right handed participants. The participants

completed a customized complex tracing task that took 10-15 minutes to complete per hand. Each participant completed an initial and retention session separated by 24 hours. It is hypothesized that the proposed training task embedded in our protocol will result in similar gains to motor performance in both the dominant and non-dominant hands, confirming task novelty.

Methods

Participants

Twelve participants completed the experiment (mean age: 22.3, SD=0.4 years) and gave written and verbal informed consent to take part in the study. To ensure homogenous participant populations participants were excluded from the study if they were taking psychoactive medication, had a history of head trauma, or had other medical ailments that would affect cortical excitability. The degree of handedness was determined using the Edinburgh Handedness Inventory (mean score: 81.25, SD=5.22) with +100 and -100 indicating strongly right and left handed participants, respectively. A cut off value of +60 was used to ensure only strong right handed participants were included. The participants were recruited from the student population at the University Of Ontario Institute Of Technology (UOIT), where the study was completed. The Research and Ethics Board at UOIT approved the study and was in accordance with the guidelines for human research determined by the Declaration of Helsinki.

Motor Training Task

Each participant completed 2 days of motor skill training using both their dominant and non-dominant hands. The participants were instructed to trace a continuous vertical sinusoidal wave composed of coloured dots (Fig. 10). The trace moved vertically down a monitor while the

participant would attempt to copy the trace, requiring repetitive abduction/adduction using only their index finger on a wireless tracking pad.

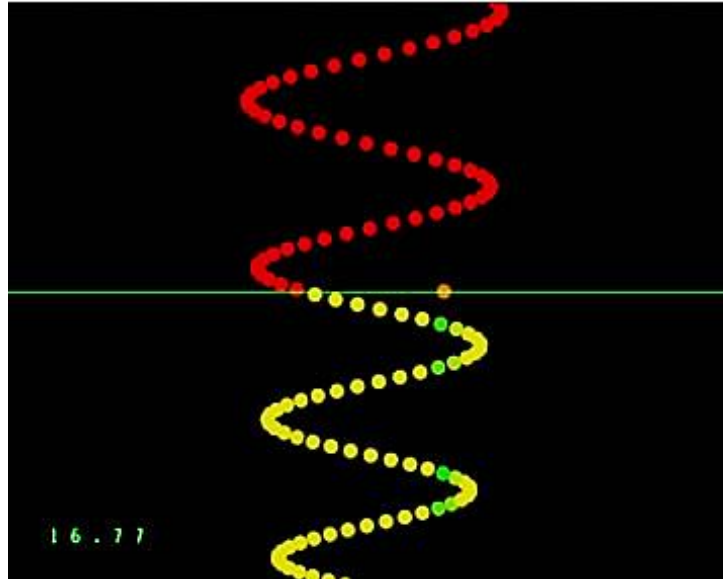


Figure 10. An illustration of the motor training task completed by each participant on the initial and retention day of training is shown.

The participant's arm was bound to the chair's arm rest with Velcro straps to minimize upper limb movement during testing and each participant was visually inspected to ensure no wrist or shoulder movement was occurring during task completion. The software limited the participant's motion to a horizontal line restricting vertical movement, with a dot cursor on the horizontal line that had the same radius as the trace dots. Colour coding of the dots indicated trace accuracy as the sinusoidal wave traveled vertically down the screen, crossing the horizontal line the participants were operating on. Each version was composed of dynamic wave forms, with each successive wave being different than the one previous. There were 4 different versions of the tracing task, each representing varying degrees of difficulty as the amplitude and frequency multiplication factor was different between each version. Version 1 was the easiest task,

requiring the participant to perform slower finger abduction/adduction movements while version 4 was the hardest which required the participant to have rapid ballistic abduction/adduction movement patterns while still attempting to have a highly accurate trace. To increase the difficulty, the amplitude and frequency was increased incrementally between task versions. Throughout each version there were waveforms requiring both ballistic and measured movements. The participants completed 3 blocks of the 4 versions totalling 12 trials per hand on both the initial and retention days of testing. The ‘start hand’ was pseudo-randomized between participants and was maintained per participant for the second day of training. Prior to the start of the experiment, each of the 4 test versions were randomly ordered across the 3 blocks giving a specific order of the 12 trials (Fig. 11). Each participant completed this same order in both hands and both training sessions.

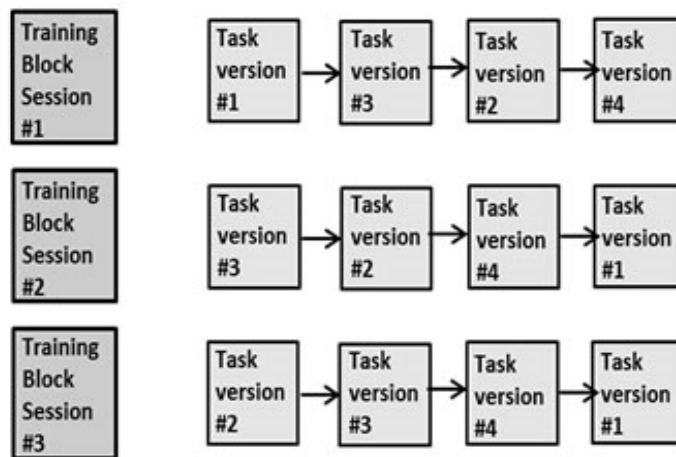


Figure 11. An illustration of the training blocks as well as the order of the 4 different task variations is shown. The training task version and block order was identical for all subjects on both initial and retention days of testing.

EMG Collection

EMG data was collected from the first dorsal interosseous muscle (FDI) using a muscle belly-tendon configuration. A ground strap (Ag/AgCl) was used to ensure signal quality. EMG data was recorded at 1k samples/s throughout the first and last trial of each 12 trial session. A low-pass filter with a cut off of 50Hz was used (Merletti and Di Torino 1999). A mean power frequency (MPF) calculation was completed on the raw EMG signal during the same time stamp of the first and last trial recordings to ensure a homogenous comparison, as each of these time stamps were of the same difficulty from the same respective trace version.

Statistical Analysis

The training software captured the distance the participant's cursor dot was from the 'perfect' trace and recorded the average distance the cursor was from each dot as it passed the horizontal axis the participant was operating on. The error was recorded as a percent that participant's trace was from the original 'perfect' trace. The mean percent error in every trial attempt was averaged for each block of initial and retention sessions for both hands. The initial block completed by each hand on the initial session was considered the 'baseline' measure for which the successive blocks were compared back too. A percent error of 100% indicated that on average the participant missed the trace by 1 dot. A mixed-design ANOVA was used to determine if there was a significant change in the motor training effect between the right and left hand, with the 'hand used' as the grouping variable. Post-Hoc analysis between each of the 6 blocks completed by each hand (3 blocks on each training day) were completed to look at the effect of training progression as a time course on motor error. Effect of motor consolidation was completed using

a paired t-test to compare the change in motor error between the initial and second day of training for both the right and left hands individually.

