

IMPACT OF EXPIRATORY MUSCLE STRENGTH TRAINING ON CORTICAL
EXCITABILITY OF THE LATERAL ABDOMINAL MUSCULATURE

By

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To my parents Shanta and Shanker Chhabra, who have always encouraged me to follow my dreams

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Strength gains in skeletal muscles typically occur within the first few weeks of exposure to an overload stimulus and have been associated with changes within the central nervous system. Documented neural adaptive changes following strength training include increased motor unit firing rate, reduced motor unit recruitment threshold, maximum surface EMG amplitude and area, as well as decreased agonist-antagonist co-activation. Increased corticospinal drive has been suggested as the underlying neural mechanism supporting these adaptations. However, evidence supporting cortical involvement in these adaptations is inadequate. This study specifically explored the cortical adaptations in response to an expiratory muscle strength training (EMST) stimulus in 10 healthy adults between 19-31 years. Transcranial magnetic stimulation (TMS) was used to examine the cortical adaptations in response to 4 weeks of EMST. In the present study, cortical excitability measures of active motor threshold (AMT) and input output (IO) curve slope were found to be reproducible across three baseline sessions. EMST resulted in a significant reduction in AMT. No significant change in IO curve slopes was found following EMST. These findings indicate changes in cortical excitability to the lateral abdominal wall muscles following 4 weeks of EMST.

CHAPTER 1

INTRODUCTION AND REVIEW OF THE LITERATURE

Introduction

This study established the test-retest reliability of cortical excitability measures including active motor threshold (AMT) and input output (IO) curves for the lateral abdominal wall muscles and the impact of expiratory muscle strength training (EMST) on these measures using transcranial magnetic stimulation (TMS). To date, little documentation exists of the cortical adaptations associated with expiratory muscle activity, particularly as a function of a treatment paradigm that focuses on expiratory muscle recruitment as its target. The following sections discuss bulbar and cortical control of abdominal muscles, activation of abdominal muscles in forced expiratory tasks, abdominal muscle weakness and the rehabilitation tools used to intervene with abdominal muscle weakness, neurogenic adaptations in response to strength training, TMS and its use in the study of adaptations following EMST.

Bulbar and Cortical Control of the Abdominal Muscles

The caudal portion of the ventral respiratory group or the ventral respiratory group-expiration (VRG-E) in the brainstem contains neurons that project to the abdominal motor neurons. These neurons control expiratory functions of abdominal muscles as they discharge during the expiratory phase of respiration (Bongianni, Corda, Fontana, & Pantaleo, 1994; Miller, Bianchi & Bishop, 1997; Miller, Ezure, & Suzuki, 1985; Miller, Tan, & Suzuki, 1987). There is some evidence supporting the existence of large projections from the VRG-E to the lumbar portion of the spinal cord but there are only a few direct monosynaptic connections between VRG-E and abdominal motoneurons (Miller, Ezure & Suzuki, 1985). VRG-E terminals most commonly synapse on the spinal interneurons and are therefore thought to be a seat for segmental, intersegmental and suprasegmental inputs directing the output of the abdominal motor neurons.

VRG-E firing is controlled through many inhibitory bulbar neurons including the pre-Botzinger complex which is a part of the VRG and participates in respiratory rhythm generation (Miller et al., 1997).

Many areas of the brain including the premotor cortex, motor cortex, cerebellum, hypothalamus and pons project to the VRG-E and spinal abdominal motoneurons (Miller et al., 1997). The cortex controls the abdominal motor neuron output via two main crossed pathways: the corticospinal and corticorubrospinal tracts. It is thought that voluntary control of abdominal muscles for tasks like prolonged speech, playing wind instruments, and volitional cough is cerebral (Ramsay et al., 1993). There is clinical evidence that automatic and voluntary expiration have two separate descending pathways (Miller et al., 1997). Evidence for involvement of specific cerebral structures in volitional expiration has mainly come from studies employing direct electrical stimulation or transcranial electrical stimulation (TES), TMS, fMRI and positron emission tomography (PET) (Loucks, Poletto, Simonyan, Reynolds, & Ludlow, 2007; Maskill et al., 1991; Plassman & Gandevia, 1989; Ramsay et al., 1993; Tunstill et al., 2001).

Using PET scans during expiration against an expiratory threshold load, Ramsay et al., (1993) showed increased regional cerebral blood flow in both motor cortices just lateral to the vertex, both motor cortices in ventrolateral portion, supplementary motor area, right lateral pre-motor cortex, ventrolateral thalamus bilaterally, and in the cerebellum. Voluntary expiration is associated with activation of larger areas compared to voluntary inspiration. This large activation across the cortex may be associated with preparatory activation for previously learnt, frequently occurring, precise tasks such as phonation (Ramsay et al., 1993) and voluntary cough. In fact, Loucks et al. (2007) used an fMRI study to document an extensive overlap in the brain regions (left primary sensorimotor regions and frontal operculum, bilateral insula and thalamus and right

supramarginal gyrus) controlling expiration and rapid changes in voice onset and offset during speech. Furthermore in a recent fMRI study, Simonyan, Saad, Loucks, Poletto, & Ludlow (2007) reported that both voluntary respiration and voluntary cough result in a widespread pattern of sensorimotor activation along the Sylvian fissure whereas with voluntary cough there is specific activation of ponto-mesencephalic region. Some studies have also shown a predominance of left hemisphere activation in the inferolateral sensorimotor cortex during expiratory tasks (Loucks et al., 2007; Ramsay et al., 1993) while others have not found similar hemispheric bias for expiration (McKay, Evans, Frackowiak, & Corfield, 2003). Therefore, it is not clear whether there is a hemispheric influence on expiratory tasks.

Corticospinal control of the external obliques (Fujiwara, Sonoda, Okajima, & Chino, 2001), internal obliques (Strutton et al., 2004), Transverse abdominis (Tsao, Galea, & Hodges, 2008) and the rectus abdominis (Tunstill et al., 2001) muscles has a strong ipsilateral component relative to limb muscles. Also, in the external and internal oblique and transverse abdominis muscles there appears to be a hemispheric asymmetry in corticospinal projections with a bias towards either the left or the right hemisphere (Fujiwara et al., 2001; Strutton et al., 2004; Tsao et al., 2008). However, TES and TMS studies in both abdominal muscle groups (Plassman & Gandevia, 1989; Tsao et al., 2008; Tunstill et al., 2001; Walker et al., 1997) have helped establish that contralateral pathways are stronger with shorter response latencies compared to ipsilateral connections. Therefore, even though abdominal muscles receive more ipsilateral input than limb muscles both are similar in that the primary input in both cases is contralateral.

Supporting Evidence of Abdominal Muscle Representation in the Human Brain

Foerster (1936) reported that within the motor cortex the abdominal muscles are represented in the vicinity of the diaphragm. Since then, studies employing direct electrical stimulation of the cortex as well as TMS have documented the location of representation as well

as the properties of the connections from the motor cortex to the abdominal muscles. Using TES, Plassman & Gandevia (1989) studied the motor cortical projection output to the abdominal muscles and showed that the abdominal muscle response latencies were comparable to those for limb muscles. These response latencies using TES were 13.9ms for oblique muscles with surface electrodes placed on the lateral abdominal wall and 16.0 ms for the rectus abdominis muscle (Plassman & Gandevia, 1989). This study explored the impact of static contraction of varied strengths ranging from 0 to 100% maximum voluntary contraction (MVC) on response latency and surface electromyography (sEMG) response amplitude. Background contraction of 10-20% MVC using trunk flexion, loaded expiration and expulsive efforts resulted in the shortest latencies while contractions of 60% MVC had the highest amplitude. These findings support the existence of a rapidly conducting pathway from the motor cortex to the abdominal muscles in humans and draws similarities between the corticospinal connections to the abdominal musculature with those to the distal upper extremity muscles. Therefore, in conjunction with some previous evidence that cortical stimulation inhibits bulbospinal respiratory neurons (Lipski et al., 1986), Plassman and Gandevia's (1989) study showed that response latencies to abdominal muscles are short and thus no mediating input from pontomedullary respiratory centers is received in case of cortically evoked responses in abdominal muscles. In terms of anatomical localization of abdominal muscles in the motor cortex, this study (Plassman & Gandevia, 1989) also documented vertex and the surrounding area as the most excitable sites for abdominal muscle representations.

Walker et al. (1997) conducted the first TMS study documenting the corticospinal connections between the motor cortex and rectus abdominis muscles. In this study, EMG recordings were made from both the right and left rectus abdominis muscles in response to TMS

during facilitation using expiratory resistance. Based on these findings, the site for rectus abdominis muscle representation was located 2cm lateral and 2cm anterior to the vertex. This study also confirmed that the optimal coil placement for the largest MEP in rectus abdominis muscles was anterior or anterior-medial which is similar to that in hand muscles.

Plassman and Gandevia (1989) speculated that the direct connections between motor cortex and these muscles may be attributable to the need for frequent and rapid adjustments made in abdominal musculature during speech tasks. It is also important to note that there exist task dependent differences in corticospinal input in abdominal muscles. According to Tunstall et al., (2001) there is greater facilitation during trunk flexion tasks indicating an increase in corticospinal drive in comparison to forced expiration tasks. This finding has been attributed to the possibility of extrapyramidal inputs from bulbospinal tracts during forced expiration tasks. Thus, it is likely that forced expiratory tasks may be associated with some bulbospinal input in addition to corticospinal input to rectus abdominis muscles.

Abdominal Muscle Activation during Forced Expiratory Tasks: Speech and Cough

Abdominal wall muscles are the principle muscles involved in active expiration along with subcostal muscles, transverse thoracis, serratus posterior inferior, quadratus lumborum, and latissimus dorsi muscles which play a secondary role. In general, muscles of active expiration upon contraction reduce thoracic cavity volume by contracting in anterior-posterior and transverse dimensions of the chest wall by lowering of the rib-cage and or the sternum (Hixon, 1991). This action causes an increase in abdominal pressure that in turn forces the diaphragm upwards resulting in a reduction of the thoracic volume/dimensions.

The relationship between the lung volume, relaxation pressure, alveolar pressure and muscular effort is important for understanding the role of the expiratory muscles primarily the abdominal musculature in speech generation. Relaxation pressure refers to the pressure that is

generated by non-muscular forces in the respiratory system (Agnosti & Mead, 1964; Hixon, 1991). While the respiratory muscles are relaxed, varying levels of relaxation pressure is developed in the airways and is determined by the extent to which the lung volume is above or below the resting expiratory level. When the lung volume levels exceed the resting expiratory level, relaxation results in production of positive alveolar pressure associated with passive expiration. Whereas, when lung volume level is less than resting expiratory level, relaxation produces alveolar pressures that lie below the atmospheric pressure level (Hixon, 1991). At the mid-lung volume levels (~35 – 50% vital capacity), there is a somewhat proportional change in relaxation pressure with lung volume. On the other hand, there is a greater stiffness in the lungs at higher lung volumes and the thorax at low lung volumes resulting in abrupt changes in relaxation pressures at both high and low lung volumes (Agostoni & Mead, 1964; Hixon, 1991). At a given lung volume, activation of various respiratory muscles allows for the attainment of alveolar pressures that differ from the relaxation pressure (Mead, Bouhuys, & Proctor, 1968). To attain a given alveolar pressure, the need for “net” inspiratory versus expiratory muscular effort is determined by the relaxation pressure. Inspiratory muscular activation is needed to achieve desired alveolar pressures that lie below the relaxation pressure whereas expiratory muscular effort is required to attain alveolar pressures higher than the relaxation pressure.

The relaxation pressure curve (Agostoni & Mead, 1964) in Figure 1-1 is useful in understanding the relationship between lung volume and the associated alveolar pressure needed for speech production at different loudness levels and with prolonged speech. In order to meet the demands of prolonged speech production, a desired level of alveolar pressure needs to be maintained (average = ~7 cm H₂O for utterances of normal loudness). As the lung volume drops expiratory muscular forces are recruited to help maintain the desired alveolar pressure levels

(Hixon, 1991). Once the lung volume reaches a level below resting expiratory level, expiratory muscles are always active.

Functional residual capacity or FRC is commonly defined as the lung volume level after a normal expiration/exhalation. However, FRC cannot be measured directly and can only be best estimated using a gas/helium dilution method or a body plethysmography (West, 1995). End expiratory volume level (EEL) can be used as an approximate measure of FRC as two measures closely approximate during rest breathing.

During loud speech production when the alveolar pressures required are greater than those required for speech production at normal and soft loudness levels, expiratory muscle effort enables the generation of large expiratory pressures (Hixon, 1991) at lung volumes where relaxation pressure falls below the alveolar pressure needed for the desired loudness level. In fact, it has been widely documented that during speech, abdominal muscles are most commonly recruited with increased loudness levels and when speech is generated at low lung volumes (Draper et al., 1959; Hoit et al., 1988; McFarland & Smith, 1989).

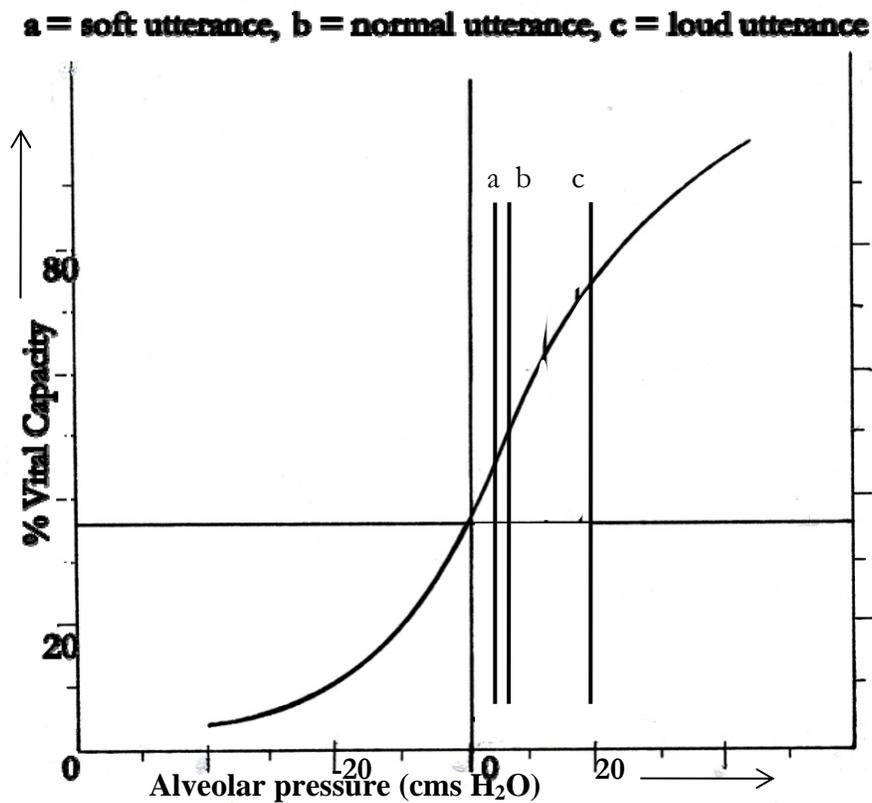


Figure 1-1: Depiction of lung volume and alveolar pressure during relaxation and during vowel production at different loudness levels through various levels of vital capacity (VC). In this figure a = soft utterance, b = normal utterance, and c = loud utterance.

In fact, there is evidence that abdominal wall musculature can be active during speech production throughout the vital capacity (Hixon, 1973; Hixon 1976; Hixon & Weismer, 1995). This work by Hixon and colleagues indicates that both rib cage and abdominal muscles are frequently co-activated throughout the vital capacity in order to produce net expiratory pressures needed for speech production. This is achieved as the expiratory pressures outweigh the inspiratory pressures resulting in a net expiratory pressure supporting speech. Using needle electrodes in combination with high-resolution ultrasound, De Troyer and colleagues (De Troyer, Estenne, Ninane, Gansbeke, & Gorini, 1990) have provided supporting evidence for the activation of abdominal musculature, specifically the transverse abdominis during speech production task of number counting.

The abdominal muscles also participate in other expiratory tasks including cough as well as loaded and/or forced expiration (Campbell & Green, 1952; De Troyer et al., 1990; Fontana & Widdicombe, 2007; Strohl, Mead, Banzett, Loring, & Kosch, 1981). Activation of rectus abdominis, external oblique, internal oblique and transverse abdominis have been shown during compressive and expulsive phases of cough (De Troyer et al., 1990; Strohl et al., 1981). An increase in external oblique muscle activation has been documented with increased intensity of cough stimulus and maximum expiratory flow during cough (Fontana & Widdicombe, 2007; Vovk et al., 2007). In specific comparisons of the differential activation in rectus abdominis muscle and the internal and external oblique muscles in the abdominal wall, the oblique muscle group has been shown to provide for the greatest mechanical contribution for subglottic pressure generation during cough production (Floyd & Silver, 1950; Fontana & Lavorini, 2006; Strohl et al., 1981).

In summary, abdominal muscle contraction during loud speech and cough helps in the generation of high alveolar pressures that are essential to these tasks.

Abdominal Muscle Weakness

Expiratory muscle weakness resulting from disease and/or disuse reduces exercise tolerance and cough efficiency (Mellies, Dohna-Schwake, & Voit, 2005; Weiner et al., 2003). As the expiratory muscle weakness can cause reduced cough efficiency (Weiner et al., 2003), it has also been associated with populations experiencing prolonged muscle disuse such as sedentary elderly, spinal cord injury patients, and those with neuromuscular disorders such as Parkinson's disease, Multiple System Atrophy, Multiple Sclerosis, and Muscular Dystrophy (Aiello et al., 2008; Dittmer & Teasell, 1993; Fontana et al., 1998; Gallien et al., 2007; Glendinning & Enoka, 1994; Kang, Kang, Sohn, Park, & Moon, 2006; Nishino et al., 2004; Wilmore, 1991). Thus, the reduced expiratory muscle strength and the related compromised cough efficiency have been

related to frequently occurring aspiration pneumonia in these populations (Chang & Widdicombe, 2007; McHorney et al., 2000; Simonyan et al., 2007). This point can be elaborated using the example of impact of aging in terms of muscle atrophy following both disuse and selective loss of fast motor units resulting in reduced muscle strength (Brooks, 2003). Further, in the case of Parkinson's disease, which is sometimes referred to as "accelerated aging" (Barbeau, 1984) irregular motor discharge patterns, recruitment of greater number of motor units at low thresholds and abnormal co-activation of antagonist muscles have been documented (Glendinning & Enoka, 1994). Although, reduced physical activity is thought to be a symptom of Parkinson's disease, it has also been shown to be responsible for worsening of the neuromuscular degeneration process (Tillerson et al., 2002). Thus, increased physical activity including endurance and or strength training is an important part of rehabilitation in this population and in others experiencing disuse related muscle weakness (Gallien et al., 2007; Glendinning & Enoka, 1994; Narici, 2004; Vignos, 1983; Milner-Brown, 1988).