Results:

Effect of motor training between hands-used groups

The findings from motor training, with associated decrease in performance error, are shown in Figure 12. Comparative analysis indicated that the magnitude of motor skill acquisition between the hands of right handed participants were not statistically significant with no group effect, as both had a similar decrease in performance error over both days of training ($F(1,11) = 0.193$ $p=0.665$; 40% and 41% decrease in error for right and left hands, respectively). Both the right and left hand showed similar trends of skill acquisition through the 3 blocks that each hand performed during each of the 2 days of training as well (Fig. 12). Statistical analysis of the initial training block showed that the right hand (mean error: $149.5\% \pm 15.7\%$) was initially better than the left hand (mean error: $183.8\% \pm 15.7\%$) at performing the task ($p<0.05$). The right hand (mean error: $109.5\% \pm 14.5\%$) was significantly better than the left (mean error: $142.5\% \pm 14.5\%$) in the final block trial as well ($p<0.001$).

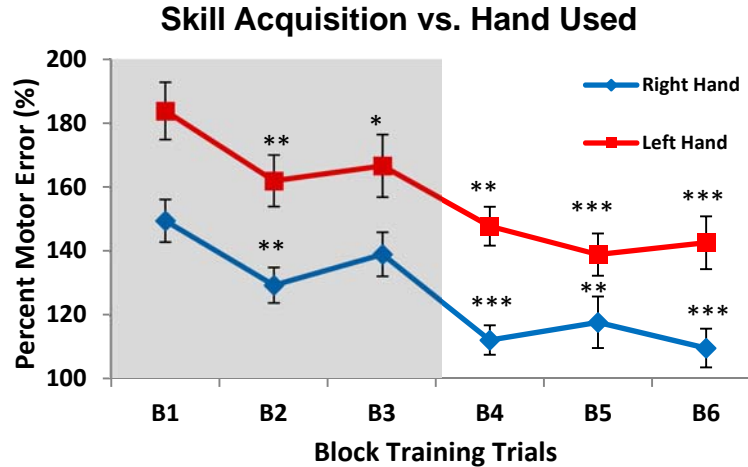


Figure 12. The effect of motor skill acquisition between the right and left hand-used samples. The shaded area represents the initial day of training while the non-shaded area shows the retention day of training. The ‘*’, ‘**’, and ‘***’ indicates a significant difference of $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively, between the training block and B1 which was the baseline measure.

Effect of motor training within hands-used groups

Six blocks of training were completed, three on day one (B1, B2, B3) and three on day two (B4, B5, B6). The initial block training session was the ‘baseline’ measure which the successive blocks were compared to. The dominant hand had significant motor training effect relative to baseline for all blocks except one ($p < 0.05$). The non-dominant hand showed a significant motor training for every block comparison ($p < 0.05$). Post-Hoc analysis indicated that in the right hand-used group, there were significant increases in motor performance between B1 & B2 ($p < 0.01$) and B3 & B4 ($p < 0.01$). For the left hand-used sample there was a significant increase in motor performance between B1 & B2 ($p < 0.01$) while B4 & B5 approach significance ($p = 0.67$).

Fatigue Analysis

The same time stamp for the initial and final trials of each training session were compared. The MPF indicated a significant increase between the first and last trial (Fig. 13). However, only one participant had a decrease in the MPF across the two measures with the remaining participants having increases in MPF. The one participant who had a drop in MPF did not exceed the 8% threshold for drop in MPF indicating there was no onset of muscle fatigue.

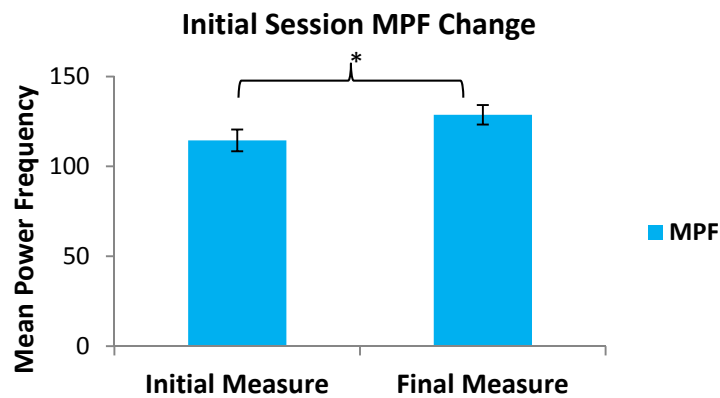


Figure 13. Difference in MPF between the initial trial of B1 and final trial of B3 of the first training session is displayed. ‘*’ indicates a significant increase ($P < 0.05$) in MPF between the initial and final trials.

Discussion:

Past research has not compared the differences between the dominant and non-dominant motor hemispheres’ magnitude of skill acquisition following a discrete complex tracing task. Few have used the intrinsic hand muscles as targets for skill acquisition (Cirillo et al. 2011; Classen et al. 1998; Koeneke et al. 2006). The majority of the literature on motor skill acquisition is composed of motor training using multi-joint or multi-muscle tasks in healthy participants (Garry et al.

2004; Lotze 2003; Perez et al. 2004; Tinazzi et al. 2003), in addition to several studies involving injured or diseased participant populations (Harris-Love et al. 2011; Liepert et al. 2000). Few of these studies have focused on developing a novel training task in order to validate its efficacy in evoking adaptations to skilled performance, prior to using the task to manipulate cortical excitability. The goal of this study was to compare the difference of discrete motor skill acquisition between the two hemispheres of healthy right handed participants using a custom made tracing task. This work will act as a precursor to another experiment involving adaptations to cortical excitability following discrete motor training using the same task.

The main finding indicates that both the right and left hand acquire motor performance with similar trajectories as both the dominant and non-dominant hand had similar increases in skill as they advanced through the trial blocks (Fig. 12).

The dominant hand was significantly better than the non-dominant in both the initial and final block trials however both hands showed a similar drop in motor error throughout the training block sessions. This indicates that even though the right hand was initially better at performing the motor task, both the right and left hand have similar abilities in acquiring motor skill through training. This also confirms our hypothesis that the tracing task would be novel in design and equally strain both hands without augmenting motor training in one hand more than the other. This mirrors one past study showing comparable learning profiles through task progression for right and left hand having (Gallasch et al. 2009) though a second day of training was not included in that study.

The block to block analysis for each hand showed that both hands had significant amounts of training from the first block trial with continued skill acquisition in each successive

block (Fig. 12). The left hand had continued training through each successive block however the right hand had a block trial where no significant training effect was measured. This may suggest that the left hand is more sensitive to initial training, as it had no point during the trial blocks where it did not continue to get better at performing the task, while the right hand did.