Strength training for individuals with abdominal muscle weakness may benefit from strength training rehabilitation as it offers a mechanism for generating adequate expiratory forces for tasks including cough and loud speech. If the strength training program for expiratory muscles results in changes in corticospinal output which is associated with enhanced performance, then it is likely that such improvement is at least in part due to these changes within the central circuitry. This study will thus aid our understanding of the underlying central mechanisms that drive the training related performance outcomes and may then ultimately help with designing and modifying rehabilitation programs aimed at optimizing corticospinal output in specific diseased/disordered populations. This could potentially be achieved by manipulation of various

training parameters such as number of repetitions and training duration and their relationship with changes in corticospinal output.

How is Abdominal Muscle Weakness Rehabilitated?

Strength training as well as prosthetic devices to aid expiratory muscle function have been proposed as rehabilitation strategies for dealing with expiratory muscle weakness (Saleem, Sapienza, & Okun, 2005; Sapienza & Wheeler, 2006; Silverman et al., 2006; Watson & Hixon, 2001). Prosthetic devices include abdominal binding and trussing and mainly target those individuals with a paralyzed abdominal wall following spinal cord injury or muscular dystrophy. Abdominal trussing provides support for the paralyzed abdominal wall by providing fixation for the abdominal wall in an inward position (Watson & Hixon, 2001). Results using this treatment strategy show an increase in vital capacity, maximum inspiratory and expiratory pressures (Goldman, Rose, Williams, & Denison, 1986; Hultgren, Fugl-Meyer, Jonasson, & Bake, 1980; Sataloff, Heur, & O'Conner, 1984) as well as utterance duration during an oral reading task (Watson & Hixon, 2001). Abdominal binders have been used similarly for cough rehabilitation, but have not shown improvements in cough efficiency as measured by peak expiratory flows (Lin, Lai, Wu, Wang, & Wang, 1998).

Abdominal muscles participate in many tasks including expiration, speech, cough, weight bearing, and postural maintenance. These task specific roles assumed by this muscle group should be kept in mind when designing strength training programs to counter expiratory muscle weakness as task specificity is a well known contributor to task dependent differential performance within the same muscle groups (Sale, 1988; Shepherd, 2001). A comparison of the postural role of abdominal muscles or leg lifts with an expiratory function in terms of loaded expiration has shown both qualitative and quantitative differences in motor unit activation (Campbell & Greene, 1953; Puckree, Cerny, & Bishop, 1998). Postural tasks are associated with

greater abdominal muscle activation than expiratory tasks (Campbell & Greene, 1953). In addition, postural and expiratory tasks differ in terms of breathing patterns, recruitment of separate motor units, and most prominently recruitment levels and firing patterns for internal oblique and transverses abdominis muscles (Puckree et al., 1998). Thus, it is thought that motor units for internal oblique and transverses abdominis muscles likely receive different synaptic input specific to the expiratory task (Puckree et al., 1998). These differences in motor unit activity of abdominal muscles during postural versus expiratory tasks has implications for training programs targeting this muscle group. In fact, Tunstill et al. (2001) conducted a study comparing corticospinal output for rectus abdominis muscle during forced expiration for a breath holding task versus a bilateral trunk flexion task. Using TMS this study documented differences in facilitation patterns for the trunk flexion and the breath hold task. It is important to note that further differences may exist between motor unit activation and corticospinal output between different expiratory tasks like loaded expiration, speech and cough. It can logically be deduced that a strength training program using sit-ups is unlikely to have high impact on performance of expiratory tasks like maximum expiratory pressures or cough. Due to such task specific aspects of muscle activation, strength training on a postural task is less likely to transfer to an expiratory task than the transference between two different expiratory tasks like loaded expiration and cough. This assumption is based on the findings from exercise physiology literature showing greater transference to motor tasks that are more similar to the trained movement (Sale, 1988). Therefore, using a paradigm like expiratory threshold training to target improved performance in speech and cough may not be as specific but is likely better than sit ups given speech is more of a respiratory task than a postural task.

EMST is one such training program that targets expiratory muscles using a pressure threshold device. The effectiveness of the EMST as a tool to increase maximum expiratory pressures (an indirect index of expiratory/ abdominal muscle strength) has been reported in individuals that are healthy, aging as well as those with neuromuscular disorders and spinal cord injuries (Baker, Davenport, & Sapienza, 2005; Chiara, Martin, Davenport, & Bolser, 2006; Fitsimones, Davenport, & Sapienza, 2004; Kim & Sapienza, 2005; Saleem, Sapienza, & Okun, 2005; Sapienza, Davenport, & Martin, 2002; Sapienza & Wheeler, 2006).

Neurogenic Adaptations with Skeletal Muscle Strength Training

Strength training programs have been used for many years in limb rehabilitation to aid muscle strength and performance (Folland & Williams, 2007; Lexell, 1999; Powers & Howley, 2001). Adaptations occurring in response to strength training that account for increased strength can be divided into two categories: neurogenic and myogenic. Neurogenic adaptations are thought to account for the strength gains measured during the first few weeks of strength training whereas myogenic adaptations likely account for strength gains in the later phases of training (Leiber, 2002; Moritani & deVaries, 1979; Sale, 1988). While hypertrophy or increased cross-sectional area resulting from increased myofibrillar size and number is the primary index of myogenic adaptations (Folland & Williams, 2007), other morphological adaptations include fiber type changes, hyperplasia, alteration of muscle architecture, and structural changes in the connective tissue and tendons (Folland & Williams, 2007). On the other hand, neurogenic adaptations include increases in motor unit synchronization, inter-muscular co-ordination, corticospinal drive and motor unit recruitment (Enoka & Duchateau, 2002).

Neural adaptations can occur at various locations along the neuraxis. Neural adaptations occur cortically, to the motor command, descending drive and muscle activation, motor unit, and sensory feedback (Duchateau & Enoka, 2002). Some evidence for supra-spinal sites for

neurogenic adaptations has come from studies that have looked at V-wave changes and compared it to H-reflex changes with strength training.

V-wave is a methodology involving artificial elicitation of H-reflex during maximum voluntary contraction that is thought to provide an indirect measure of efferent motor neuronal activity (Folland & Williams, 2007). Some studies (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002; Sale et al., 1983) have used this methodology to study the adaptive neurogenic changes with strength training. These studies (Aagaard et al., 2002; Sale et al., 1983) have shown that with strength training there is a significant increase in V-wave amplitude indicating augmented neural drive from greater firing frequency of motoneurons. In addition, a comparison of H-reflex and V-wave amplitude change with strength training has shown a greater increase in V-wave amplitude compared to that in H-reflex which in turn is thought to result from increase in supra-spinal activation (Aagaard et al., 2002).

Studies investigating adaptations at the cortical level following strength training have commonly used TMS in humans and intracortical micro-stimulation in animals to help understand the changes within the cortex and corticospinal pathways following training (Carroll, Reik, & Carson, 2002; Griffin & Cafarelli, 2006; Jensen, Marstrand, & Nielson, 2005). The overall evidence from research investigating the impact of strength training on cortical motor map representations so far is inconclusive. Animal studies in this area are extremely limited and have focused mainly on forelimb muscles and show no changes in the cortical motor map representations with strength training (Remple, Bruneau, Vandenberg, Goertzen, & Kleim, 2001). However, current literature shows three human studies investigating cortical adaptations following strength training (Carroll et al., 2002; Griffin & Cafarelli, 2006; Jensen et al., 2005). Carroll et al., (2002) strength trained participants' first dorsal interosseous muscle for 4 weeks

and then compared the pre and post training measures derived from TMS and transcranial electrical stimulation (TES). Results from both TMS and TES have shown no change in corticospinal excitability with strength training. Another investigation comparing strength training with skill training of the biceps brachii muscle has shown similar results with no significant changes in the corticospinal excitability with strength training (Jensen et al., 2005). In contrast, a recent study showed increased corticospinal excitability as measured by increased MEP amplitude following a 4-week resistance training program with the tibialis anterior muscle (Griffin & Cafarelli, 2006). There is some speculation that various muscles from the upper and lower limb may respond differentially to strength training (Griffin & Cafarelli, 2006). Future research in this area will confirm the present reports and should investigate strength-training responses from other muscles including expiratory muscles specifically the abdominal muscles.

Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive methodology that is used to excite neurons in the cortex and is used for study of neural circuitry including both intra-cortical and corticospinal/corticobulbar connections. TMS set up includes a capacitor that generates an electric current of up to 8kA and this current is discharged into the TMS coil. The magnetic pulse generated by the TMS coil generates a maximum magnetic field of 2 Tesla (Walsh & Pascual-Leone, 2003). A quickly changing magnetic field induced by a high intensity and short duration (1 msec) magnetic pulse results in production of an electric field. This electric field changes the resting potential of the cortical neurons below the coil and thus stimulates them.

As the current leaves the neuron cell bodies, axons and dendrites it causes them to depolarize. Once depolarization reaches the threshold level a propagating action potential is generated (Mills, 1999). The extent of depolarization depends on the intensity and duration of the current which in turn is dependent upon the specifications of the magnetic stimulator. It is also

important to note that different neuronal sub-components differ in terms of their threshold for excitation with cell bodies possessing higher threshold than axons (Ranck, 1975). Bent neural structures such as mammalian and amphibian neurons have lower threshold of excitation and the extent of bending has been documented to share an indirect relationship with threshold of stimulation (Amassian, Eberle, Maccabee, & Cracco, 1992; Maccabee, Amassian, Eberle, & Cracco, 1993). Consequently, excitation mainly occurs at branching points or at the points where axon and cell body for the neurons meet (Durand, Ferguson, & Dalbasti, 1992).

Circular versus Figure of Eight Coil

The TMS coils commonly used are either circular or figure of eight coils. The distribution of the induced electric field under the coil is different for the two coil types. Figure 1-2 shows the both the circular as well as figure of eight coils. The two coils target different areas of the brain when placed at the same position with respect to the scalp. The figure of eight coil consists of two circular coils. Due to this configuration in the figure of eight coil the current flows in two opposite directions generating two electric fields. These two electric fields overlap and add up where the two coils meet in the center. This provides for an increased focus of stimulation using the figure of eight coil than a more diffused magnetic field generated by a circular coil.

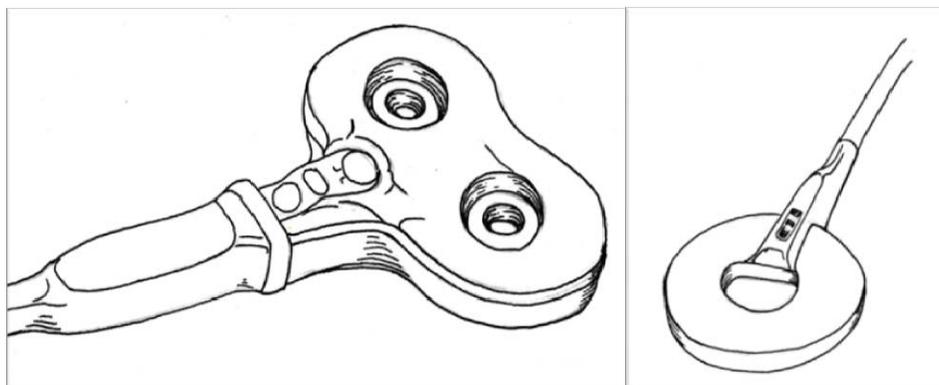


Figure 1-2: Circular versus figure of eight magnetic stimulation coils.

TMS and Skeletal Muscle Stimulation

In the case of motor cortex stimulation a sufficiently strong magnetic results in a direct or indirect stimulation of the motor cortex neurons. TMS is thought to more commonly activate the corticospinal and corticobulbar neurons indirectly via the interneurons and neurons that synapse over them (Kamen, 2004). The change in resting potential of the motor cortex neurons from the descending impulse results in stimulation of the corticospinal or corticobulbar neurons which in turn stimulates the bulbospinal or spinal neurons which transfer the nerve impulse to the muscle that can be recorded using an EMG electrode (Figure 1-3). This response is called the motor evoked potential or the MEP and measures the end product of the excitatory and inhibitory effects on the descending corticospinal or corticobulbar neurons.

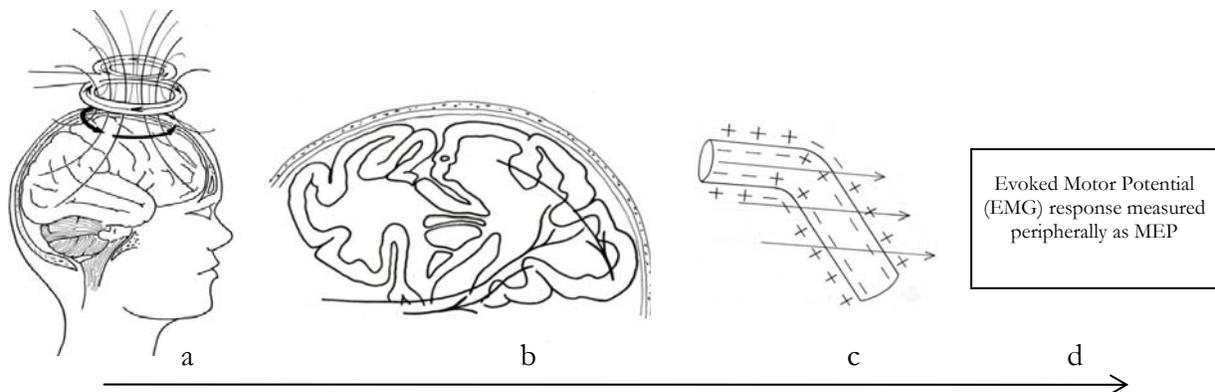


Figure 1-3: Schematic representation of the events involved in the single pulse TMS for skeletal muscle stimulation. a) Magnetic field is generated by the figure of eight coil on top of the scalp, which in turn induced an electric field. b) An intracranial electric field causes an electric pulse to travel down the pyramidal axons. c) Depolarization occurs at the level of the axonal membranes. d) EMG signal is transduced at the level of the muscle.

Applications of Single Pulse TMS

Single pulse TMS can be used to measure changes in motor map excitability as well as to assess motor map representations within the motor cortex. Motor threshold and recruitment curves provide estimates of cortical excitability and motor maps can be used to quantify the area covered by a cortical motor representation. Further descriptions of these measures and their implications are provided below.

Motor threshold

This refers to the lowest stimulus intensity needed to elicit an MEP of set amplitude. This amplitude is most commonly set to 50 μ V (Chen, 2000). This parameter is thought to provide an index of neuronal membrane excitability. Motor threshold is usually lower for upper extremity muscles and has been associated with stronger corticospinal projections to these muscles (Chen et al., 1998). Motor threshold can be measured with the muscle of interest at rest and is referred to as rest motor threshold or when the muscle is in a low intensity sustained contraction referred to as active motor threshold or AMT. Using facilitation or low intensity background contraction lowers the motor threshold by increasing MEP amplitude (Darling, Wolf, & Butler, 2006) and can therefore be useful in testing muscles with higher motor threshold example- lower limb and trunk muscles. In addition, low intensity muscle contraction during TMS testing allows for reduced variability in cortical and spinal excitability (Darling et al., 2006) reflected in measures such as motor threshold and IO curve (described below) measures.

Input output (IO) curves

This measure plots the change in MEP amplitude with change in TMS intensity. Recruitment curves are also known as input-output curves or IO curves and their slope has been linked to the strength of corticospinal connectivity between the motor representations in the cortex and the muscle group of interest (Chen, 2000). The slopes of hand muscles that are known

to have strong corticospinal projections and have steeper recruitment curve slopes (Chen et al., 1998).

Cortical maps

This measure is obtained by stimulating multiple sites on the scalp to obtain the most excitable cortical site as well as the number of excitable cortical sites which in turn provide an estimate of the cortical area dedicated to a given muscle (Chen, 2000). Motor maps have been shown to shrink with disuse (Leipert et al, 1995) and expand with learning of skilled tasks (Pascuel-leone et al., 1993; Svensson et al., 2003).

Reproducibility of TMS Measures

TMS has been employed to study corticospinal output using measures of cortical excitability such as motor threshold, IO curves and motor maps in various skeletal muscles. Therefore, as indicated earlier, TMS has application in not only understanding the cortical connectivity to the motor systems but can also be used to study neuroplastic changes following disease, injury and rehabilitation of the motor cortex. However, in order to use TMS methodology to measure neuroplastic changes, it is important to establish reproducibility of its specific measures for each muscle of interest. In fact, some studies have addressed this issue by testing reliability of TMS measures over multiple testing sessions (Carroll et al., 2001; Kamen, 2004; Malcolm, et al., 2006; McMillan et al., 1998; Mortifee et al., 1994; Wolf et al., 2004). There likely exist differences between skeletal muscles in terms of reliability of TMS measures depending upon cortical representation area dedicated to the muscle of interest, spontaneous changes in cortical outflow to the motor cortex, daily activity patterns, and electrode as well as coil placement (Malcolm et al., 2006). In addition, even within the same muscle and testing session, trial-to-trial variability has been documented (Ellaway et al., 1998; Kobayashi & Pascual-Leone, 2003; Truccolo, Ding, Knuth, Nakamura, & Bressler, 2002; Wassermann, 2002)

and is attributed to excitability changes in the motoneurons and the corticospinal pathways (Funase et al., 1999; Weber & Eisen, 2002).

An average of multiple trials or a trial “block” has been suggested to achieve greater reliability of measures across sessions (Kamen, 2004). Kamen (2004) has demonstrated that increased number of trial blocks and days results in increased consistency of the MEP amplitudes. Therefore, using multiple trial blocks as well as multiple baseline testing sessions is helpful when designing studies lasting several days/weeks to ensure the stability of MEP measures.

McDonnell, Ridding, and Miles (2004) have compared three different methods for analyzing the MEP data for first dorsal interosseous and flexor carpi ulnaris muscles. They compared the MEP magnitude obtained from averaging the individual peak-to-peak amplitudes with amplitude of the ensemble waveform and amplitude of the maximal response. Even though their study showed no significant difference between the MEPs from the three methods, the amplitude of average MEP was higher than the ensemble MEP and the maximal response was the greatest. Study findings may thus be somewhat affected based on the methodology used. Given the large amount of variability seen in the MEPs obtained, the investigators concluded that in order to use MEP amplitudes to detect an intervention induced change in corticospinal output to a given muscle large number of trials would be needed or the change would need to be large enough to be detected in spite of the variability in MEP amplitude. A similar finding in terms of large variability indices has also been documented in the diaphragm muscle (Sharshar et al., 2003). Therefore, it is likely that diaphragm and possibly other respiratory muscles may not lend themselves to the detection of small changes in corticospinal output following various training interventions.