Motor training occurs in a number of stages. Fast learning is the rapid onset of skill acquisition between performance trials (Karni et al. 1998). Consolidation of motor training occurs during the hours following initial training session, while slow learning is the incremental increase in performance that occurs with continued training sessions over successive days and weeks (Karni et al. 1998). These learning phases have individualized effects on the neural structures responsible for motor elicitation and skill refinement. Specifically, fast learning results in long term potentiation (LTP) like changes to existing cortical synapses while slow learning results in motor map reorganization with synaptogenesis (Rosenkranz et al. 2007; Ziemann et al. 2004). The findings of increased motor performance in both the right and left hands represents fast learning, consolidation of a new motor skill, and the beginning stages of slow learning due to two days of training. The rapid onset of motor learning seen in both hands is indicative of fast learning, which suggests that the existing neural networks in the motor hemisphere were strengthened with successive trials. The consolidation phase of motor training is characterised by the hours following the completion of a motor training task which is thought to be where a large portion of motor training occurs (Classen et al. 1998). The brain continues to process the required activation of numerous cortical structures for several hours following motor training. For up to 6 hours post-training there is increased activation in the premotor, posterior parietal and cerebellum structures in order to 'stabilize' motor learning and decrease the influence of behavioural intrusion (Shadmehr and Holcomb 1997). In the current study, there was a

significant consolidation of motor performance between the two days of training. The right hand had a significant improvement in motor performance between the final block of the initial training session and the first block of the second training session. The left hand however showed no significant improvement between these blocks. This suggests that the dominant hand had more activation of the motor hemispheres and supporting cortical structures following the initial training session. This increased activation may be a result of increased neuronal development in the dominant hemisphere through stronger and more refined horizontal pyramidal cell connections. These activity dependant connections are much stronger in dominant hemisphere of right handed participants and are not as prominent in the non-dominant hemisphere (Amunts et al. 1996; Foundas et al. 1998). The second day of training, and the resulting increase in skill performance, may indicate the beginning processes of slow learning with the formation of new neural connections through synaptogenesis. These neural developments can have profound influences on the cortical excitability of the motor hemispheres.

Past research has shown that motor activation is increased following a motor training task (Sanes and Donoghue 2000), however to our knowledge a discrete novel tracing task using the index finger has not been used in order to induce these changes. We suggest that using a single finger tracing task is more appropriate than multi-joint or multi-muscle tasks as it reduces the confounding variables of numerous muscle activations as well as introduces a novel movement not typically required in day to day usage, such as finger abduction/adduction. The results from the current study show that the adopted training methodology caused robust motor training in both the dominant and non-dominant hand. We suggest that this task provides an appropriate methodology to study changes to excitability in the motor hemispheres.

Future work will focus on identifying the changes of this excitability between the two hemispheres and quantifying the magnitude of this difference to see if one hemisphere has greater changes in excitability following a learning task than the other.

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Manuscript #2

Time-Course Hemispheric Differences to Excitability in the Primary
Motor Cortex Following a Novel Training Task

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Abstract Transcranial magnetic stimulation (TMS) can be used to non-invasively activate the primary motor cortex (M1) of the dominant (dM1) and non-dominant (NdM1) hemispheres (Civardi et al. 2000; Daligadu et al. 2013; Lotze 2003). When elicited between 90-150% of resting motor threshold, the slope of the recruitment-curve can be used as a measure of global motor excitability (Cirillo et al. 2010; Daligadu et al. 2013). To our knowledge however a validated novel complex training task that is equally challenging for both hands, has not been used to investigate differences in modulation of the excitability in the dM1 and NdM1. The right and left hands of 32 right handed participants were tested across two days in 2 different experiments. The first sought to determine whether there were greater motor training induced changes in excitability in one hemisphere than the other. The second experiment was performed to identify the time-course over which these changes took place. In experiment 1 there were similar amounts of highly significant increases in motor performance in both the right ($57\% \pm 12\%$ motor error) and left ($40\% \pm 9\%$ motor error) hands, with a clear difference in excitability change as the right hand significantly decreased while the left hand data returned a non-significant trend of increased excitability. In experiment two significant increases in motor performance were again seen in the right hand ($55\% \pm 10\%$ motor error) while significant decreases to motor excitability was noted on the first day of training only. We conclude that the dominant hemisphere of right handed participants' has a more sensitive response profile to a novel motor training task as no such differences to excitability were seen in those participants who used their non-dominant hand and the majority of the excitability change occurs on the first training day.

Key Terms *Primary Motor Cortex, Novel Motor Training Task, Handedness, Excitability*

Introduction

The primary motor cortex (M1) is involved in dynamically modulating descending motor signals in order to fine tune motor output. The M1 is a dynamic structure with the ability to reorganize itself depending on use-dependant plasticity remodeling the cortical map (Sanes and Donoghue 2000). The result of this reorganization is the basis for neural plasticity with associated synaptic potentiation of neuronal cell populations within the cortical motor structures. These changes are augmented with the use of complex motor training tasks which can require the participant to use either repetitive ballistic (Cirillo et al. 2009; Classen et al. 1998) or less rapid and more accurate (Gallasch et al. 2009) finger movement tasks. Motor training tasks can induce both fast (Muellbacher et al. 2001) and slow (Karni et al. 1998; Koeneke et al. 2006) changes to neural connections within the M1 with rapid onset of motor training and prolonged repetition of a given movement respectively. Fine motor skill of the right and left hands are controlled by the contralateral motor cortices. Typically the anatomical structure of the dominant hand is more developed in both macro and microstructure, resulting in hemispheric motor control differences (Amunts et al. 1996; Rioult-Pedotti and Donoghue 2003; Rioult-Pedotti et al. 1998; Sanes and Donoghue 2000). This hemispheric control is stronger and more developed in the left hemisphere/right hand, and is based on use-dependant plasticity (Butefisch et al. 2000; Ziemann et al. 2004). Hand usage can be classified as hand dominance and hand preference. Hand preference suggests *a priori* contribution to hand selection while hand dominance is a result of life long conditioning (Guiard 1987). Typically motor training methodologies used to study these differences involve tasks that give an advantage to the dominant hand, such as with pegboard tasks or similar reaching tasks (Garry et al. 2004; Przybyla et al. 2012). A novel task which equally challenges both hands, with movements not commonly practiced in daily motor

acquisition, is critical in order to compare changes in motor excitability between dominant and non-dominant hemispheres.

Changes in motor excitability as a result of these motor training tasks can be identified using stimulus response (input-output) curves with single pulse TMS. Stimulus response curves (Cirillo et al. 2010) may be a more appropriate measure of cortical excitability than other methods, such as looking at changes to specific motor evoked potential (MEP) amplitudes from inhibitory or facilitatory mechanisms of cortical refinement (Civardi et al. 2000; Gallasch et al. 2009; Triggs et al. 1999). Stimulus response curves take into account excitability at a number of different stimulation intensities and thus may be a more exact measure of overall excitability compared to other methodologies which rely on changes to MEPs at a single intensity (Daligadu et al. 2013). The resulting linear portion of a stimulus response curve gives a direct indication of the level of excitability within the motor hemisphere (Siebner and Rothwell 2003), with increases or decreases to the slope indicating increases or decrease to excitability respectively. Past research has indicated that the non-dominant hemisphere had increased excitability in comparison the dominant hemisphere demonstrated by comparing the slopes of stimulus response curves (Daligadu et al. 2013), however it not known whether one hemisphere will show a greater change in excitability in response to a complex motor training task which is equally novel for both hands.