Another consideration in improving the reproducibility of TMS measures is accuracy of coil positioning. Various strategies are recommended for positioning the coil including use of anatomical landmarks, functional characteristics, the 10-20 EEG system and stereotaxic positioning of TMS (Herwig et al., 2001; Herwig, Satrapi, & Schonfeldt-Lecuona, 2003; Kleim et al., 2007; Schonfeldt-Lecuona et al., 2005). Accuracy of stereotaxic TMS positioning using optically tracked neuronavigational systems has been documented as superior when compared to other coil positioning methodologies including the 10-20 EEG system (Herwig et al., 2003) with variability of 1.6mm for within session stability and 2.5mm for inter-session reproducibility (Schonfeldt-Lecuona et al., 2005). Spatial accuracy of stereotaxic devices has been established in neurosurgical settings (Galloway, Maciunas, & Latimer, 1991; Kaus, Steinmeier, Sporer, Ganslandt, & Fahlbusch, 1997) but given that participants during TMS are not fixed to stereotaxic frames as in case of neurosurgical situations this can give rise to some inaccuracies in TMS measurements (Schonfeldt-Lecuona et al., 2005). The two main sources of error include movement of the dynamic reference frame (tracks the position of the participant's head in space and is attached to their head, example: eye-glasses) with respect to the head and the referencing method used for co-registration of the head and coil position with the MRI scan (Kleim et al., 2007; Schonfeldt-Lecuona et al., 2005). Therefore, it is important to consider these sources of error when using stereotaxic methods for TMS measurements. However, it is important to note that at present time such stereotactic neuronavigational systems likely provide the most accurate way to assure accurate coil positioning during TMS procedures. Infact, Kleim et al. (2007) have documented a useful and detailed experimental protocol using frameless stereotaxic TMS for measurement of training induced changes in corticospinal output to hand. Such protocols can be

modified for different study designs for the hand muscles as well as to measure corticospinal output changes in other muscles including respiratory and specifically the abdominal muscles.

Use of TMS in the Study of Inspiratory Muscle Control

Cortical control of the inspiratory muscles has been most extensively studied in the diaphragm muscle (Demoule, Verin, Locher, Derenne, & Similowski, 2003; Demoule, Verin, Tezenas du Montcel, & Similowski, 2008; Locher et al., 2006; Mehiri et al., 2006; Ross, Nowicky, & McConnell, 2007; Straus, Locher, Zelter, Derenne & Similowski, 2004; Verin et al., 2004; Wang, Similowski, & Series, 2007). Validation of the use of surface EMG electrodes in contrast with the needle electrodes to reliably obtain diaphragm response to TMS along with the delineation of this response from cross-talk effects from other respiratory muscles has been documented (Demoule et al., 2003).

Verin et al., 2004 used single pulse TMS, paired pulse TMS and the comparison of TMS and peripheral stimulation of the phrenic nerve to document the central fatigue following maximal exercise. This study showed that with exhaustive treadmill exercise MEP amplitude decreased in healthy adults whereas no changes in the MEP amplitude occurred during rest condition. This study also documented shortened latency of MEP for the diaphragm with exhaustive aerobic exercise. In addition, hypercapnia has been found to induce facilitation of EMG response from the diaphragm muscle following TMS (Straus, Locher, Zelter, Derenne, & Smilowski, 2004).

In addition, effects of using inspiratory resistance to facilitate diaphragmatic response to TMS have been investigated in healthy adults (Locher et al., 2006; Ross et al., 2007). In a study conducted by Locher et al., 2006 healthy volunteers were asked to breathe against no resistance, 5 and 20 cms H₂O resistance. TMS presented during early inspiration and late expiration found no change in MEPs amplitudes but decreased latency of response during inspiratory TMS

obtained from surface electrodes targeting the diaphragm muscle. They concluded that imposition of the inspiratory load resulted in facilitation of the TMS response indicated by the reduced latency. Ross and colleagues (Ross et al., 2007) studied the effect of an acute bout of inspiratory muscle loading on TMS responses in the diaphragm. Participants inspired forcefully through no resistance as well as against loads equivalent to 40% of their maximum inspiratory pressures (two sets of thirty breaths each). MEP amplitude for the diaphragm in response to TMS decreased following both conditions of inspiratory muscle loading as well as nonloaded forced inspiration. Use of peripheral stimulation in addition to TMS revealed that inspiratory loading resulted in increased muscle strength along with increased peripheral excitability and reduced corticospinal excitability.

Recently Demoule et al. (2008) discussed the neuroplastic changes in the diaphragm following skill training. In this study, healthy participants were taught to produce diaphragm contractions during volitional inspiratory maneuvers. Findings documented a reduction in motor threshold and response latencies for the diaphragm along with an expansion of diaphragm motor representation area in the cortex. These findings show that respiratory muscles and specifically the diaphragm show similar responses to skill training as has been documented in other skeletal muscles.

The above-mentioned studies provided useful insights into the corticospinal connectivity from the cortex to the inspiratory muscles and their similarities to the other limb muscles. However, there continues to be very little information on the corticospinal output to the expiratory muscles as well as the impact of muscle loading (acute or chronic) on the expiratory muscles (Lissens et al., 1995; Plassman & Gandevia, 1989; Tunstill et al., 2001; Walker et al., 1997).

TMS and Study of Cortical Adaptations following EMST

Many studies have shown increased EMG activation following strength training (Moritani & DeVries, 1979; Narici, Roi, Landoni, Minetti, & Cerretelli, 1989; Sale, 1988) which in turn is thought to be indicative of elevated corticospinal drive (Griffin & Cafarelli, 2006). Examining strength training induced adaptations within the motor cortex and in corticospinal and corticobulbospinal tracts is important in order to understand the central mechanisms underlying strength training induced change in muscle performance. TMS described above is a safe, noninvasive procedure which permits identification of cortical motor representation of specific muscles (Kleim et al., 2007) and has been recently employed to study changes in cortical motor maps and corticospinal drive following strength training in limb muscles including first dorsal interosseus, biceps brachii, and tibialis anterior muscles (Carroll et al., 2002; Jensen et al., 2005; Griffin & Cafarelli, 2006). However, there is no conclusive evidence for or against the adaptive changes in corticospinal excitability following strength training that is applicable to all skeletal muscle groups.

Sharshar et al. (2003) documented a reliable method to study recruitment or IO curves in the diaphragm. In addition, validity of cortical excitability measures was documented in the diaphragm (Demoule et al., 2003). However, no previously reported study has attempted to establish a reliable methodology to study cortical excitability for abdominal muscles and the impact of training paradigms on cortical excitability measures. Given the adaptations associated with strength gains following EMST are thought to occur within the nervous system in a manner similar to other strength training programs it is expected that there is likely be a change in cortical excitability with EMST.

Therefore, this study aimed at establishing the test-retest reliability of AMT and IO curves for lateral abdominal wall muscle group and to study the impact of EMST on these measures.

Specific Aims

Aim I

To determine the test-retest reliability of AMT and IO curve corresponding to the lateral abdominal wall muscles as measured by TMS.

Hypothesis Aim I

The AMT and IO curve corresponding to lateral wall abdominal wall muscles as measured by TMS will demonstrate test-retest reliability when assessed over three testing sessions in young healthy individuals.

Aim II

To determine the change in AMT for lateral abdominal wall muscles with EMST.

Hypothesis Aim II

The AMT corresponding to the lateral abdominal wall muscles using TMS will significantly decrease following 4 weeks of EMST.

Aim III

To determine the change in slope of IO curve corresponding to lateral abdominal wall muscles with EMST.

Hypothesis Aim III

The slope of the IO curve corresponding to the lateral abdominal wall muscles will significantly increase following 4 weeks of EMST.

CHAPTER 2 METHODOLOGY

The purpose of this study was to measure the test-retest reliability of cortical excitability measures of AMT (active motor threshold) and IO (input output) curves for lateral abdominal wall musculature and to assess the impact of EMST on these measures. The reliability of cortical excitability measures of AMT and IO curve slope were measured across three baseline testing sessions (conducted on three separate days within a period of three to ten days) and the influence of a 4 week EMST (expiratory muscle strength training) program on these measures was established by comparing the average values of three baseline and three post training measures in young healthy adults (18-31 years). All of the participants in this study underwent the same treatment and thus acted as their own control for pre and post EMST measures.

Experimental Design

This was a phase I study with a prospective design. The independent variable for the first hypothesis (The AMT and IO curve corresponding to lateral wall abdominal wall muscles as measured by TMS will demonstrate test-retest reliability when assessed over three testing sessions in young healthy individuals) was the testing session and independent variable for the second and third hypotheses (hypothesis 2: The AMT corresponding to the lateral abdominal wall muscles using TMS will significantly decrease following 4 weeks of EMST ; hypothesis 3: To determine the change in slope of IO curve corresponding to lateral abdominal wall muscles with EMST) was the EMST program. The dependent variables for all hypotheses were AMT and IO curve slope. Assessing the dependent variables over three different sessions on three separate days tested the first hypothesis. Following the baseline sessions all participants underwent a 4 week EMST program during which period they met with the Principal Investigator once every week to reassess changes in their expiratory muscle strength (maximum expiratory pressures)

and the participants' new training loads for that week's training using expiratory muscle strength training or EMST device (EMST150, Aspire Solutions). Upon completion of the EMST program all participants returned to the laboratory for post training measures that were repeated over three post-training sessions conducted on three separate days over a three to ten day period. The comparison of dependent measures obtained during pre and post training measures was used to test the second and third hypotheses.

Participants

Ten healthy adult (age: 18-31 years; 3 males and 7 females) volunteers participated in this study. All participants were right-handed as based on self-report. Participants were screened for contraindications to TMS as well as to the maximum expiratory pressure maneuver (see screening questionnaires in Appendix 1 (TMS) and Appendix 2 (health screening)). Only participants who did not report contraindications to TMS and maximum expiratory pressure maneuver were offered participation in this study. Participants reporting any history of smoking in past 5 years, untreated hypertension, respiratory, neurological and cardio-thoracic disease were excluded from this study. Participants were asked to maintain their pre-study physical activity level over the course of the study and none of them reported practicing singing, theater arts, tai chi and yoga. In addition, professional or extreme athletes in the areas of both endurance and strength training were excluded. All participants were instructed to not consume caffeine before testing sessions and get adequate sleep the night before TMS testing sessions were conducted as these factors have been documented to impact TMS response characteristics (Civardi et al., 2001; Gandevia & Taylor, 2006). Written informed consent was obtained from all participants and the Internal Review Board of the University of Florida approved this study.

Experimental Set Up/Procedures

AMT and IO curves for the lateral abdominal wall muscles were generated using TMS. Three baseline measures were collected within a ten-day period and tested for reproducibility. Following the baseline measures, participants underwent 4 weeks of EMST. Post training measures were made during three sessions over a ten-day period following completion of training.

Maximum Expiratory Pressure Measurement

Maximum expiratory pressure was measured at the mouth using a manometer (Micrompm by Micromedical, Inc.) and served as an indirect measure of maximum expiratory muscle strength. The participants wore a nose clip and were instructed to inspire to their total lung capacity and then place the manometer mouthpiece in their mouth and expire as fast and as hard as possible. This maneuver was repeated with one-minute rest periods until three pressure readings within 5% were collected. These three readings were averaged to provide the maximum expiratory pressure measure.

Facilitation during TMS Measures

All TMS measures were made with voluntary abdominal muscle facilitation at 20% of the participant's maximum expiratory pressure. A low-level background contraction level was chosen as it has been shown to provide increased stability in cortical and spinal excitability and thus increased reliability of MEP responses following TMS (Darling et al., 2006). In addition, during the course of our pilot work for this study, we observed that use of facilitation in this manner resulted in reduction of motor thresholds enabling us to test the MEP response change over a range of stimulator intensities and thus allowing for measurement of the IO curve slope parameter. Chest and abdominal wall movement during respiration was monitored using inductotrace bands (Ambulatory Monitoring, Inc.) and was displayed on an oscilloscope

(Tektronix, Inc.). During rest breathing, participants were asked to blow from end expiratory level through the expiratory muscle strength training device (EMST150, Aspire Solutions). End expiratory level was used as an approximate estimate of resting expiratory level. EMST device was set at 20% of their maximum expiratory pressure (as measured above). Participants were asked to maintain the expiratory phase for ~3 seconds until they felt the TMS stimulus. A trial was discarded if any of the above criteria were not fulfilled. The participant wore nose clips and an experimenter pressed the participant's cheeks during expiration through the trainer to ensure a good seal around the trainer mouthpiece. Ten TMS stimuli were applied for each of the stimulation intensities (described below) with approximately 20 second intervals (or 3 breath cycles) between stimuli. Facilitation of the muscles involved in expiration was used during all TMS measures in this study. The participants were otherwise at rest.

TMS Setup

Each participant came to the TMS laboratory for three baseline and three post-training measures. The baseline sessions as well as the post-training sessions were conducted on three separate days within a period of three to ten days. The participants were seated with their arms on a chair armrest. A chin rest and head support at the back of the head was used to stabilize the head throughout the course of the experiment. Bipolar active surface electrodes (Delsys, Boston, MA) with an inter-electrode distance of 1 cm were placed over the right lateral abdominal wall as recommended by McFarland & Smith (1989). The surface electrode was placed parallel to the external oblique muscle orientation however it is possible that this signal may have received contributions from internal oblique and transverse abdominis muscles. A marker with indelible ink was used to mark the electrode placement site to ensure consistent placement across the pre-training and post-training sessions. A ground electrode was placed on the clavicle. The surface

electromyographic (sEMG) signals were sampled at 2500 Hz, amplified with a gain of 1000 and band-pass filtered at 6-450 Hz and measured using Scope software (Scope v3.6.10).

Each participant's head was co-registered with a stock brain using stereotaxic software (BrainSight). The stock brain image was constructed using T1-weighted anatomical magnetic resonance images (MRI). This MRI image was obtained in accordance with the MRI acquisition previously described for use with the Brainsight neuronavigational program (Kleim et al., 2007). This MRI scan was then imported into a computer and a 3-D composite image was constructed using Brainsight and the outline for 10 coronal sections starting with the mid-sagittal section was traced. Then using the surface peeler function in Brainsight software 6mm of surface was peeled to obtain a clean view of the cortex. The stock brain image used was enlarged to match the actual size of the brain using the nose length measurement technique described by Kleim et al. (2007). A 1cm² grid was superimposed on to the brain image and required measurements were made using micro-calipers and digital markers along the successive coronal images and the lateral aspects of each of these coronal slices were placed (Keim et al., 2007). This grid later served as a reference for recording TMS responses for all of the participants. For the co-registration, four landmarks on the participant's head - nasion, tip of the nose, left pre-auricular point and right pre-auricular point – were digitized using a pointer tool fitted with reflective sensors while the participant wore goggles also fitted with reflective sensors. These points were also identified on the stock brain MRI and were used to do the co-registration. The stock brain was then used to guide a figure of eight 70-mm stimulation coil (also fitted with reflective sensors) connected to a Magstim 200² magnetic stimulator (Magstim) over the participant's primary motor cortex area. Two separate monitor screens were used for viewing the static image of the stockbrain serving as guide for coil placement and the second for viewing MEP waveforms using a software program

(Scope, AD Instruments). For all TMS measures the stimulator coil was held over the left cortex at a 45 degrees angle to the mid-sagittal plane and the coil handle oriented backwards. It was ensured that the participants' glasses with the reflective sensors were not displaced or removed until the completion of each of the screening and the experimental sessions. This ensured consistent registration throughout the course of each testing session. MEPs elicited in the right abdominal muscles were measured with the sEMG setup mentioned above. Figure 2-1 below shows an example of a MEP obtained from the lateral abdominal muscles.

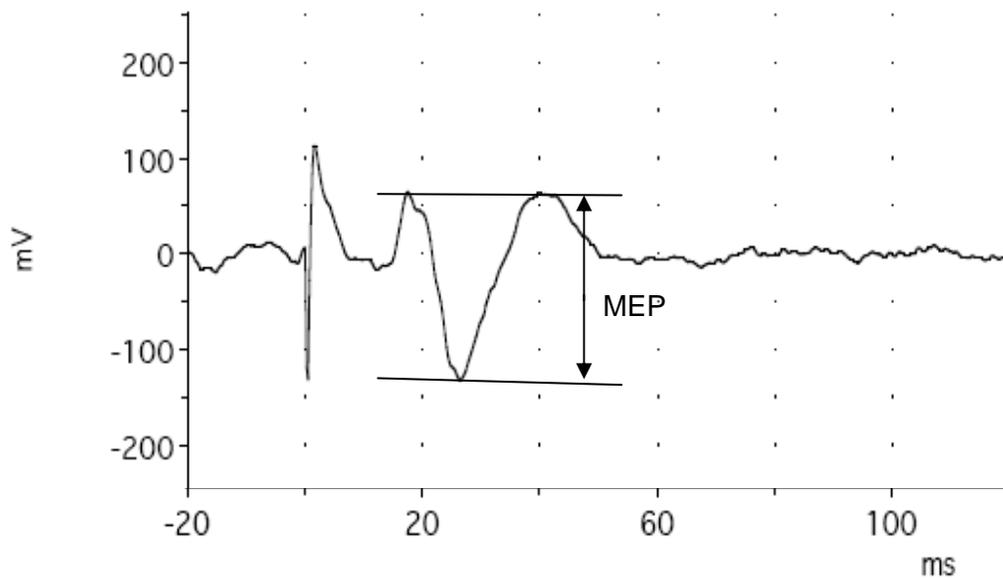


Figure 2-1: A MEP obtained from EMG electrode placed on lateral abdominal wall following application of TMS to the motor cortex area corresponding to the lateral abdominal muscle group. The first deflection in this signal is the stimulation artifact whereas the amplitude of the second deflection provides a measure of the MEP.

Screening Session

Prior to being offered participation all participants came in for a screening session that lasted about 60 minutes. During this session the primary investigator obtained the informed consent and determined qualification for participation. First, the participants filled out the TMS and Health Screening questionnaires (Appendix 1 and 2). Next each participants' maximum

expiratory pressure was ascertained by the primary investigator as described earlier and an EMST device was set at 20% of their maximum expiratory pressure. The experimenter connected the participants to the inductotrace bands (Ambulatory Monitoring, Inc.) and monitored their respiration on an oscilloscope (Tektronix, Inc.) instructing them to cease expiration when they reached end expiratory level. Then they were asked to practice blowing through the EMST training device and continue the airflow over a period of ~3 seconds.