Several studies in the past have employed motor training tasks in order to characterise changes to cortical refinement mechanisms, however they are typically gross movements involving multiple muscles and joints (Garry et al. 2004) or movements involving non-skilled ballistic finger movements (Cirillo et al. 2010; Classen et al. 1998). We suggest that a more complex skilled

motor training task which is equally challenging for both the dominant and non-dominant hand is required to validly compare excitability differences between the dominant and non-dominant motor hemispheres' capacity for neural plasticity, in response to a novel motor training task. Only one study to our knowledge has used such a precise training task, however a different training methodology and measure of cortical excitability was used (Gallasch et al. 2009). We recently developed a novel tracing task that varied both amplitude and frequency of a sinusoid to create a task that resulted in significant increases to motor performance for both hands across two days of training. Having developed and validated a task which is sufficiently novel for both hemispheres, we sought to investigate which motor hemisphere (the dominant or the non-dominant) will have a greater modulation of neural excitability, following the training task. In a second experiment, we sought to determine the time-course of neural plasticity onset, indicating which hemisphere has a greater amount of plastic potential. We hypothesized that the dominant hemisphere would have increased ability to modulate excitability levels due to a conditioning effect as a function of dependant plasticity.

Methods

Participants

Testing was completed on 32 naïve right handed males (mean age: 21.9, SD=0.5 years) who took part in one of two experiments. Participants were recruited from the student population at the University of Ontario Institute of Technology (UOIT) which was the site of data collection. Participant exclusion criteria included a history of head injury or the current use of neuro-active medications. Participants also completed a standard TMS safety checklist which included questions on the participant's medical history such as epileptic events and implanted medical

devices. Each participant gave written consent following the explanation of either experiment. Handedness was determined using the Edinburgh Handedness Questionnaire (Oldfield 1971), which ranks handedness on a scale of -100, indicating a strongly left handed participant, to +100, indicating a strongly right handed participant (mean score: 82.22, SD=4.5). To ensure only right handed participants were used a cut off of +60 was defined. Both experiments were approved by the Research and Ethics Board at UOIT and followed the guidelines for human research as detailed by the Declaration of Helenski. All 32 participants completed the experiments and the data was collected by the same researcher.

Experimental Design

Experiment 1 included 20 participants who completed motor tracing task using either their right or left hand. Each participant was randomly placed in either the right hand or left hand group, with 10 participants in each grouping. Each participant completed two days of testing with training sessions being separated by 24 hours (Fig.14).



Figure 14. An illustration of the motor training methodology sequence performed by the right or left hand in Experiment 1. 3 blocks of training were completed on 2 days of training totalling 6 training blocks. Recruitment curves represented the measure of excitability taken before training on the initial session and following training on the second session.

On the first day of training, an initial excitability measure was recorded followed by a motor training session. The second day of training consisted of a motor training session prior to the second motor excitability recording. In Experiment 1 a significant decrease to motor excitability

was only evident in subjects who performed the motor training task with their dominant hand. Based on these findings, a follow up experiment testing only the right hand was performed. Experiment 2 included 12 participants who completed motor training using only their right hand. Each participant completed identical motor training as in Experiment 1 however to characterize changes to the motor hemisphere over a time course of motor training excitability measures were recorded before and after motor training on both the initial and second day of testing (Fig 15).



Figure 15. An illustration of the motor training methodology sequence performed by the right hand in Experiment 2 is shown. Excitability measures were collected through the use of recruitment curves before and after training on both the first and second training sessions.

Motor Training

The participant was seated in front of a desk which held a monitor that presented the tracing task. The participant's arm was bound to the chair's arm rest with Velcro straps to minimize upper limb movement during testing. The participants were instructed to trace a vertical sinusoidal wave using only the index finger on a wireless tracking pad. The participant's virtual movement was limited to a horizontal line, with sine waves moving vertically down the monitor. As the wave-forms would pass the horizontal axis, the participants would attempt to copy the trace using repetitive abduction and adduction of the index finger. Each vertical sinusoidal wave was

composed of colour coded dots to indicate the accuracy of the trace. The horizontal axis that the participant's cursor occupied had a single dot with the same radius as the dots composing the sine waves. Each trial required the participant to constantly adjust velocity and degree of abduction/adduction as the frequency and amplitude changed with each successive sine wave in a given task trial. There were 4 different versions of sine wave trials that had varying levels of difficulty as the degree of frequency and amplitude was different for each one. Each training session required the participants to complete three blocks of each of the four versions, totalling twelve attempts per training session. The order of the task versions in each block was pseudo-randomized prior to the start of the experiments. Each participant completed the same order of task versions as they progressed through the training blocks.

Motor error was characterised by determining the average distance the participant's attempted trace was away from the presented sine wave. If a participant had motor error of 100% they missed the trace by an average of 1 dot, since the cursor they were copying the trace with was of the same radius as the dots composing the sine waves.

Excitability Measures

TMS was applied to the contralateral motor cortex of the selected hand. Prior to data collection a 'hot spotting' technique was used to determine the most appropriate area for stimulation.

Stimulus-response recruitment curves (input-output curves) were collected by stimulating the motor cortex sixteen times per state, of which there were seven, totalling 112 stimulations per TMS recording. Each state represented a different stimulation intensity where 16 stimulations were elicited. The smallest magnetic stimulator output that resulted in 5/10 MEPs of 0.05mV

was first recorded, representing the resting motor threshold (rmt). During the collection of each recruitment curve, 7 states were elicited in a pseudo-randomized order. Each state's stimulation intensity varied by 10% increments from 90%-150% of the baseline rmt. The mean MEP peak-to-peak amplitude was calculated for each pulse intensity.

Data Analysis

The error from each of the 6 motor training blocks (3 on each day of training) was calculated and averaged for the two groups (those who trained the left hand and those who trained the right hand). The first training block completed on the initial day of training was the baseline performance measure. In experiment 1 the effect of motor training was determined by using a 6x2 mixed design ANOVA to categorize the motor training between hand-used populations through the progression of successive trials. Post-Hoc analysis between motor error in each of the 6 blocks were conducted to identify the time-course of motor training and to determine between which blocks significant decreases in motor error occurred. In experiment 2 a repeated measures ANOVA was conducted to identify motor training with successive decreases to motor error throughout the 6 training blocks.

The average MEP amplitude for each of the pulse intensities was individually graphed. The linear portion of the resulting recruitment curves' slope was calculated graphically applying a line of best fit, along with the R^2 in order to define the accuracy of the slope to the linear portion of the curve using Microsoft Excel. The plateau phases were excluded for those participants that had leveling off at the lower (90% rmt) or upper (150% rmt) pulse intensities, and to disregard these plateaus only the slope of the curve from the 100% intensity to 140% intensity was included in the analysis. In experiment 1, a 2x2 mixed design ANOVA was completed with

factors of “hand used” to determine the change in excitability between the pre-training measure on the initial training day and the post-training measure on the second training day of the two groups. In experiment 2, a 4x2 repeated measures ANOVA was completed to identify the change in excitability through the time-course of task progression with 2 days of training using only the right hand.