Practice session was conducted on the same day immediately following the screening sessions. This practice continued for 10-15 minutes until the participants reported being comfortable with the task, and the experimenter determined that they were performing the task accurately. Following this respiratory practice, participants were presented a few TMS stimuli (3-4) at a site that was 1cm lateral to the vertex over the left hemisphere and were asked of their comfort level after each stimulus. The session was continued only if the participant reported being comfortable with this initial TMS exposure. If the participant found the TMS stimuli presented at low stimulation levels (30-50 % maximum stimulator output (MSO)) comfortable, the stimulation intensity was increased to 60 % MSO and the TMS stimulus was presented again. Finally, the threshold for this stimulation site and if needed any other surrounding sites was assessed according to the methodology described below and the participants whose AMT was 59% MSO or lower at any of the cortical sites on the 1cm-square grid was offered participation.

Baseline and Post-Training TMS measures

The participants, who passed the screening protocol and volunteered to participate in the present study, underwent the following baseline and post-training TMS measures as well as the EMST training.

SOLMT Determination

The participants' cortical hotspot or SOLMT (site of lowest motor threshold) for activation of the lateral abdominal wall muscles and the AMT were determined with TMS. The AMT was defined as the lowest intensity needed to produce a MEP $\geq 50\mu\text{V}$ in six out of ten trials. The hotspot was defined as the location with the lowest AMT. The search for the hotspot was initiated at a site previously reported in the literature to excite the abdominal muscles (Tunstall et al., 2001; Walker et al., 1997) which was approximately 2 cm anterior and 1 cm lateral to vertex. Stimulation protocol for AMT determination was in accordance with the description provided by Kleim and colleagues (Kleim et al., 2007). Stimulator output was first set at 60-70 % MSO as this was higher than the study inclusion criteria of 59 %MSO met by all the participants. If the MEP responses of $\geq 50\mu\text{V}$ were not obtained for at least 6 out of 10 stimuli, stimulator output was increased by 2 %MSO. This was repeated until 6 out of 10 pulses resulted in an MEP $\geq 50\mu\text{V}$. Next, the stimulator output was reduced until MEP responses for 10 consecutive pulses resulted in less than 6 out of 10 MEPs with $\geq 50\mu\text{V}$. Again the stimulator output was increased in 1% MSO steps until 6 out of 10 pulses resulted in $\geq 50\mu\text{V}$ MEPs. The lowest intensity to first meet this criterion was defined as the AMT for this site. After the threshold at this site was determined the stimulation intensity was set to 1% below this AMT level and neighboring locations were investigated. A 1-cm^2 grid superimposed onto the stock brain was used to guide the search for the hotspot (Figure 2 – 2). The method described above for determination of AMT for the first stimulation site was repeated for the site immediately anterior to it. If the AMT for this second stimulation site was lower than that for the first stimulation site, the AMT for the next anterior site was determined. This process was continued until a site was found with a higher AMT than the previous site tested. At this point the AMT for the site medial to the last

tested site was determined. If the AMT was lower than all previously tested sites, this process was repeated progressively for other medial sites until a site with higher AMT was found. If needed this procedure for AMT determination was repeated for posterior and lateral sites until a site was found that was surrounded by sites with higher AMTs on all four sides. This site was labeled as the SOLMT or hotspot.

IO Curve Determination

At the hotspot, data for an input-output (IO) curve was obtained by delivering ten TMS stimuli at nine intensity levels using pseudo-randomization in the following order: 130%, 160%, 110%, 150%, 90%, 170%, 100%, 140%, and 120% AMT). The pseudo-randomized presentation order was chosen as this is thought to help with the prevention of possible additive impact of progressively increasing levels of magnetic stimulation (Keim et al., 2007). The peak-to-peak amplitude of the ensemble MEP for the ten trials was determined for each of the intensities for the I-O curve.

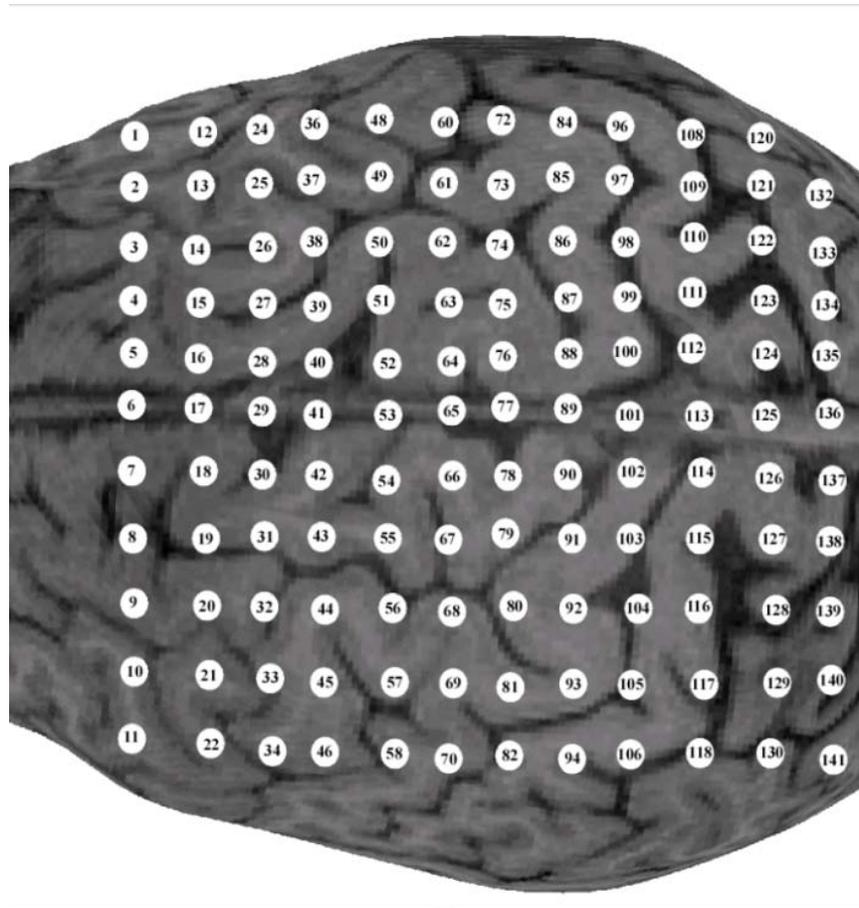


Figure 2-2: A top-down view of the stock brain image with a 1 cm² superimposed grid of drawn markers were used as reference for coil placement for finding SOLMT and its stimulation during assessment of AMT and IO curve parameters.

SOLMT – Physical Location

Physical location of SOLMT with respect to the vertex was measured at the end of each TMS testing session. These measurements were made as a secondary reference to the location of the hotspot on the 1-cm² grid superimposed on the stock brain. SOLMT was measured as a distance from various landmarks namely distances from 1) vertex to SOLMT, 2) pre-auricular point to SOLMT and 3) anterior or posterior distance from the vertex.

EMST Protocol

The EMST device was set at 75% of the participant's maximum expiratory pressure. Each training session consisted of five sets of five repetitions, with brief rest periods between each

repetition and at least one minute of rest between each set. A successful repetition was considered completed when the participant was able to generate enough expiratory pressure to open the valve of the EMST device. Participants were trained for five days per week for 4 weeks. Participants completed their daily training sessions over the phone with the primary investigator so as to ensure compliance as well as to use it as an opportunity to provide the participant feedback and to answer any of their questions. Participants returned to the laboratory once each week at which time their maximum expiratory pressures were re-measured and the EMST device reset at 75% of their new maximum expiratory pressure. This ensured that they were trained at the same difficulty level throughout the course of their 4 week training.

Statistical Design and Analysis

MEP amplitudes for all responses were measured using peak-to-peak measurements from an EMG analysis software program (SCOPE V3.6.10). An ensemble of ten stimulation trials was used to calculate MEP amplitudes for a given site and or stimulation intensity for hotspot and IO curve measurements respectively.

All the IO curves obtained during baseline as well as post training measures were fitted to linear, sigmoid (dose-response), and exponential models. The curve fits for IO curve data were obtained using Origin 8.0 software (Origin Inc.). The general equation of these models is described next. The equation used for the linear model is given below (Equation 2-1).

$$y = dx + p * x \tag{2-1}$$

In Equation 2-1, y = MEP amplitude, dx = constant and p = slope. For the exponential model the equation employed is given below (Equation 2-2).

$$y = y_0 + A1 * e^{-x/t1} + A2e^{-x/t2} \tag{2-2}$$

In Equation 2-2, y_0 = offset, $A1$ = initial value of MEP amplitude, $t1$ and $t2$ = decay constant and $A2$ = final value of MEP amplitude. The equation used for the sigmoid (dose-response) fit is provided below (Equation 2-3).

$$y = A1 + A2 - A1 / (1 + 10^{(\log x_0 - x) * p}) \quad (2-3)$$

In Equation 2-3, $A1 < A2$, $p > 0$, bottom asymptote = $A1$, top asymptote = $A2$, center = $\log x_0$ and slope = p . Goodness of fit was determined using adjusted r^2 value. All slope parameter comparisons were made using slope values obtained from both linear as well as sigmoid curve fit models.

The three AMT and IO curve slope measures obtained from single pulse TMS were compared using a repeated measures ANOVA (criterion of $p \leq .05$) to test the reproducibility of AMT and IO curves from the abdominal cortical motor area. Once the reproducibility was established, the three pre and post measures for AMT and IO curve slopes were averaged separately and pre and post comparisons were made using paired t-tests with stimulus intensity as the independent variable and AMT and IO curve slope as dependent variables. Bonferroni adjustment was made for multiple dependent variables and the p-value was set at .025. Data are presented in the mean +/- S.E. format unless mentioned otherwise.

CHAPTER 3 RESULTS

This study aimed at establishing reliability of cortical excitability measures of IO curve and AMT for lateral abdominal muscles and the impact of an EMST program on the same. The first portion of this chapter presents reliability data for these measures obtained from comparison of IO curve slope and an AMT measurement obtained during three separate sessions and thus addresses the first hypothesis for this study. The second section in this chapter documents the data findings for the second and the third hypotheses showing changes in IO curve slope and AMT with EMST as well as impact of EMST on maximum expiratory muscle strength in study participants.

Reproducibility of TMS Measures

Hypothesis 1: The AMT and IO curve slope corresponding to lateral abdominal wall muscles as measured by TMS will demonstrate test-retest reliability when assessed over three testing sessions in young healthy individuals.

Active Motor Threshold

The reproducibility of the AMT and facilitated IO curves for lateral abdominal muscle group was tested in all 10 participants (3 men and 7 women) using the statistical methods described in Chapter 2. Average values of AMT were 49.3 +/- 4.1 %MSO, 47.6 +/- 4.9 %MSO, and 50.5 +/-7.26 %MSO for three respective baseline sessions. No significant difference in AMT over three baseline testing sessions obtained on three separate days was detected using repeated measures ANOVA ($F=1.248$; $df = 2,18$; $p = .311$). The values for AMT as assessed during three baseline testing sessions are shown (Table 3-1). Repeated measures ANOVA was performed to compare AMT measures obtained during the three post EMST sessions and yielded no significant differences among the three measures ($F = .241$; $df = 2,16$; $p = .789$).

Facilitated IO Curves

The slope parameters were assessed from equations for linear as well as sigmoid models (Table 3-2 and Table 3-3). Repeated measures ANOVA showed no significant difference between the three baseline slope measures obtained using either the linear or the sigmoid models ($F=1.009$; $df = 2,18$; $p = .384$). Repeated measures ANOVA was performed to compare IO curve slope measures obtained during the three post EMST sessions and resulted in no significant differences among the three slope measures ($F = .029$; $df = 2,16$; $p = .972$).

Effects of EMST

Hypothesis II: The AMT corresponding to the lateral abdominal wall muscles using TMS will significantly decrease following 4 weeks of EMST.

Hypothesis III: The slope of the IO curve corresponding to the lateral abdominal wall muscles will significantly increase following 4 weeks of EMST.

TMS Measurements for Change with EMST

TMS measures of IO curve slope and AMT provide indices of cortical excitability and the detailed findings for these outcome measures before and after EMST are given below.

Active Motor Threshold

Strength training the expiratory muscles using the 4 week EMST program resulted in lateral abdominal muscles' average AMT obtained during the three baseline and three post EMST testing sessions to drop 7.634% from 49.134 ± 2.258 to 45.383 ± 2.224 %MSO. Data from 9 out of 10 participants showed a decrease in AMT with 4 weeks of EMST (Table 3-4; Figure 3-1 and 3-2). Paired t-test revealed a significant drop in AMT ($p = .003$) following 4 weeks of EMST. Therefore, it is indicated that EMST program resulted in reducing the AMT for the study participants.

Facilitated IO Curves

IO curves were obtained for each participant from data obtained during three testing sessions conducted before and after EMST. Each participant's average IO curves from pre and post training sessions are illustrated (Figure 3-3 through Figure 3-12). Results from statistical analysis comparing pre and post EMST IO curve slopes obtained using linear as well as sigmoid curve fitting equations are given below.

Linear Slope Change with EMST

Linear slope values obtained using the linear curve fitting equation described in Chapter two revealed that EMST did not impact this measure. Following 4 weeks of EMST there was no significant change in slope measures of IO curves (Table 3-5).

Sigmoid Slope Change with EMST

As sigmoid curve fits are most commonly used to describe IO curve slopes, slope measures obtained from a sigmoid curve fitting equation described in Chapter 2 was also used to compare pre and post EMST IO curve slopes. Following 4 weeks of EMST the slopes obtained using sigmoid curve fitting model also did not indicate a significant change in this variable (Table 3-6).

Therefore, following the results from our study, it is indicated that EMST does not influence the slope parameter obtained using the linear and or sigmoid curve fit equation.

MEP Amplitude Change across Stimulation Intensities

Additional paired t-tests were performed for average MEP amplitudes obtained pre and post EMST across all participants for each of the stimulation intensities ranging from 90 % MT to 170 % MT (Table 3-7 and Table 3-8). Comparison of change in MEP amplitude at any of the stimulation intensities across participants showed no significant difference with training after application of Bonferroni Correction (Table 3-9, Figure 3-13). Representative examples of MEPs

obtained from three participants collected at 130 %AMT stimulation intensity pre and post EMST are provided (Figure 3-14).

SOLMT – Location on Stock Brain

SOLMT location was assessed on the stock brain MRI image and was documented on the 1cm² grid markers. These locations are marked in green for SOLMTs obtained during pre-EMST measurement sessions and blue for SOLMTs obtained during post-EMST measurement sessions (Figure 3.15 – 3.24).

SOLMT – Physical Location

SOLMT measured as a distance (cms) from various landmarks namely distances from 1) vertex to SOLMT, 2) pre-auricular point to SOLMT and 3) anterior or posterior distance from the vertex provide reference data in comparison to other studies that have used the 10-20 EEG system (Table 3-10 and Table 3-11). Change in the three physical location measures are noted - 1) vertex to SOLMT (pre training: average = 1.925 +/- 0.374 cms; post training: average = 1.885 +/- 0.236 cms; p = 0.736), 2) pre-auricular point to SOLMT (pre training: average = 15.509 +/- 0.951 cms; post training: average = 15.208 cms; p = 0.322) and 3) anterior or posterior distance from the vertex (pre training: average = 0.675 +/- 0.754 cms; post training: average = 0.4 +/- 0.492 cms; p = 0.308). A statistical comparison of the pre and post training values for the three measurements obtained for physical location of the SOLMT did not yield statistical significance.

Change in Maximum Expiratory Pressure Values with EMST

Following the EMST program a significant increase in maximum expiratory pressure that is an indirect measure of force was seen in study participants. 4 weeks of EMST resulted in 61.6% gain in MEP (an indirect measure of expiratory muscle strength) from 118.7 +/- 25.574 cmH₂O to 161.6 +/- 37.334 cmH₂O (t-score = -6.3, N = 10, p = 0.000) (Table 3-14, Figure 3-25).

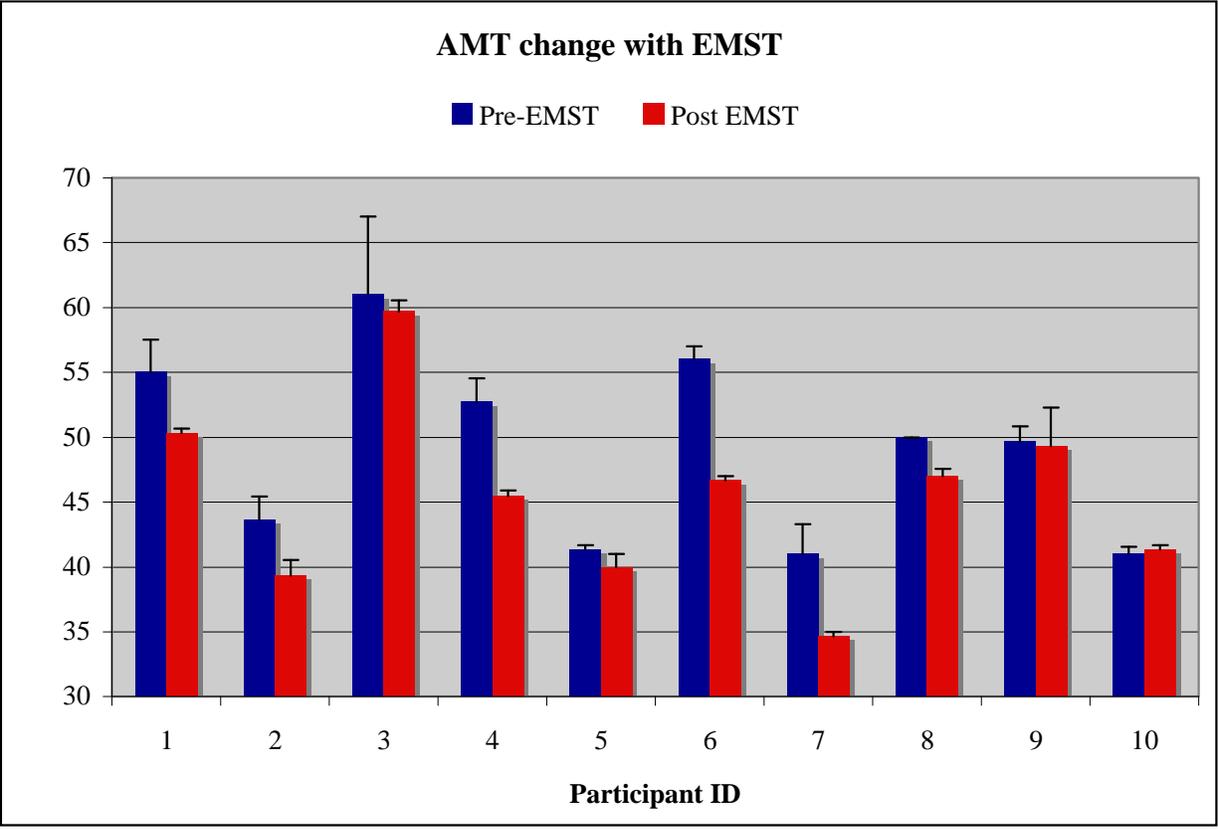


Figure 3-1: Change in AMT with EMST in each participant showed a decrease or no change and this reduction was found to be statistically significant. Values are mean +/- standard error. Note that a reduction in AMT was found for almost all of the participants.

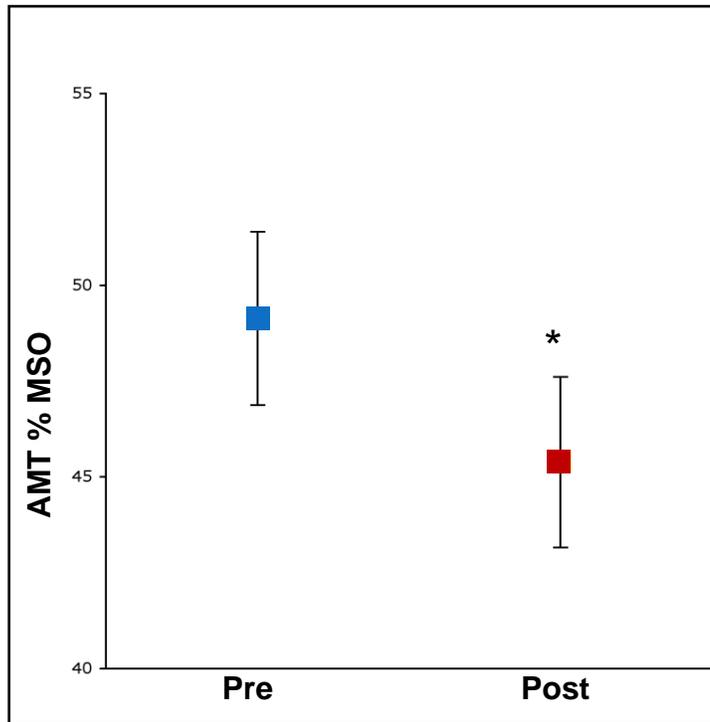


Figure 3-2: Change in AMT with EMST across participants showed a decrease that was found to be statistically significant. Values are mean +/- standard error and the asterisk sign indicates statistical significance.

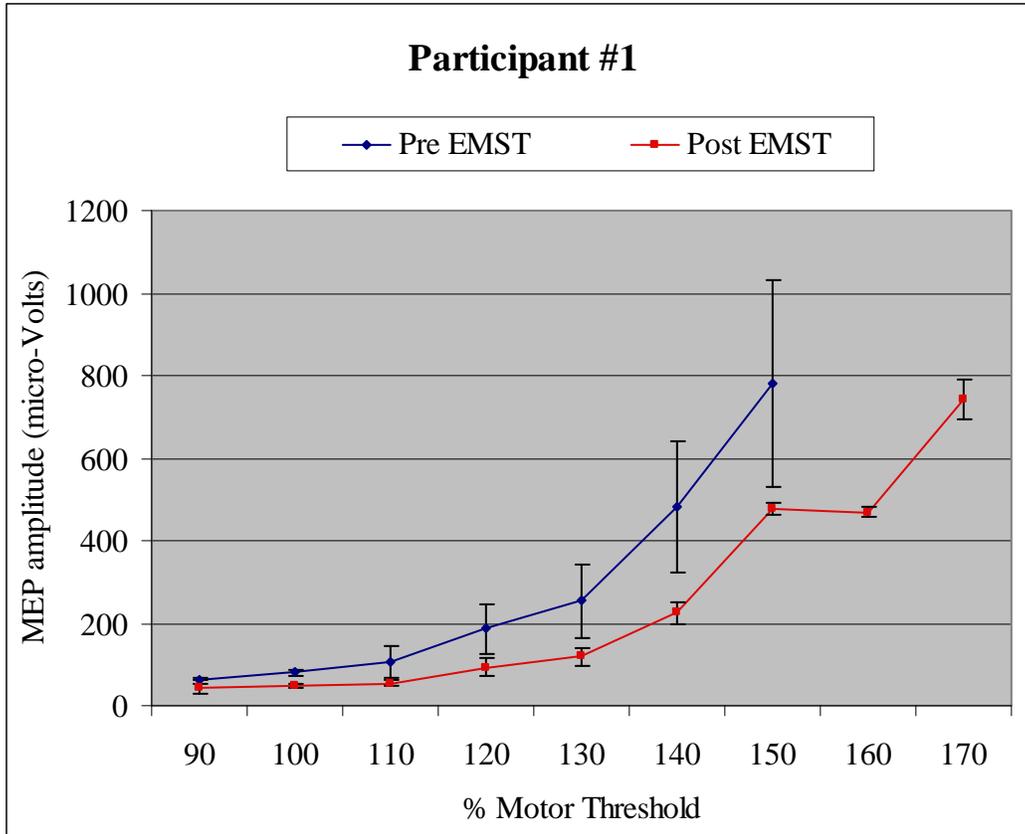


Figure 3-3: The pre and post EMST IO curves obtained for Participant 1 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

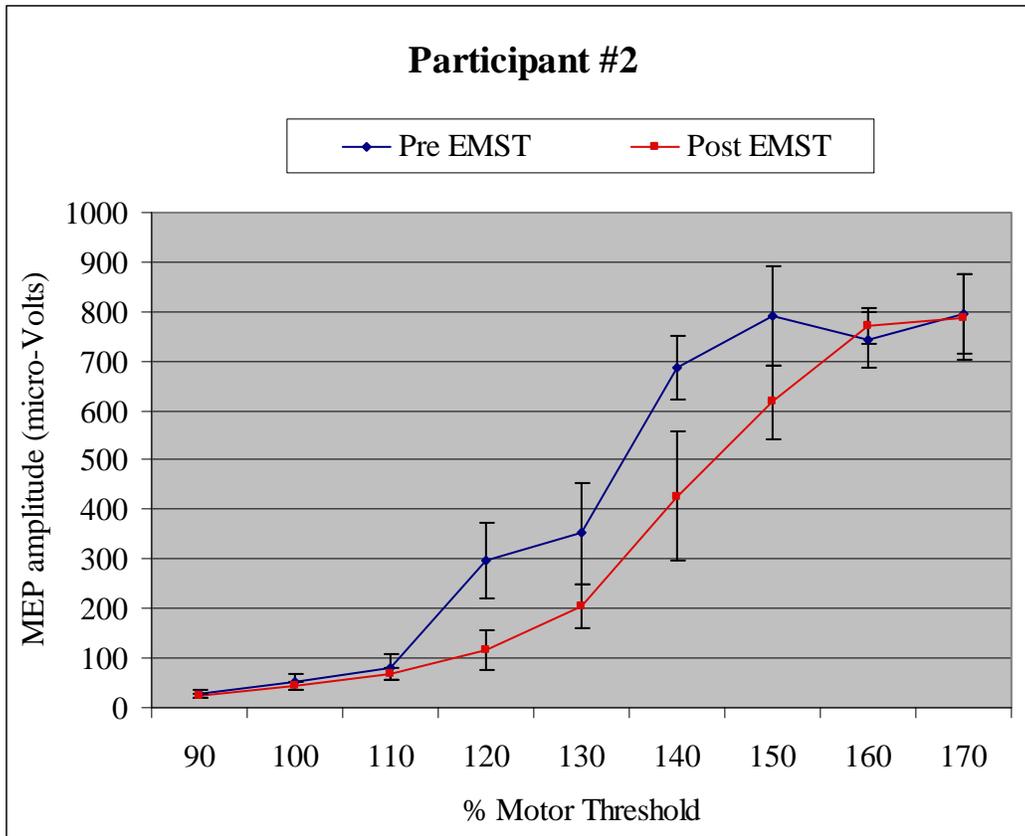


Figure 3-4: The pre and post EMST IO curves obtained for Participant 2 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

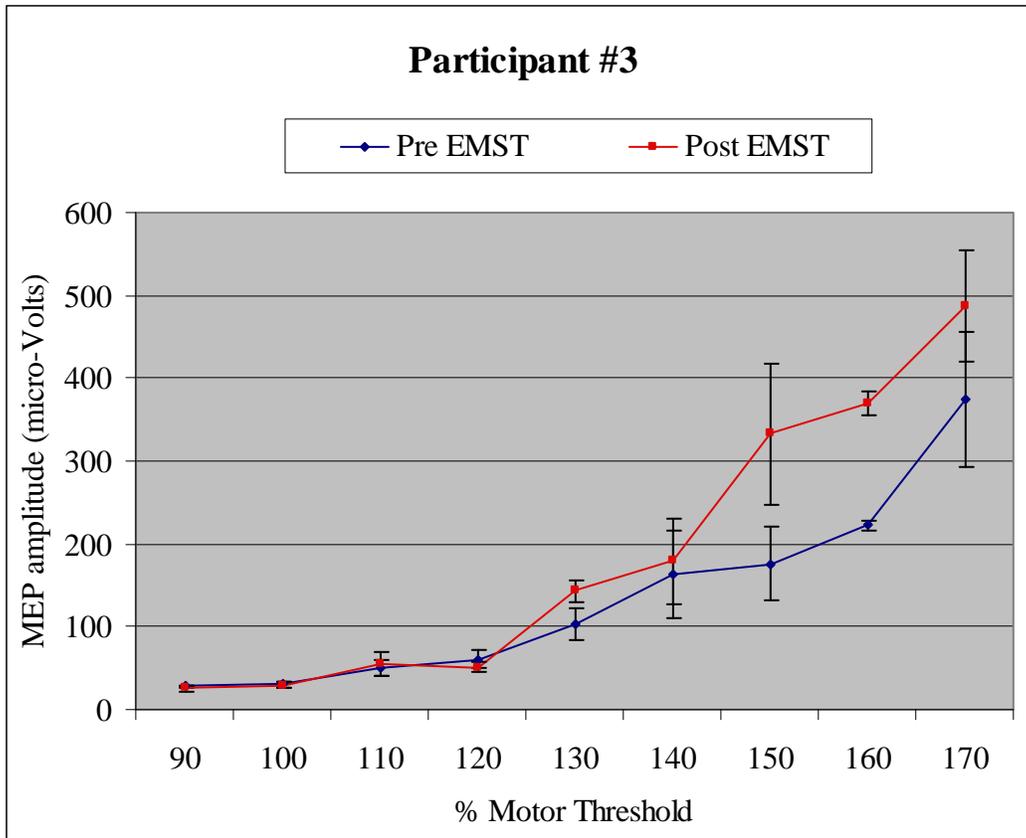


Figure 3-5: The pre and post EMST IO curves obtained for Participant 3 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

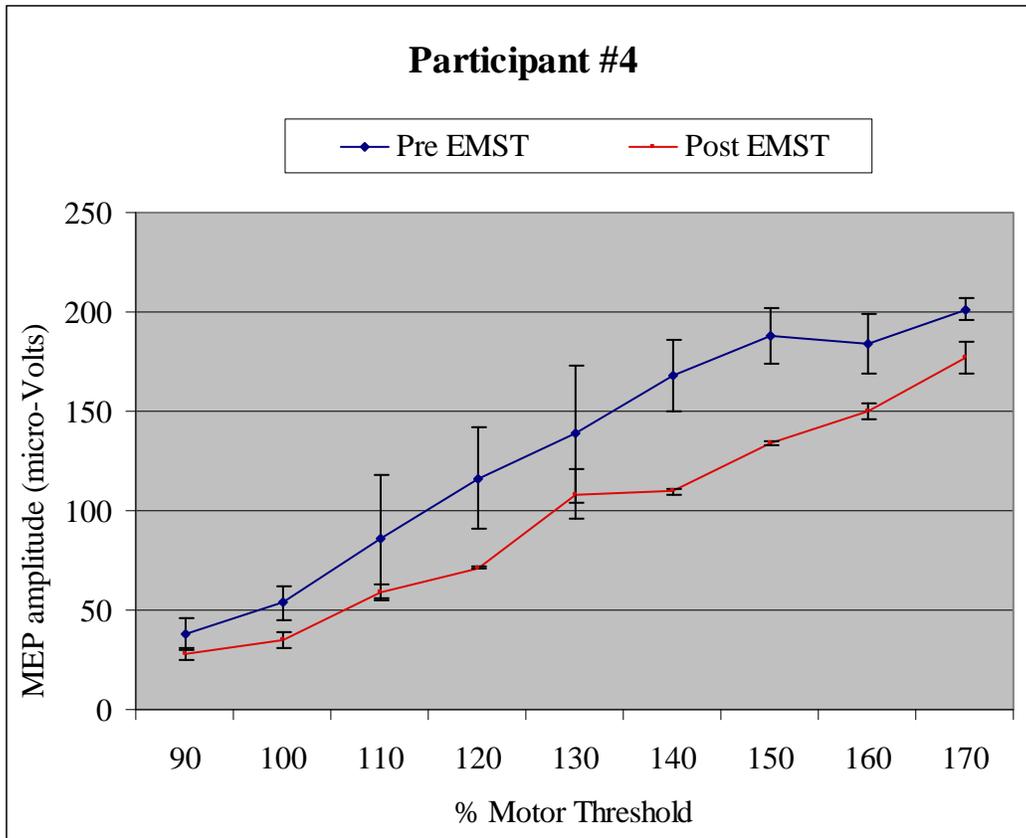


Figure 3-6: The pre and post EMST IO curves obtained for Participant 4 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

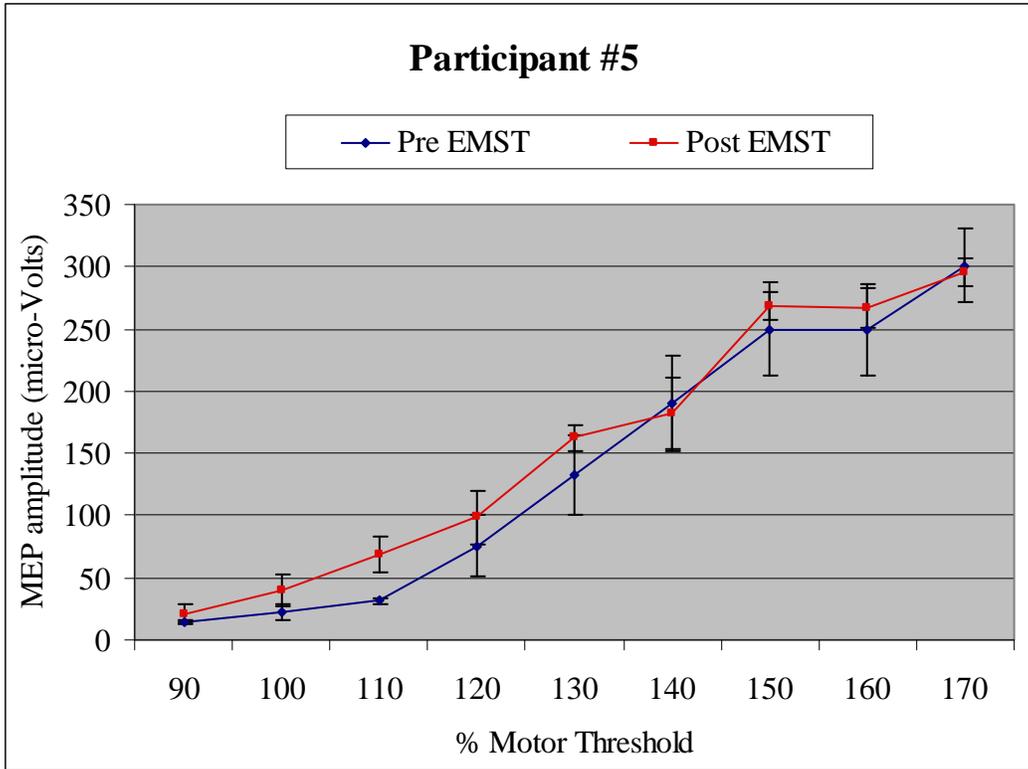


Figure 3-7: The pre and post EMST IO curves obtained for Participant 5 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

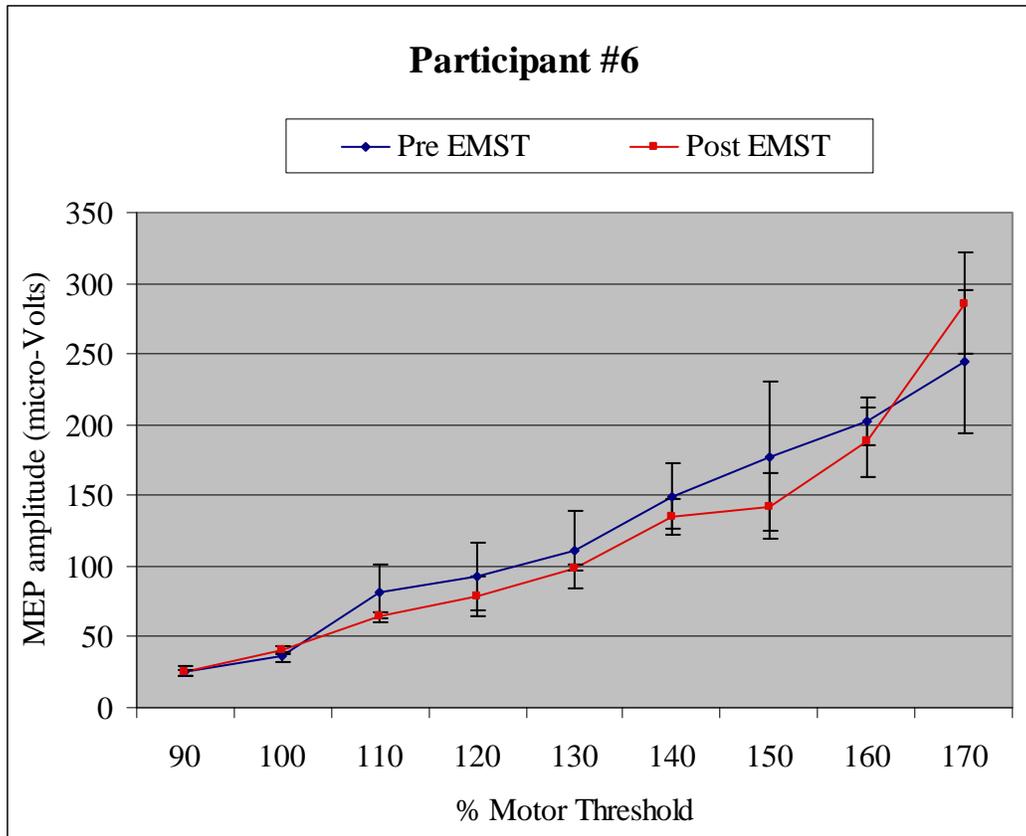


Figure 3-8: The pre and post EMST IO curves obtained for Participant 6 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