Results

Experiment 1

Motor Training: The results of motor training are shown by the change in trace error in Fig. 16. For both participant groups there were dramatic decreases in motor error across the blocks of trials. There was no significant difference between the performances of the dominant and non-dominant hands (166% error \pm 8.9% for left hand used, 168% error \pm 11.7% for right hand used). Participants who used their dominant hand had significant amounts of performance gains with a decrease in error of 31% \pm 8% on the first day ($P < 0.05$), and 24% \pm 5% on the second day ($P < 0.001$), totally a net decrease in performance error of 57% \pm 12% ($P < 0.001$). Post-Hoc analysis identified significant amounts of learning between blocks 1 and 2 ($P < 0.05$) on the initial day of training, as well as blocks 4 and 5 ($P < 0.01$) on the second day of training. The participants' motor performance did not increase significantly between the other block trials (Fig. 16). Participants who used their non-dominant hand had significant amounts of performance gains with a decrease in error of 36% \pm 8% on the first day ($P < 0.01$), and 4% \pm 4% on the second day ($P > 0.05$), totally a net decrease in performance error of 47% \pm 9% ($P < 0.001$) in the non-dominant hand. There were significant amounts of learning between blocks 1 and 2 ($P < 0.01$) as well as 2 and 3 ($P < 0.01$) on the initial day of training, with

no significant decreases in motor error between blocks on the retention day of testing (Fig. 16). Overall, there was no significant difference in the amount of motor training between the dominant and non-dominant hand ($F(1,18) = 1.013, p=0.415$).

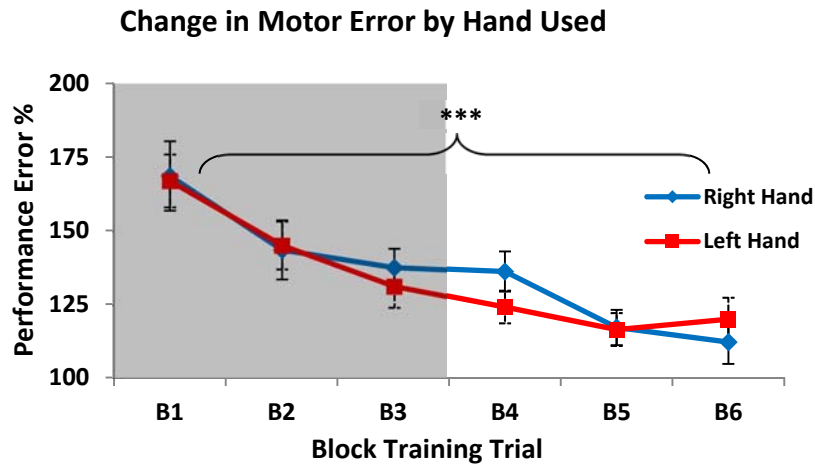


Figure 16. Effects on performance error from motor training in the right hand-used (triangular markers) and left hand-used (square markers) across two training sessions. The initial training session is shown with the shaded area with a rest period between ‘B3’ and ‘B4’ of 24 hours. ‘***’ indicates $p < 0.001$ for both hand-used samples.

Excitability Measure: In experiment 1, recruitment curves were collected prior to motor training on the initial session and following motor training on the retention session. Excitability decreased in participants who used their dominant hand to complete the motor training, while there was a non-significant trend of increased excitability in participants who used their non-dominant hand (Fig 17). The main result indicated an interaction between change in excitability and hand used ($F(1,18) = 5.239, p < 0.05$), as the right hand had a significant decrease in excitability ($P < 0.05$) while there was no significant change to the excitability of the left hand.

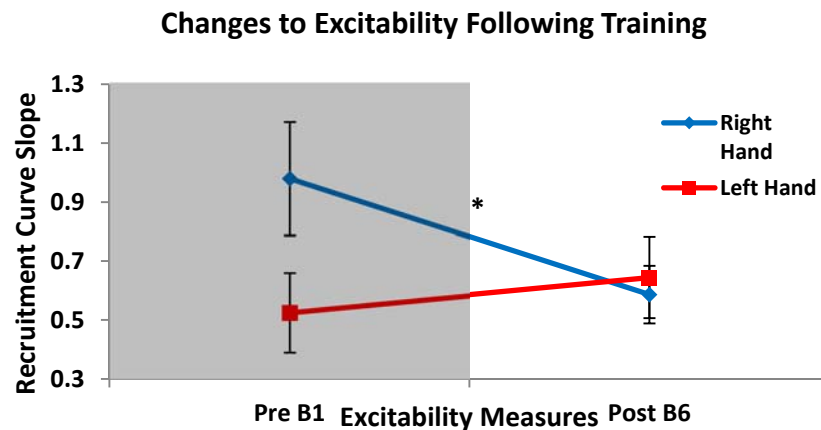


Figure 17. Changes to excitability during two measures in Experiment 1 are shown. ‘*’ indicates $p < 0.05$ for the right hand-used sample only. The shaded area represents the first day of training where the time between ‘Pre B1’ and ‘Post B6’ is the training period where subjects would complete B1-B3 on the initial day of training and B4-B6 on the second day of training.

Experiment 2

Motor Training

The effect of motor training is shown as a decrease of performance error across block trials, as shown in Fig. 18. Participants’ had significant decreases in motor performance during both the initial ($31\% \pm 7\%$ error decrease, $p < 0.001$) and retention ($19\% \pm 6\%$ error decrease, $p < 0.01$) days of training using only the dominant (right) hand. The dominant hand had continued learning throughout each training session with significant decreases in motor error between training blocks 1 and 2 ($p < 0.05$), as well as 4 and 5 ($p < 0.01$). Overall the dominant hand had a decrease in performance error of $55\% \pm 10\%$ ($F(1,11) = 35.170$, $p < 0.001$).

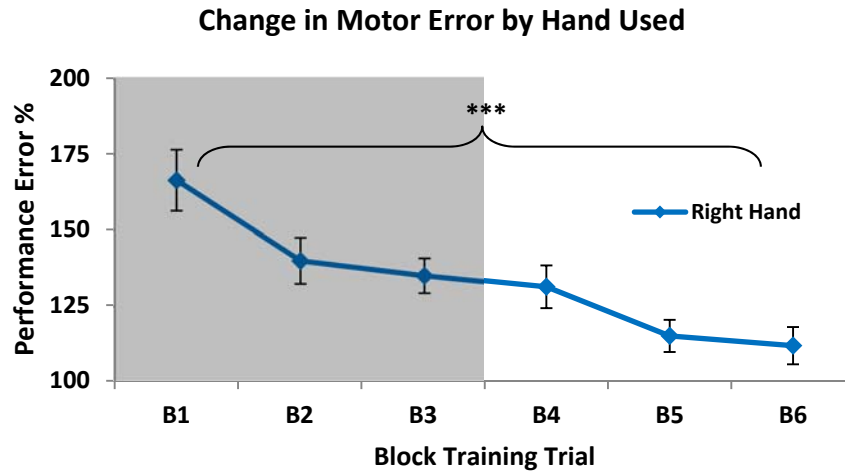


Figure 18. Effects on performance error from motor training for the right hand-used sample of Experiment 2. ‘***’ indicates $p < 0.001$. The shaded area represents the first day of training, with 24 hours between ‘B3’ and ‘B4’.