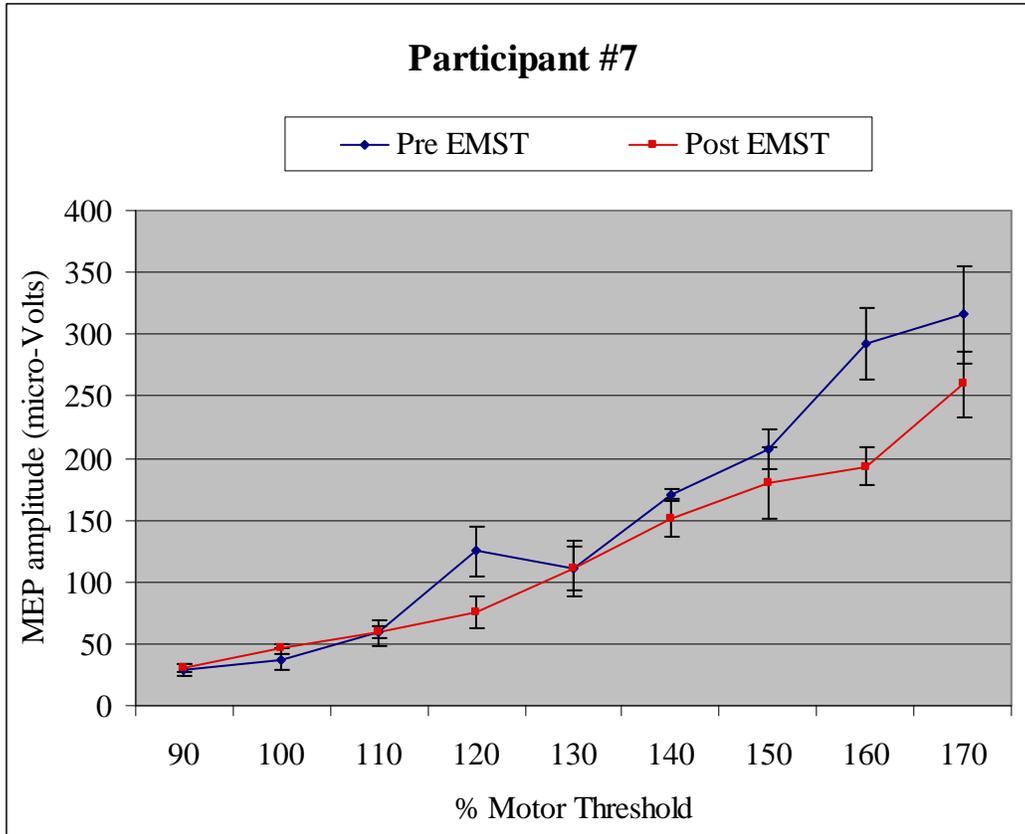


Figure 3-9: The pre and post EMST IO curves obtained for Participant 7 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

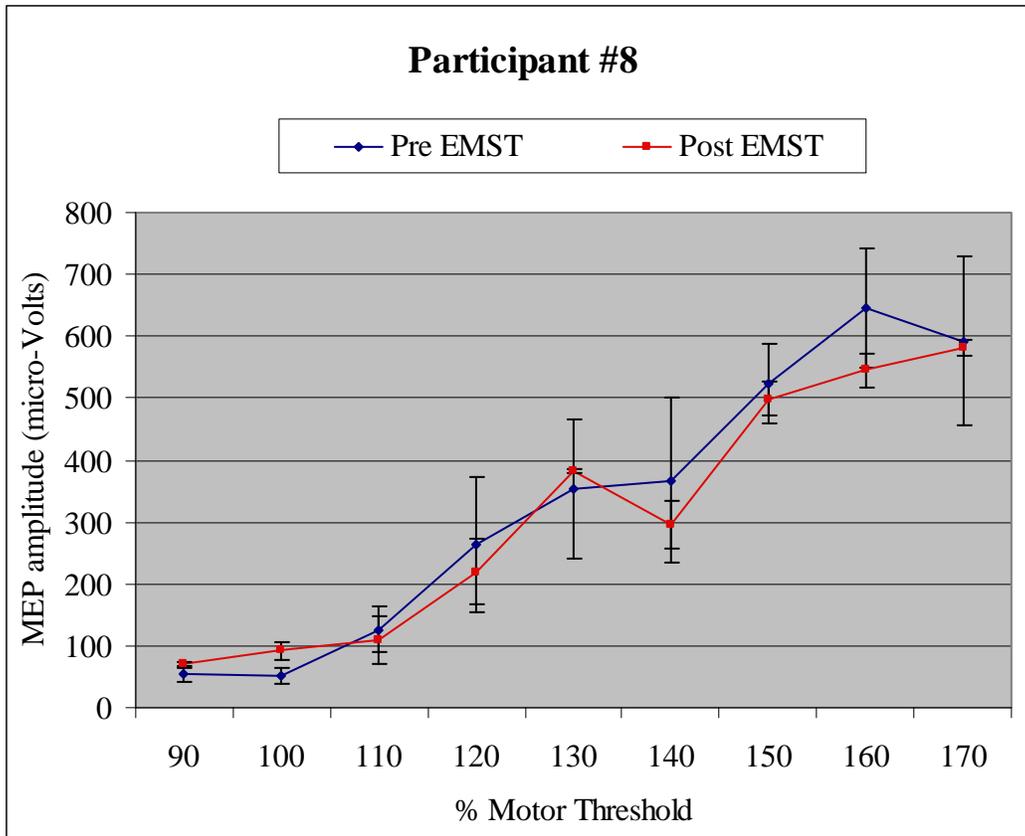


Figure 3-10: The pre and post EMST IO curves obtained for Participant 8 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

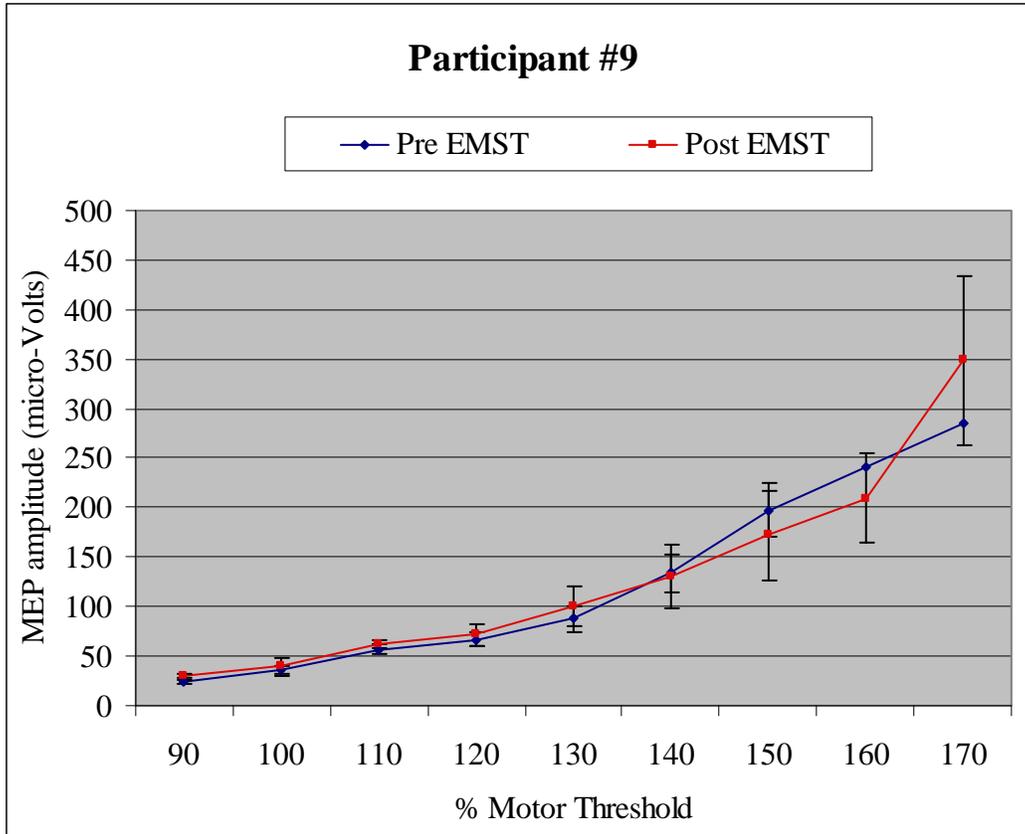


Figure 3-11: The pre and post EMST IO curves obtained for Participant 9 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

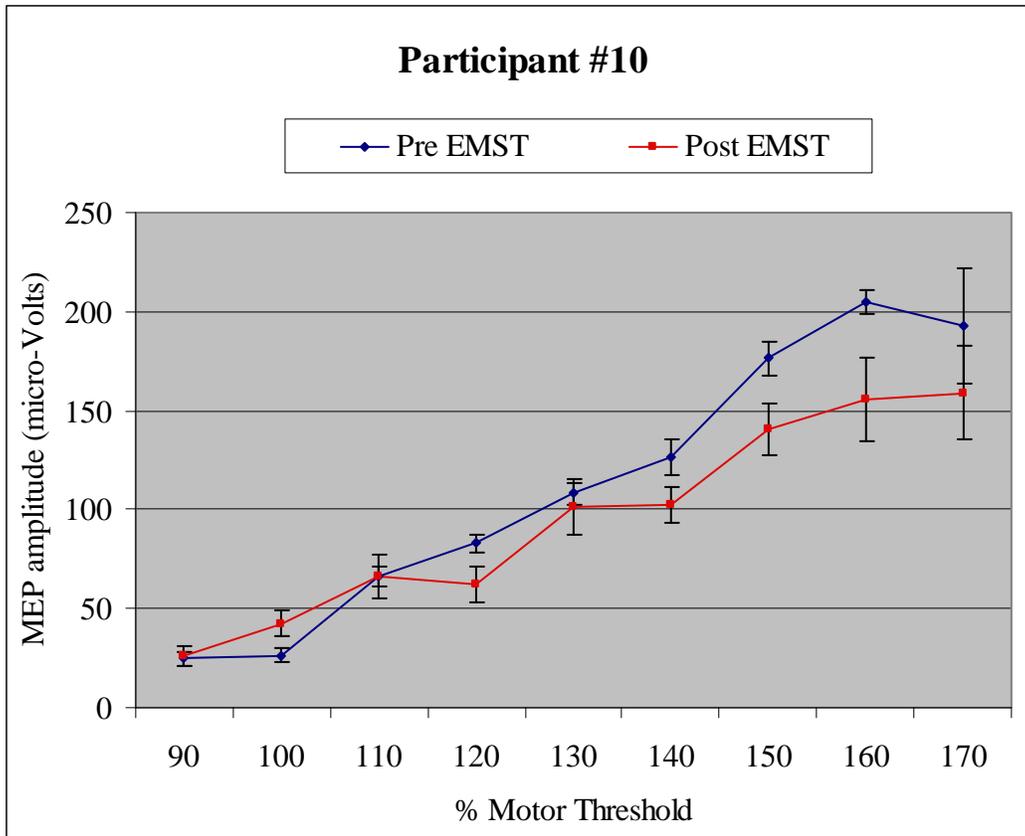


Figure 3-12: The pre and post EMST IO curves obtained for Participant 10 by averaging three pre EMST and three post EMST testing sessions. Values are mean +/- standard error.

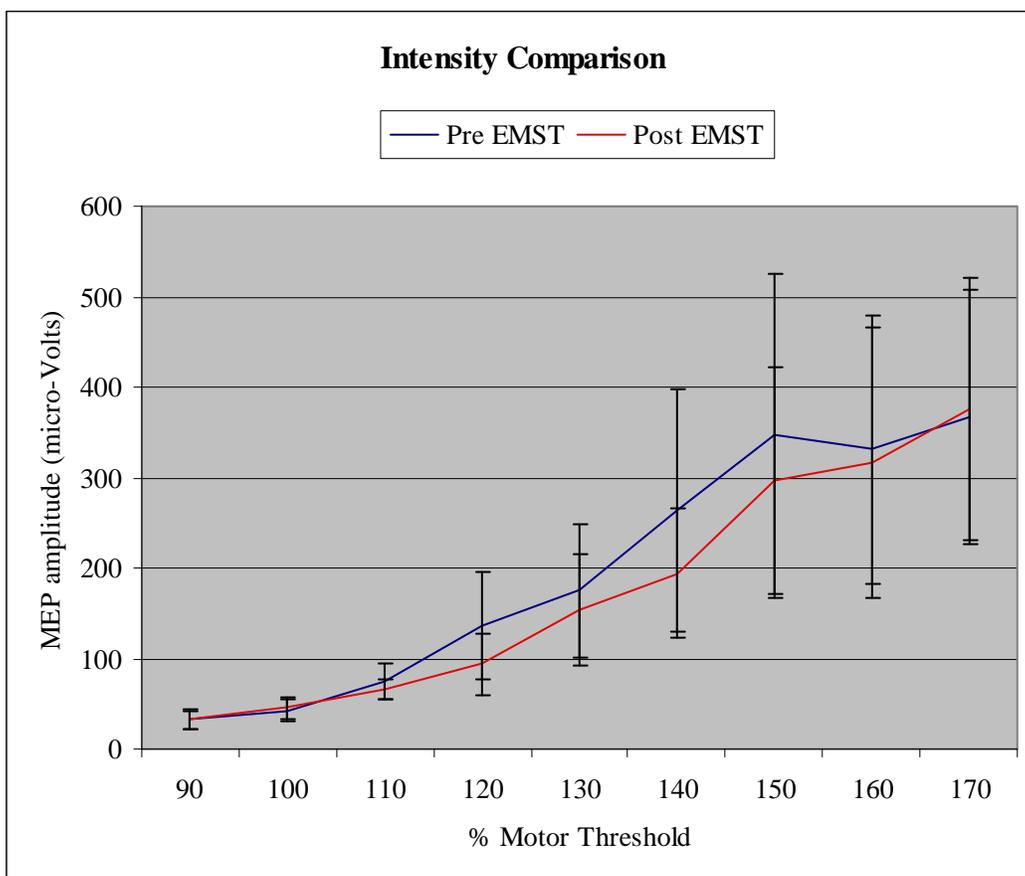


Figure 3-13: This is a graphical representation for the average for all participants' IO curves pre and post EMST plotted using an average of three pre measures for the pre-training MEP amplitude values and the average of three post training MEP amplitude values. Values are mean +/- standard error. As is clear on visual inspection, IO curve data points exhibited large degree of variability both within and across participants

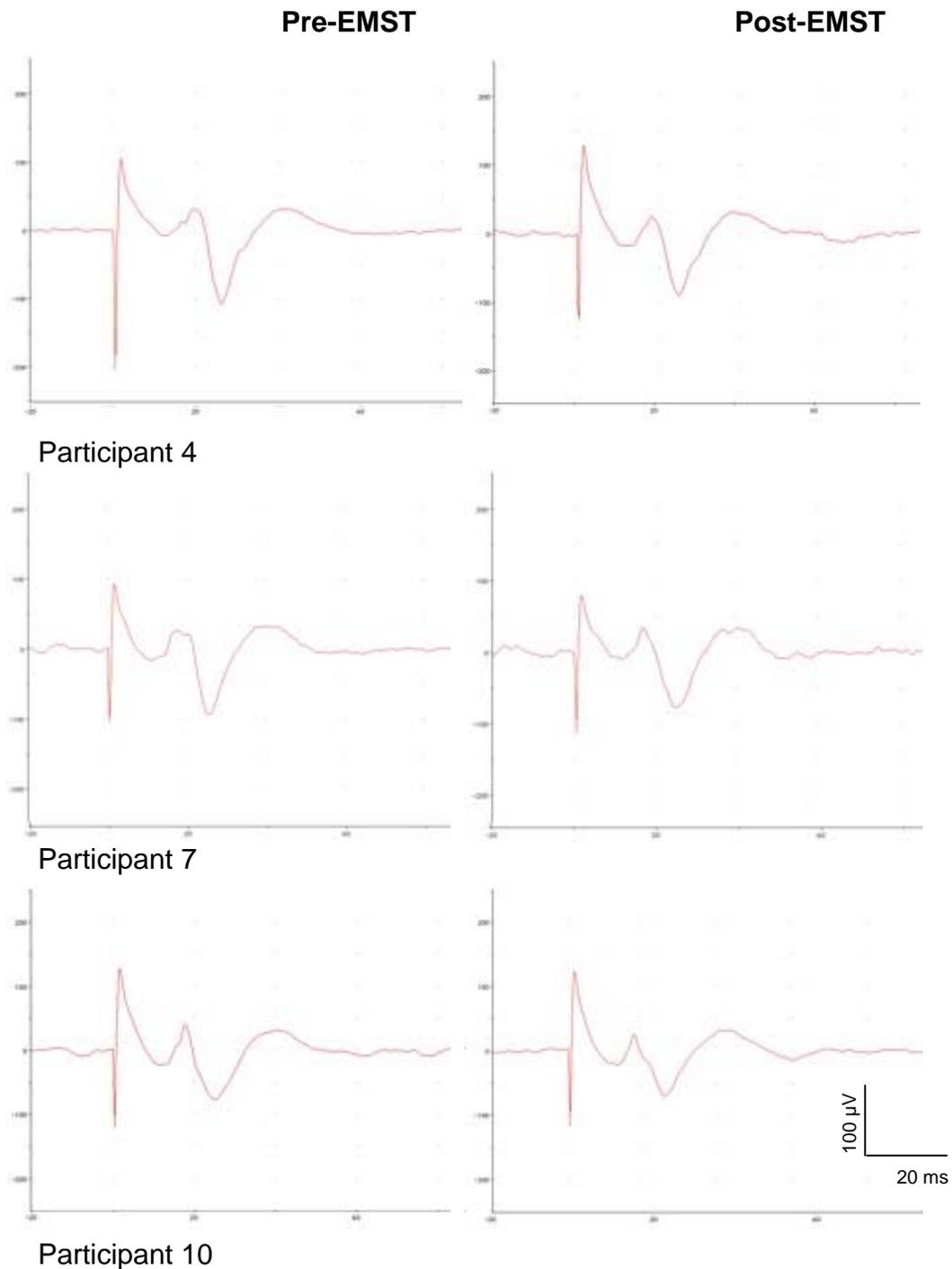


Figure 3-14: Examples from three participants in this study showing average MEP responses at 130% AMT stimulation intensity pre and post EMST. MEPs obtained pre-EMST is shown on the left and the MEPs from the post-EMST sessions are shown on the right.

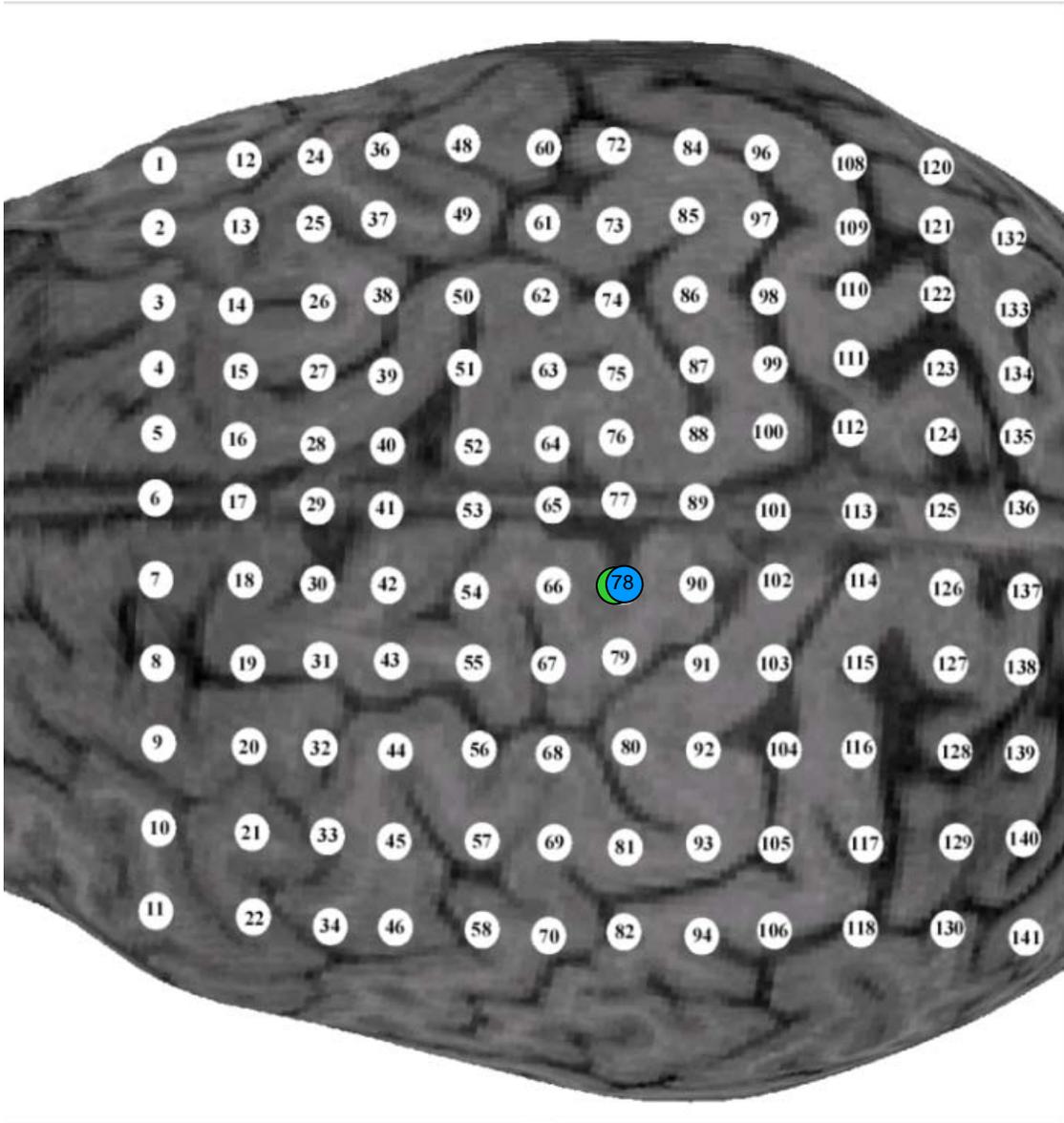


Figure 3-15: SOLMT locations for Participant 1 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 78, 78, and 78 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOLMT locations (site numbers: 78, 78, and 78 for the first, second and third post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for all pre and post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT sites for the pre-testing sessions.

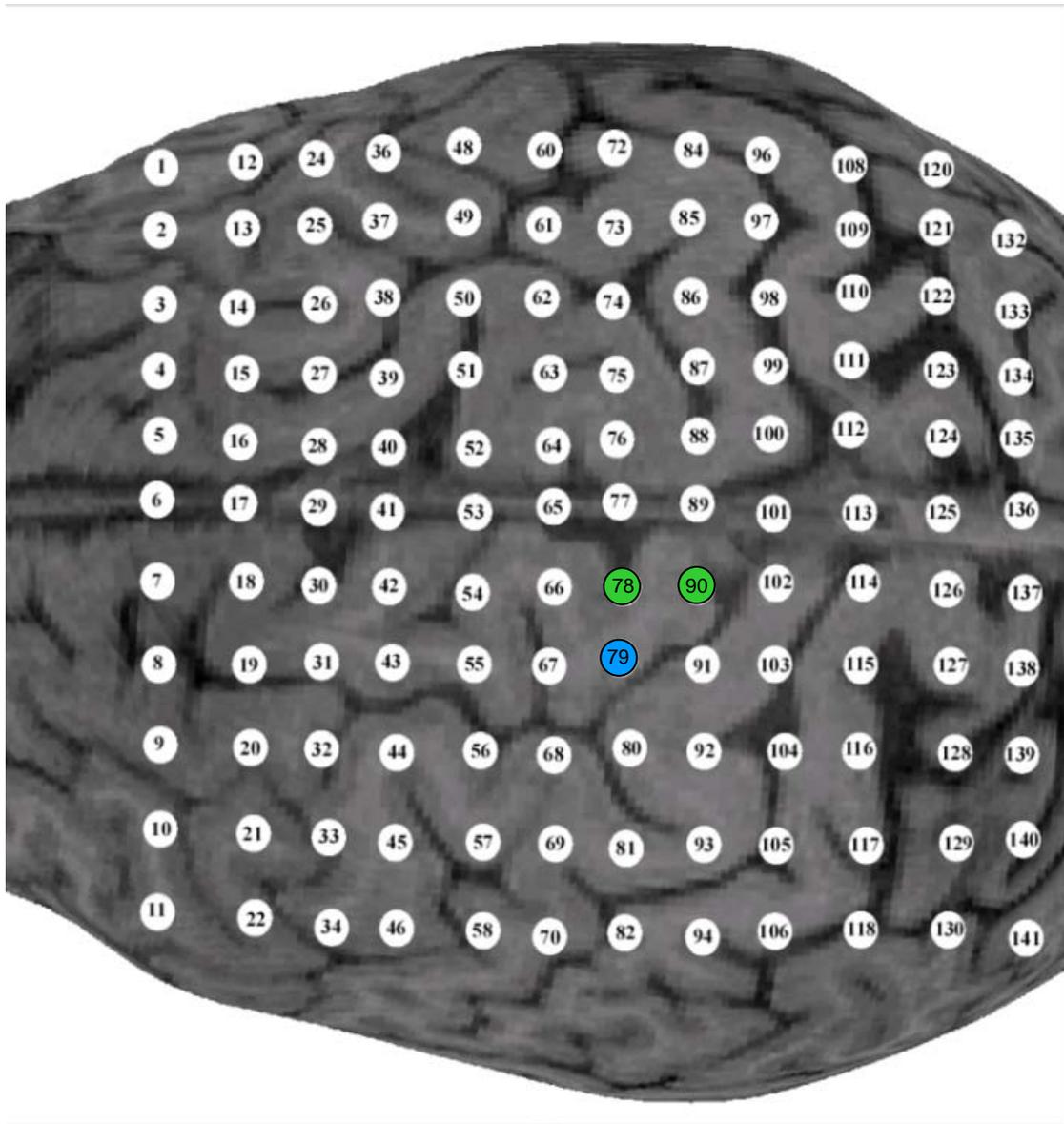


Figure 3-16: SOLMT locations for Participant 2 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 78, 90, and 90 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOLMT locations (site numbers: 79, 79, and 79 for the first, second and third post-testing sessions respectively) are shown in blue.

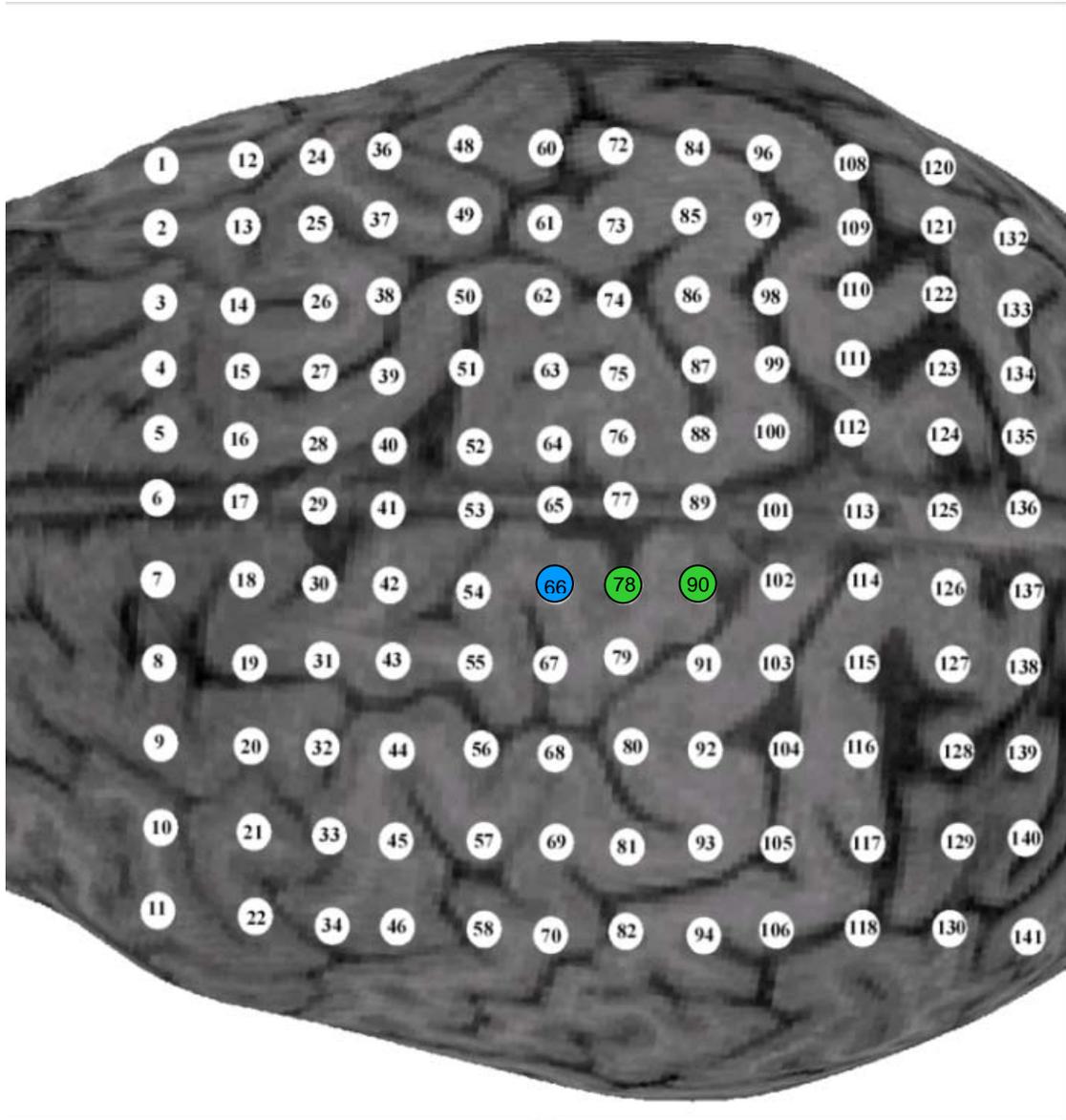


Figure 3-17: SOLMT locations for Participant 3 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 78, 78, and 90 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOLMT locations (site numbers: 66, 66, and 66 for the first, second and third post-testing sessions respectively) are shown in blue.

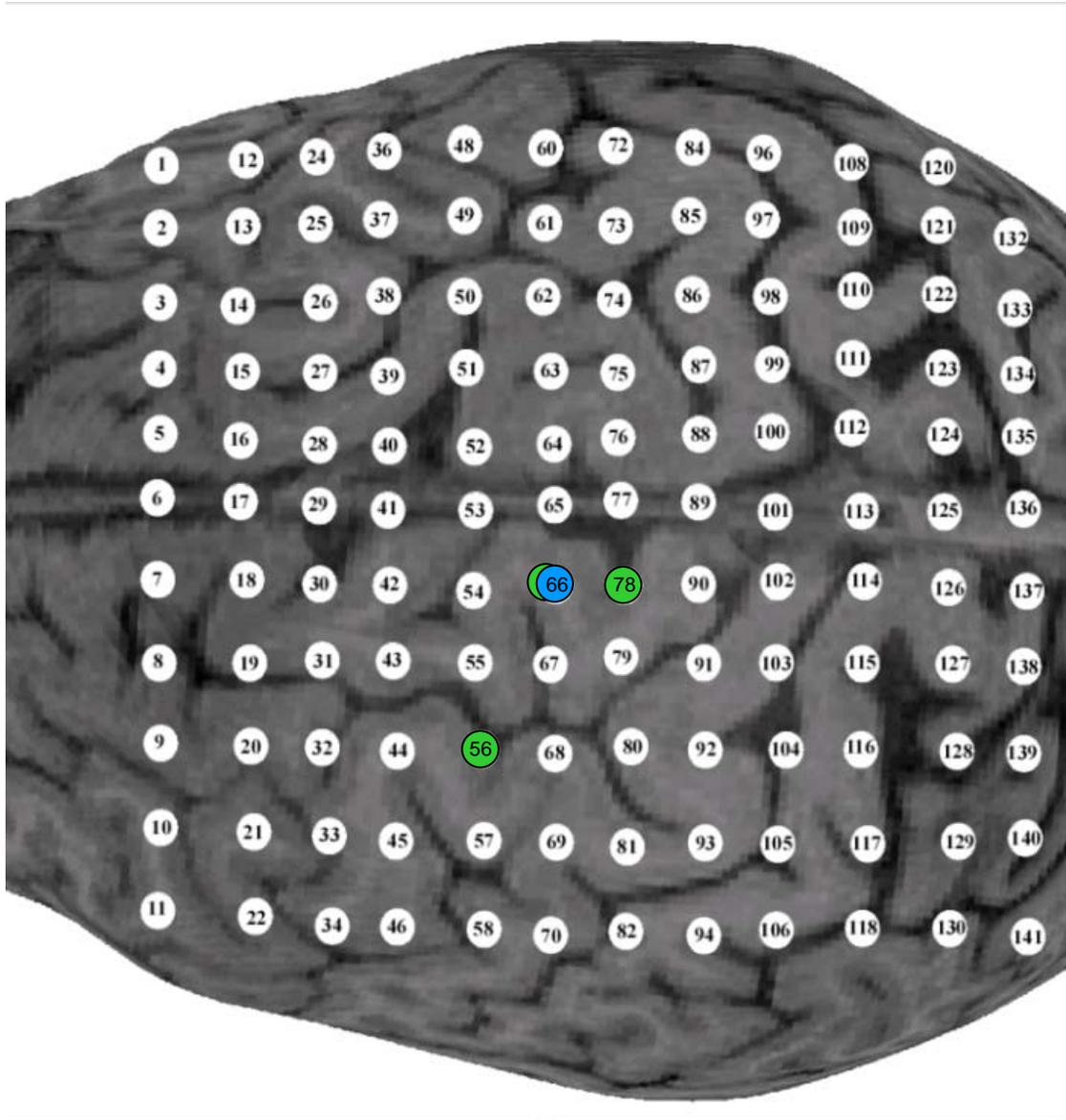


Figure 3-18: SOLMT locations for Participant 4 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 66, 66, and 56 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOMT locations (site numbers: 66 and 66 for the first and second post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for two of the pre as well as post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT sites for the pre-testing sessions. Please note that only two post-training TMS measures were obtained for this participant.