Excitability Measure

Decreases in excitability of the dominant hand of right handed participants are shown as decreases in the slope of associated recruitment curves as displayed in Fig. 19. Excitability decreased significantly across both training blocks ($F(1,11) = 5.693, p < 0.05$). The changes to excitability as a result of the time-course motor training demonstrated that only the first day of training had a significant decrease in excitability ($p < 0.01$), with this decreased excitability being sustained between the end of the initial day of testing and the beginning of the retention day of testing. Even though there was a noticeable decrease in excitability on the second day of motor training no significant relationship was found.

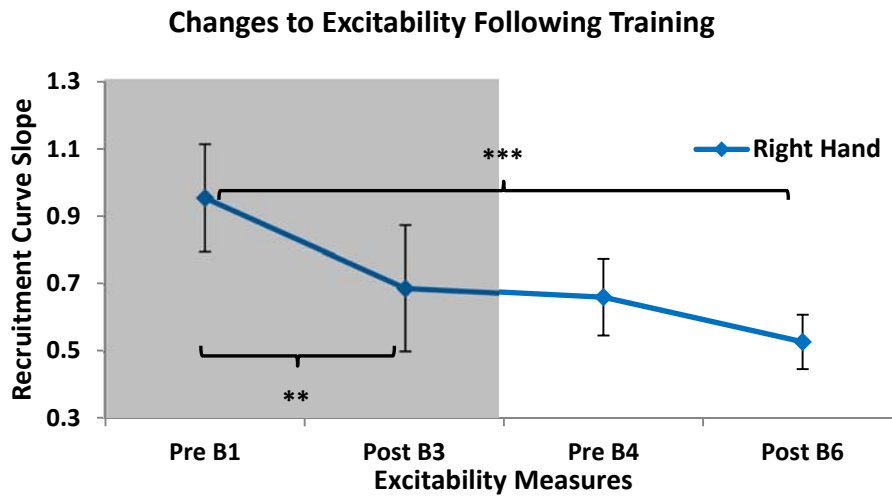


Figure 19. Changes to excitability through 4 measures. Excitability was recorded prior to and after the training sessions on both the first and second days of training. ‘*’ and ‘***’ indicates $p < 0.05$ and $p < 0.001$ respectively. The shaded area represents the first day of motor training. Subjects completed 3 blocks (B1-B3 on the initial day and B4-B6 on the second day) between the ‘pre’ and ‘post’ measures. The time between ‘Post B3’ and ‘Pre B4’ was a 24 hour rest period.

Discussion

Use-dependant plasticity, a function of hand dominance in day-to-day usage (Guiard 1987), contributes to the fundamental differences between the dominant and non-dominant motor hemispheres in their ability to refine hand movements. The dominant hemisphere of right handed males has an increased capability for motor refinement compared to the non-dominant hemisphere, and this is well documented in the literature (Amunts et al. 1996; Rioult-Pedotti and Donoghue 2003; Sanes and Donoghue 2000; Volkman et al. 1998). However it is less commonly researched which hemisphere has a greater potential for motor plasticity as well as which hemisphere has a quicker onset of adaption to the magnitude of motor refinement. In this study we looked at introducing a novel skilled training task to a group of naïve right handed

males to determine the effect that motor training has on hemispheric excitability, as well as the time-course over which these changes occur.

In the first experiment both groups had significant improvements in performance in response to 6 blocks of training with no difference between the hand-used in the decrease in motor error across both training sessions. Studies using motor training tasks have had varying amounts of increased performance with some tasks causing different performance gains between the two hands (Bagesteiro and Sainburg 2002; Przybyla et al. 2012; Sainburg and Kalakanis 2000) while some had similar amounts of performance gains in the two hands (Gallasch et al. 2009; Garry et al. 2004). However, several of these tasks are not novel and include movement patterns more frequently used by the dominant hand which may be contributing to varying amounts of performance gains between the dominant and non-dominant hemispheres (Przybyla et al. 2012; Sainburg and Kalakanis 2000). A similar decrease in motor error between the two samples presented in this study confirm findings from our previous work in suggesting that a highly skilled dynamic tracing task is equally as difficult for both the dominant and non-dominant hands in highly lateralized right handed males. In order to identify different amounts of corticomotor excitability in the two motor hemispheres a task that equally strains both hands is required to prevent bias due to the more commonly used dominant hand being more developed through daily use-dependant plasticity.

In the first experiment the corticomotor excitability was measured at baseline on day one and following completion of motor training on day two, when the training was carried out over two consecutive days. Only those participants who performed the training with their right hand had significant excitability changes with the right hand-used group having a decrease in excitability between the two measures. This is contradictory to findings of past studies as it has been well

established that MEP amplitude increases following motor training (Gallasch et al. 2009; Garry et al. 2004; Smyth et al. 2010), suggesting motor training increases excitability. However we argue our methodology of measuring excitability, using recruitment curves, is a better method of determining global hemispheric excitability as it takes into account several different stimulation intensities. Looking at changes to MEP amplitudes typically only uses a single level of stimulation, and is commonly used to investigate motor excitability (Gallasch et al. 2009; Garry et al. 2004; Smyth et al. 2010). This method may provide insights into more focal excitability levels as it does not take into account changes to alternative motor neuron populations, which require different stimulation intensities, which may contribute to the global excitability of the motor hemisphere. Other studies using recruitment curve excitability measures, such as the one used in the current study, found increases to excitability which contradicts our findings (Lotze 2003; Perez et al. 2004). We suggest that part of this confusion is in part due to variance in the types of motor training tasks and methodologies as these studies adopt movements more typically used with the dominant hand.

In the current study, even though no significant changes to excitability occurred on the second training session, it is important to consider changes that occur through the ‘consolidation phase’ which is the hours following the training of a new task (Karni et al. 1998; Rosenkranz et al. 2007). We categorize this phase as the time between the end of the first training session and the start of the second training session. This phase allows the motor hemispheres’ to associate the requirements of performing a new task with the abilities of the neural network in order to minimize performance error during successive trials (Karni et al. 1998). In Experiment 1 there was a significant increase to motor performance for the group that trained with the left hand during the consolidation phase. In Experiment 2 there was no significant change to motor

performance during the consolidation phase of the group that trained with the right hand. For Experiment 2, there was no significant change in motor excitability during the consolidation phase, suggesting that modulation to motor excitability is maintained for at least 24 hours. Additional days of testing would indicate if the motor-adaption is sustained for longer than this time.

Based on the results of Experiment 1, we sought to identify the time-course of excitability modulation in a right hand-used sample with Experiment 2. Motor training identified a significant decrease in motor error similar to Experiment 1, with no significant difference between the amounts of motor training in the two experiments. The motor excitability changed similar to experiment 1 with a significant decrease in excitability between the initial measure on the first day and the final measure on the second day. The time-course measures identified that only during the initial training day was there a significant decrease in excitability, as there was a trend of further decrease to excitability on the second day of training though no significant relationship was found. This may indicate that motor plasticity, and the resulting decrease in corticomotor excitability, is an effect of rapid learning. Rapid learning is the initial onset of learning a new motor skill during the first training session (Karni et al. 1998; Kleim et al. 2004). Rapid learning is the process by which the most efficient route of neural connections is determined when performing a new task (Karni et al. 1998). Adaptions to the current neuronal structures have been suggested to adapt from long term potentiation (LTP) like changes during this phase (Rosenkranz et al. 2007). This precedes slow learning which may cause the formation of new neuronal networks throughout the corticomotor hemispheres (Kleim et al. 2004), which is associated with synaptogenesis (Rosenkranz et al. 2007). The finding of changes to only the dominant motor hemisphere suggests that the dominant hand had a more reactive motor profile

compared to the non-dominant hand, and that adaption to motor plasticity is dependent on day-to-day conditioning. This has implications with respect to LTP-like changes associated with the earlier phases of motor training (Rosenkranz et al. 2007), and may suggest an association with motor plasticity being a function of rapid changes to current neural structures as no significant change to excitability was seen on the second day. However, in order to identify changes to later phases of learning, causing synaptogenesis (Kleim et al. 2004), more than two training sessions may be required. Based on previous research, five days of motor training may be sufficient to result in new synaptic connections within the motor hemisphere (Rosenkranz et al. 2007). We suggest that continued significant modulation of global motor excitability beyond two days of training may indicate synaptogenesis in the motor hemisphere(s) as adaption to motor excitability within a 2 day time frame, as presented in the current study, may suggest LTP-like changes to current neuron connections.

In behavioural context we would also suggest that analysis and further discussion adopting a dynamical systems theoretical orientation coupled with a mathematical modelling approach may offer insight into the focal patterns of how these systems constantly adapt and influence the dynamic physiology of the underlying internal cortical reorganization (Kelso 1991; Kelso 1997; Schoner and Kelso 1988). This dynamic reorganization initiated by the motor training task employed in this study involve the interaction s of both open and closed systems, as well as discrete and continuous movements. Though outside the scope of the current work these systems and the effect they have on motor training and resulting neuron-excitability require further investigation to determine the effect of intra-training phase transitions of sinusoidal tracing on motor excitability.

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Thesis Summary and Conclusions

The excitability differences between the dominant and non-dominant hemispheres have been established in past literature; however the relationship between the strength of plasticity between these hemispheres has not been answered. Typically motor training tasks that have not been validated to be novel in functional performance are used, or a measure of excitability is adopted which we argue is not appropriate to categorize global excitability measures. Here two studies were performed in order to validate a tracing task using only the index finger in highly skilled repetitive abduction/adduction movements during two days of motor training. It was questioned which hemisphere had stronger potential for plastic modulation of the motor hemisphere's refinement mechanisms as well as the time course over which these changes took place.

In the first study a novel tracing task was confirmed to be non-fatiguing and resulted in significant increases to motor performance over both initial and retention days of testing in the dominant and non-dominant hands of healthy right handed males. The finding of no interaction between time-course effects of increased motor performance and hand-used sample indicated that the implemented training task was indeed novel and would be appropriate to use in further study of motor plasticity and lateralized motor excitability.

The second research project confirmed findings from the first project suggesting a robust training task capable of consistent training effects with a reproducible increase to motor performance.

The dominant hemisphere was identified to have a significant decrease to motor excitability while no change to the non-dominant hemisphere was noted. This suggests that the dM1 has a greater potential for plastic modulation that may be a function of the lateralized conditioning effect attained through life long use-dependant plasticity. The second research project also

detailed that only the first day of training resulted in significant alteration to the motor excitability profile as the second day of training had a similar trend of decreased excitability however no significant trend was found. This finding suggests these early changes to motor excitability are a function of fast learning with rapid changes to current neural structures in consolidating the demands of the new motor training task, and that this effect is not sustained during a second training session.

Based on the reproducibility and robust increase to performance we suggest further studies using training tasks employ a complex repetitive tracing task using a single joint such as the one outlined here. Future work may also build on the highly significant findings of this work with identifying changes to motor excitability over several days of training in order to quantify changes to neural processes over slow learning phases.

SECTION III: APPENDICES

Appendix #1: Written Consent Form



Associate Professors Paul Yielder & Bernadette Murphy
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Research Information for Participants

Title: *Cortical Adaption Influences Excitability In the Dominant and Non-Dominant Hands Following Complex Novel Motor Training*

Research is taking place in the University of Ontario Institute of Technology Neurophysiology and Motor Control Laboratory, and is being conducted by Dr. Paul Yielder, Dr. Bernadette Murphy and MHS candidate Luc Holland. We are investigating how motor training and learning tasks alters neurophysiological function in the central nervous system. In order to do so we will need to collect some information on how the brain and associated structures control hand muscles both before and after a motor training task. We will also get you to complete some questionnaires, which will provide information regarding your current state of health and on your handedness.

You are invited to participate in our research and we would appreciate any assistance you can further offer us. Your participation in this study is entirely voluntary (your choice) and you are free to decline taking part in this study. You may also withdraw from the study at any time without giving a reason. This will in no way affect your academic progress (if applicable) and/or any benefits you may receive from the testing. We are seeking people who are in good and normal health and who have no known associated neurophysiological disorders, and are between the ages of 18 and 35. To participate in this study you must complete an eligibility checklist in conjunction with one of the researchers, to ensure you are eligible to participate in this research. You will also need to complete a TMS safety checklist.

Measurement Sessions

Should you agree to participate you will only need to attend a single evaluation session. During the evaluation session we will collect some information about the way your brain is controlling a distal hand muscle. To do this it will be necessary to place some electrodes over the investigated muscle to record the signals from your brain to the muscle. You may experience some mild discomfort as your skin is prepared for the electrodes by rubbing them with special abrasive tape, or shaving the hand with a disposable razor, and then wiping the area with alcohol. It is important to note that these are recording electrodes only and do not pierce the skin nor run current through the body. The stimulation will only be over the scalp. Occasionally, some people experience mild, transient nausea or scalp and neck discomfort, due to the

activation of the scalp muscles by the stimulator. If you feel uncomfortable at any time during the experiment please notify the experimenter. Each evaluation session will take about 2-3 hours and you will be given feedback about your results following the procedure.

Risks and Benefits

The benefits of this study will be that you will be contributing to our understanding of how the brain and associated structures aids in the control of bodily movement. You will also further our knowledge of how motor training tasks can evoke cognitive learning, and how this subsequently affects the neural system. The surface EMG techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these are uncommon and not serious. Magnetic stimulation is a safe procedure that allows us to study the nerve pathways that go to the muscles of the hand. The stimulator produces a clicking sound and then a mild twitching feeling can sometimes be felt in the scalp muscles as well as the hand muscles. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the stimulation. Some people may also experience nausea or a mild headache. Both these reactions are uncommon and not serious. We recommend that students having any strong reaction or skin irritation, or strong headache contact the researchers and also go to campus health services if you are really concerned or you need medication to deal with the discomfort. Certain people such as those with epilepsy, metal plates in their skull or prior brain surgery are not suitable candidates for magnetic brain stimulation, and this will be determined through the use of a screening questionnaire prior to your participation in this aspect of the study. Because the magnetic field discharges so quickly there is far less electromagnetic radiation than that from a television or mobile phone. At any time during the experiment, at your request we will stop the stimulation immediately.

If the information you provided is reported or published, it is done in a way that does not identify you as its source. The data will be stored in a password protected computer, which will be located in a locked room for 10 years from the completion of the study after which it will be destroyed. You are free to withdraw from the data collection at any time during the testing procedure. Taking part in this study is voluntary and your decision to take part in this study (or not) will in no way influence your relationship with your teacher.

Thank you very much for your time and help in making this study possible. If you have any queries or wish to know more please contact Dr. Bernadette Murphy, an associate professor at the University of Ontario Institute of Technology, Faculty of Health Sciences, 2000 Simcoe St North, Oshawa, Ontario L1H 7K4, phone (905) 721-8668 ext. 2778, fax (905) 721-3179.

For any queries regarding this study, please contact the UOIT Research and Ethics Committee Compliance officer (compliance@uoit.ca and 905-721-8668 ext. 3693).

The data from this research will be submitted to scientific conferences and peer reviewed journals. At the completion of the study you will be sent a summary of the research findings and any place where the data has been published. All published data will be coded so that your data is not identifiable.

Please read the following before signing the consent form and remember to keep a copy for your own records.

- I understand that taking part in this study is voluntary (my choice) and that I am free to withdraw from the study at any time without giving reason and that this will in no way affect my academic progress, irrespective of whether or not payment is involved.
- This consent form will be kept in a locked filing cabinet at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.
- The data collected in this study will be kept in a password protected computer, at UOIT, Oshawa Ontario for a period of ten years before being destroyed.

I, agree to take part in this research.

- I have read and I understand the information sheet dated September 2011 for volunteers taking part in the study designed to investigate the neurophysiological effects of motor learning and training. I have had the opportunity to discuss the study. I am satisfied with the answers that have been given.
- I will be attending one session where measurements will be taken of the electrical activity in my hand muscles following magnetic stimulation of my brain
- I have completed an eligibility checklist to ensure I am eligible to participate in this research.
- I have completed a TMS safety checklist.
- I understand that I can withdraw any data I supply up to the completion of the end of the measurement session.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I have had time to consider whether to take part.
- I know who to contact if I have any side effects to the study.
- I know who to contact if I have any questions about the details of the study.

I give consent for the data from this study to be used in future research as long as there is no way that I can be identified in this research.

YES

NO

Signed.....

Date.....

SECTION COMPLETED BY RESEARCHER ONLY

Project Explained by:

Project Role:

Signature:

Date:

Appendix #2: TMS Safety Checklist

TMS safety checklist:

The following questions are to ensure it is safe for you to have TMS applied. If you answer yes to any of the questions below, we may need to exclude you from TMS experiments.

QUESTION	ANSWER	
	Yes	No
1. Do you suffer from epilepsy, or have you ever had an epileptic seizure?		
2. Does anyone in your family suffer from epilepsy?		
3. Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings)		
4. Do you have an implanted medication pump?		
5. Do you wear a pacemaker?		
6. Do you suffer any form of heart disease?		
7. Do you suffer from reoccurring headaches**?		
8. Have you ever had a skull fracture or serious head injury?		
9. Have you ever had any head surgery?		
10. Are you pregnant?		
11. Do you take any medication or use recreational drugs (including marijuana)*?		
12. Do you suffer from any known neurological or medical conditions?		

Comments _____

Name _____

Signature _____

Date _____

*Note if taking medication or using recreational drugs please read through the medication list on the next page to see if you use contraindicated drugs or medications. You do not need to tell the researcher which medications or drugs you use, unless you wish to. However, all researchers have signed confidentiality agreements and this information will not be recorded in writing, if you do wish to discuss this issue.

**Dr. Murphy will meet with participants who answer yes to this question to seek further information.

Medications contraindicated with magnetic stimulation:

1) Tricyclic antidepressants

Name	Brand
amitriptyline (& butriptyline)	Elavil, Endep, Tryptanol, Trepiline
desipramine	Norpramin, Pertofrane
dothiepin hydrochloride	Prothiaden, Thaden
imipramine (& dibenzepin)	Tofranil
iprindole	-
nortriptyline	Pamelor
opipramol	Opipramol-neuraxpharm, Insidon
protriptyline	Vivactil
trimipramine	Surmontil
amoxapine	Asendin, Asendis, Defanyl, Demolox, Moxadil
doxepin	Adapin, Sinequan
clomipramine	Anafranil

2) Neuroleptic or Antipsychotic drugs

A) Typical antipsychotics

Phenothiazines:	Thioxanthenes:
o Chlorpromazine (Thorazine)	o Chlorprothixene
o Fluphenazine (Prolixin)	o Flupenthixol (Depixol and Fluanxol)
o Perphenazine (Trilafon)	o Thiothixene (Navane)
o Prochlorperazine (Compazine)	o Zuclopenthixol (Clopixol and Acuphase)
o Thioridazine (Mellaril)	<input type="checkbox"/> <input type="checkbox"/> Butyrophenones:
o Trifluoperazine (Stelazine)	o Haloperidol (Haldol)
o Mesoridazine	o Droperidol
o Promazine	o Pimozide (Orap)
o Triflupromazine (Vesprin)	o Melperone
Levomepromazine (Nozinan)	

B) Atypical antipsychotics

Clozapine (Clozaril)	Quetiapine (Seroquel)
<input type="checkbox"/> <input type="checkbox"/> Olanzapine (Zyprexa)	<input type="checkbox"/> <input type="checkbox"/> Ziprasidone (Geodon)
Paliperidone (Invega)	<input type="checkbox"/> <input type="checkbox"/> Amisulpride (Solian)
<input type="checkbox"/> <input type="checkbox"/> Risperidone (Risperdal)	

C) Dopamine partial agonists: Aripiprazole (Abilify)

D) Others

Symbyax - A combination of olanzapine and fluoxetine used in the treatment of bipolar depression.

Tetrabenazine (Nitoman in Canada and Xenazine in New Zealand and some parts of Europe

Cannabidiol One of the main psychoactive components of cannabis.

Regular Cannabis use more often than once per week and/or cannabis use in the past 4 days.

Regular use of other recreational drugs, or single episode within the past three weeks.

Appendix #3: Edinburgh Handedness Inventory

Edinburgh Handedness Inventory

Please indicate your preference in the use of hands in the following activities *by putting a check in the appropriate column*. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, *put 2 checks*. If in any case you are really indifferent, *put a check in both columns*.

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted to indicated in parentheses.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

Task	Left		Right	
1. Writing				
2. Drawing				
3. Throwing				
4. Scissors				
5. Toothbrush				
6. Knife (without fork)				
7. Spoon				
8. Broom (upper hand)				
9. Striking match (match)				
10. Opening box (lid)				
Total (count checks in both columns)				

Difference	Cumulative TOTAL	Result

Scoring:

Add up the number of checks in the 'Left' and 'Right' columns and enter in the "TOTAL" row for each column. Add the left total and right total and enter in the "Cumulative TOTAL" cell. Subtract the left total from the right total and enter in the "Difference" cell. Divide the "Difference" cell by the "cumulative TOTAL" cell (round to 2 digits if necessary) and multiply by 100; enter the result in the "Result" cell.

Interpretation (based on Result)

below -40 = left-handed
 between -40 and +40 = ambidextrous
 above +40 = right-handed