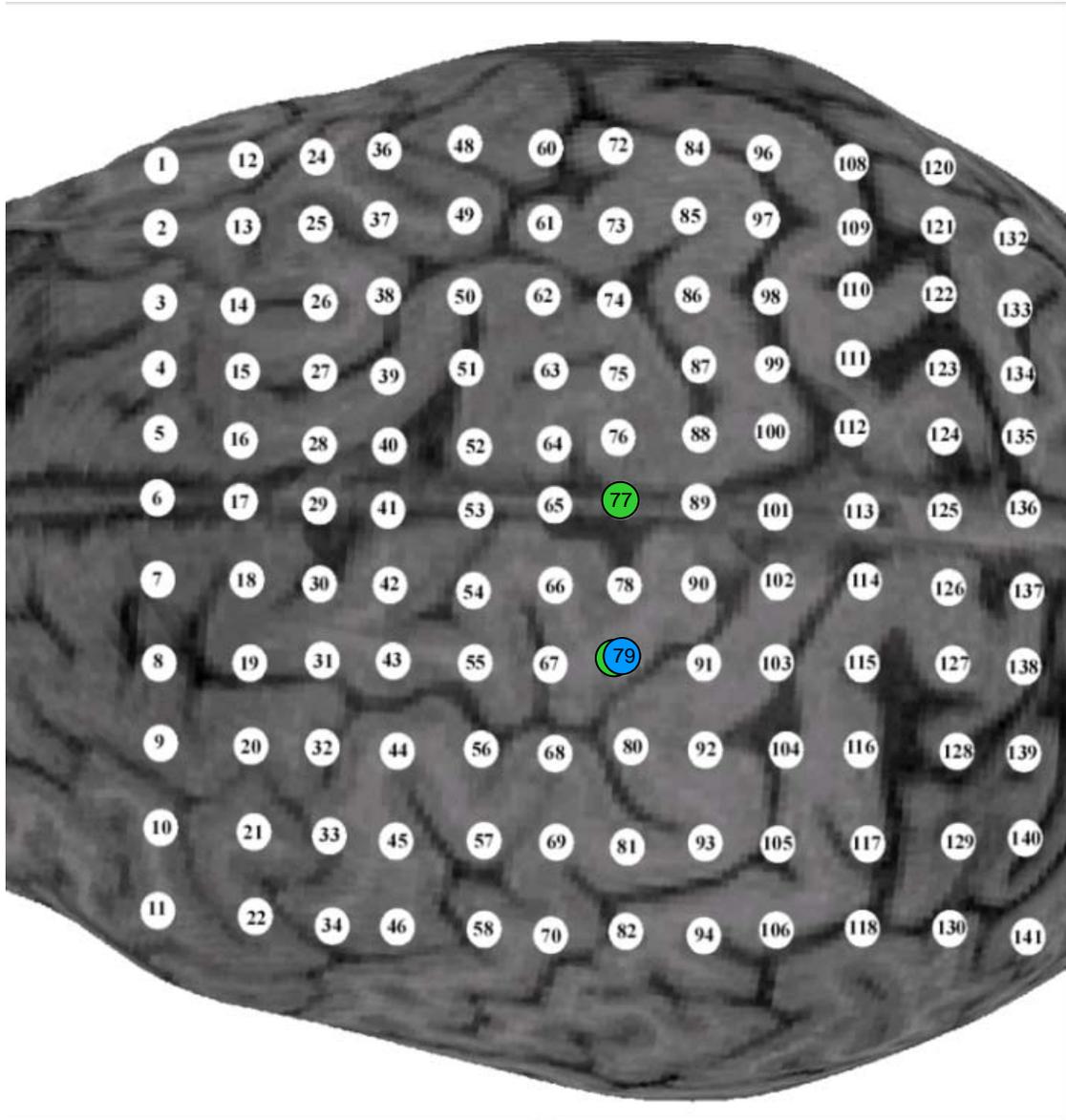


Figure 3-19: SOLMT locations for Participant 5 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 79, 79, and 77 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOMT locations (site numbers: 79, 79, and 79 for the first, second and third post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for two of the pre testing sessions as well as all of the post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT site for the pre-testing session.

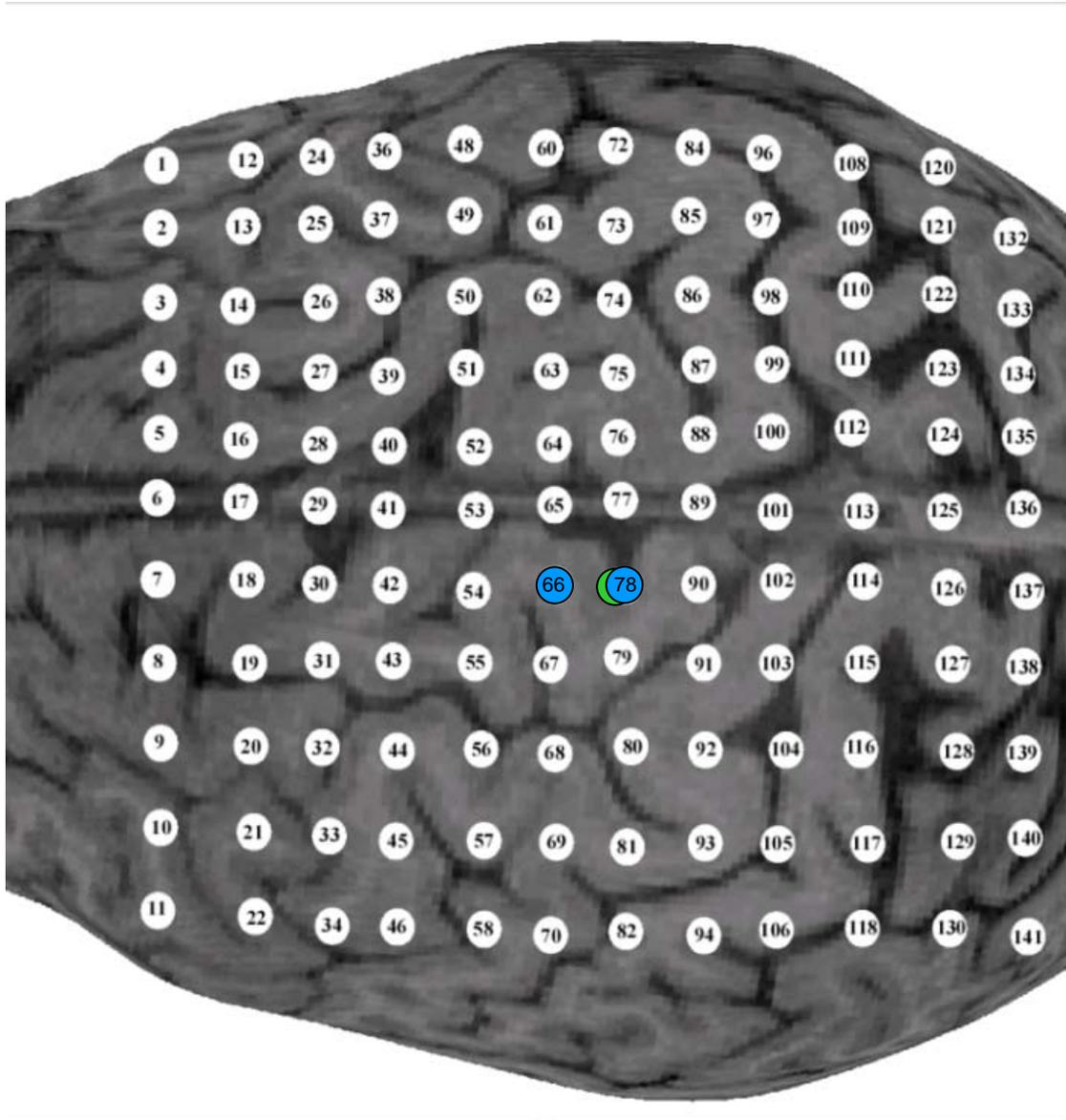


Figure 3-20: SOLMT locations for Participant 6 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 78, 78, and 78 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOLMT locations (site numbers: 78, 66, and 66 for the first, second and third post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for all pre and one of the post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT site for the pre-testing sessions.

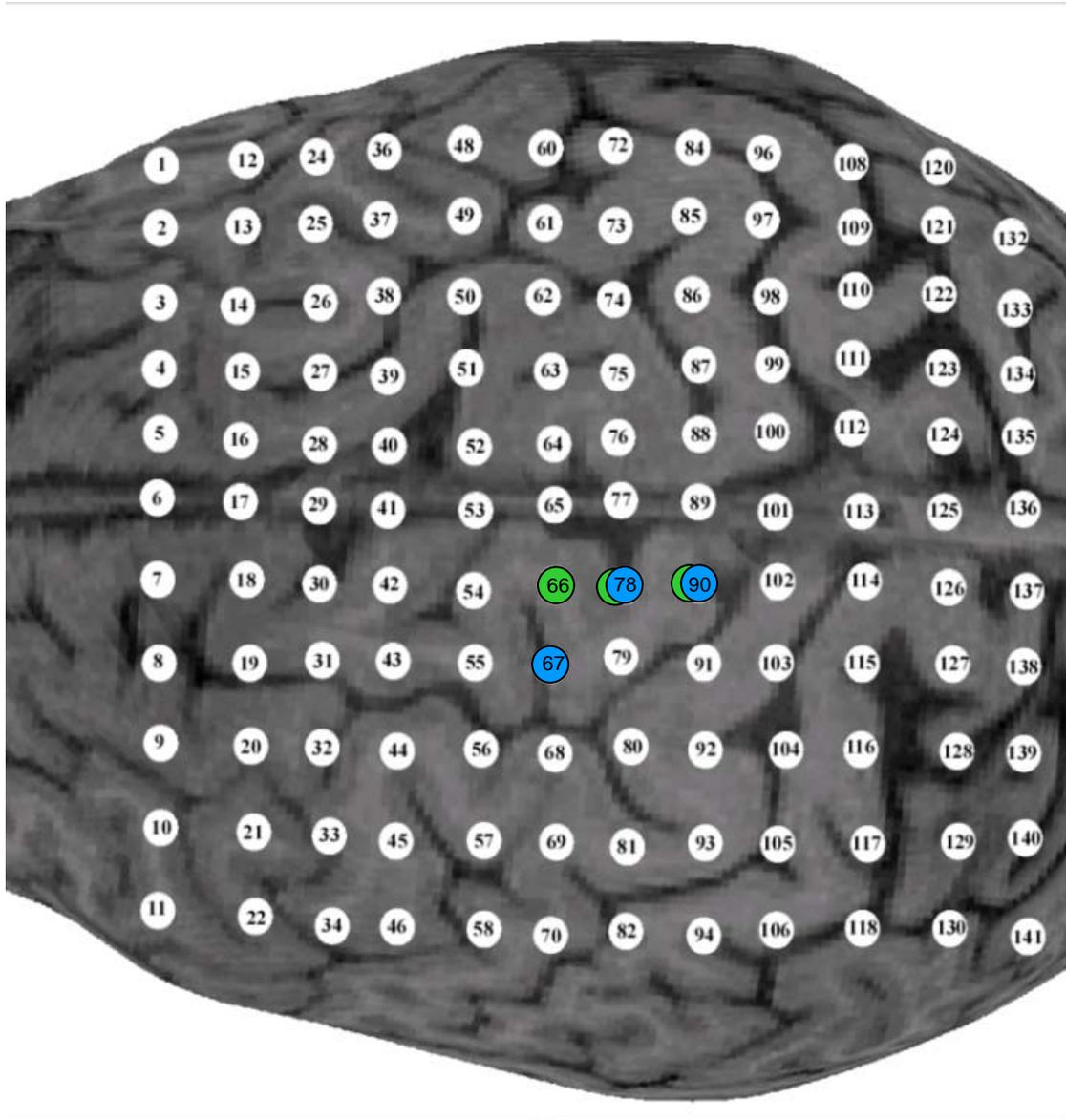


Figure 3-21: SOLMT locations for Participant 7 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 90, 78, and 66 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOLMT locations (site numbers: 78, 67, and 90 for the first, second and third post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for two of the pre and post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT sites for the pre-testing sessions.

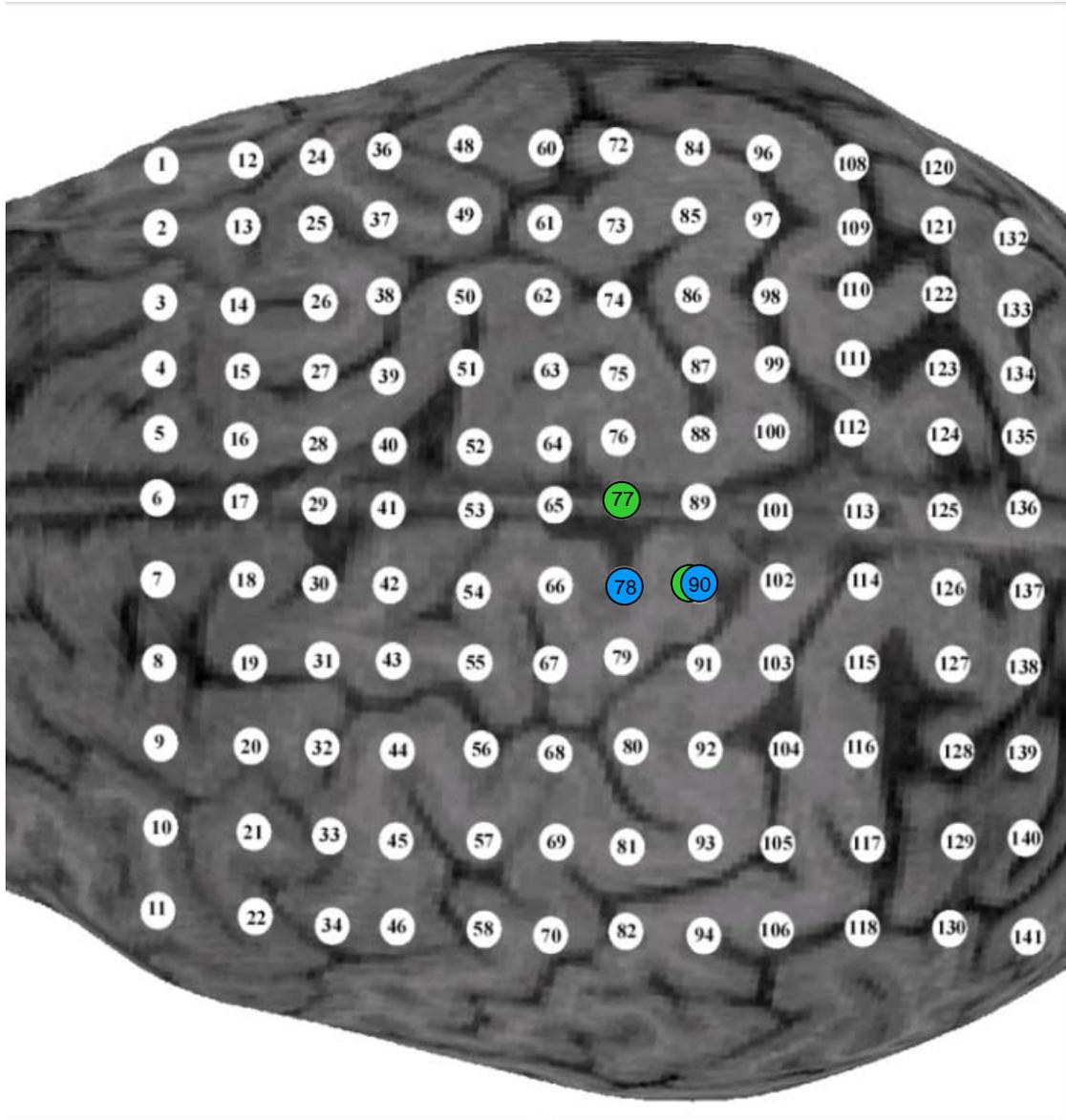


Figure 3-22: SOLMT locations for Participant 8 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 90, 77, and 90 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOMT locations (site numbers: 90, 78, and 78 for the first, second and third post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for two of the pre and one of the post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT site for the pre-testing sessions.

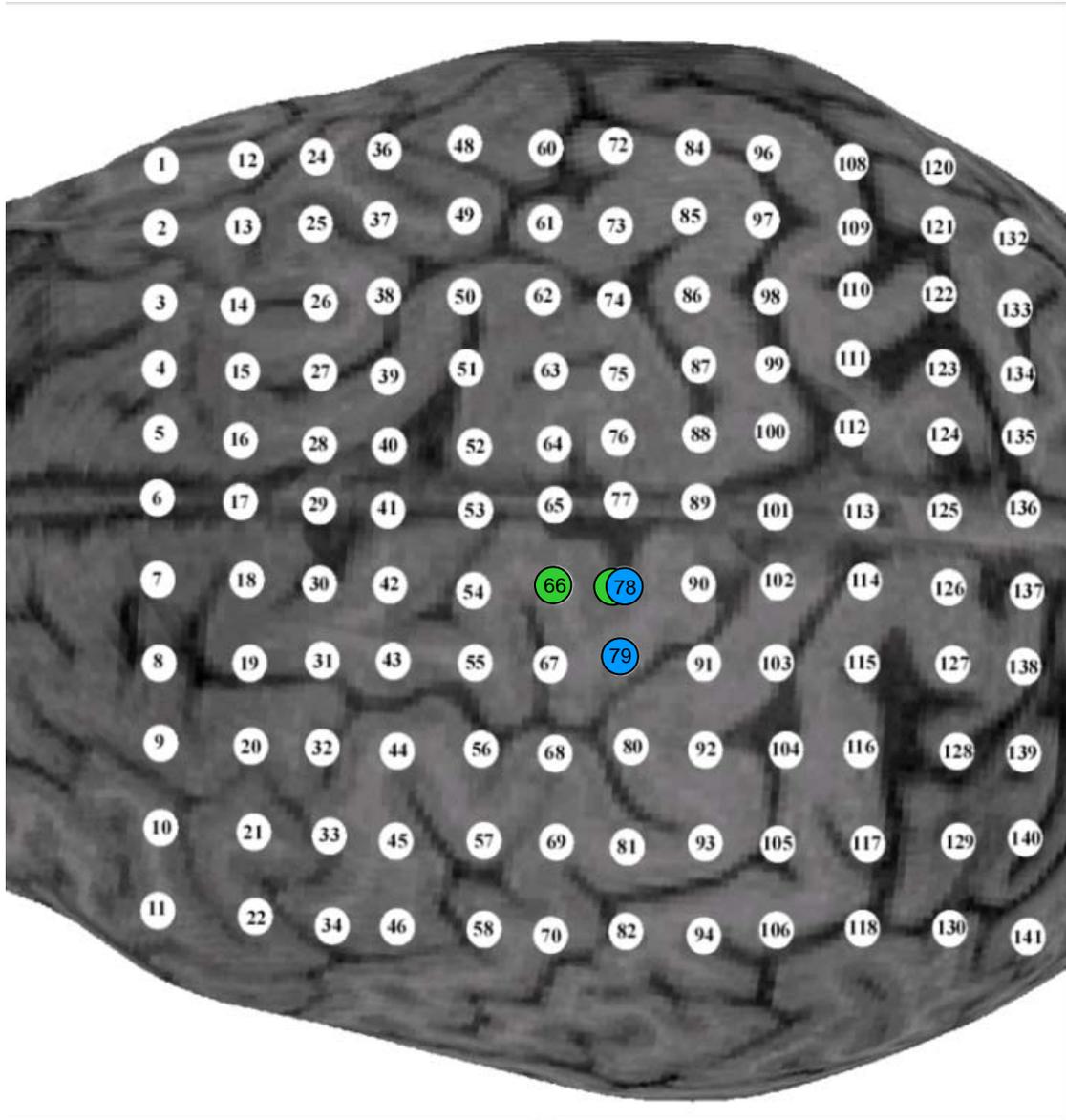


Figure 3-23: SOLMT locations for Participant 9 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 78, 78, and 66 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOLMT locations (site numbers: 78, 79, and 78 for the first, second and third post-testing sessions respectively) are shown in blue. As the SOLMT was located at the same site for two of the pre as well as post testing sessions, the post testing session site marker in blue is superimposed over the green marker indicating the SOLMT site for the pre-testing sessions.

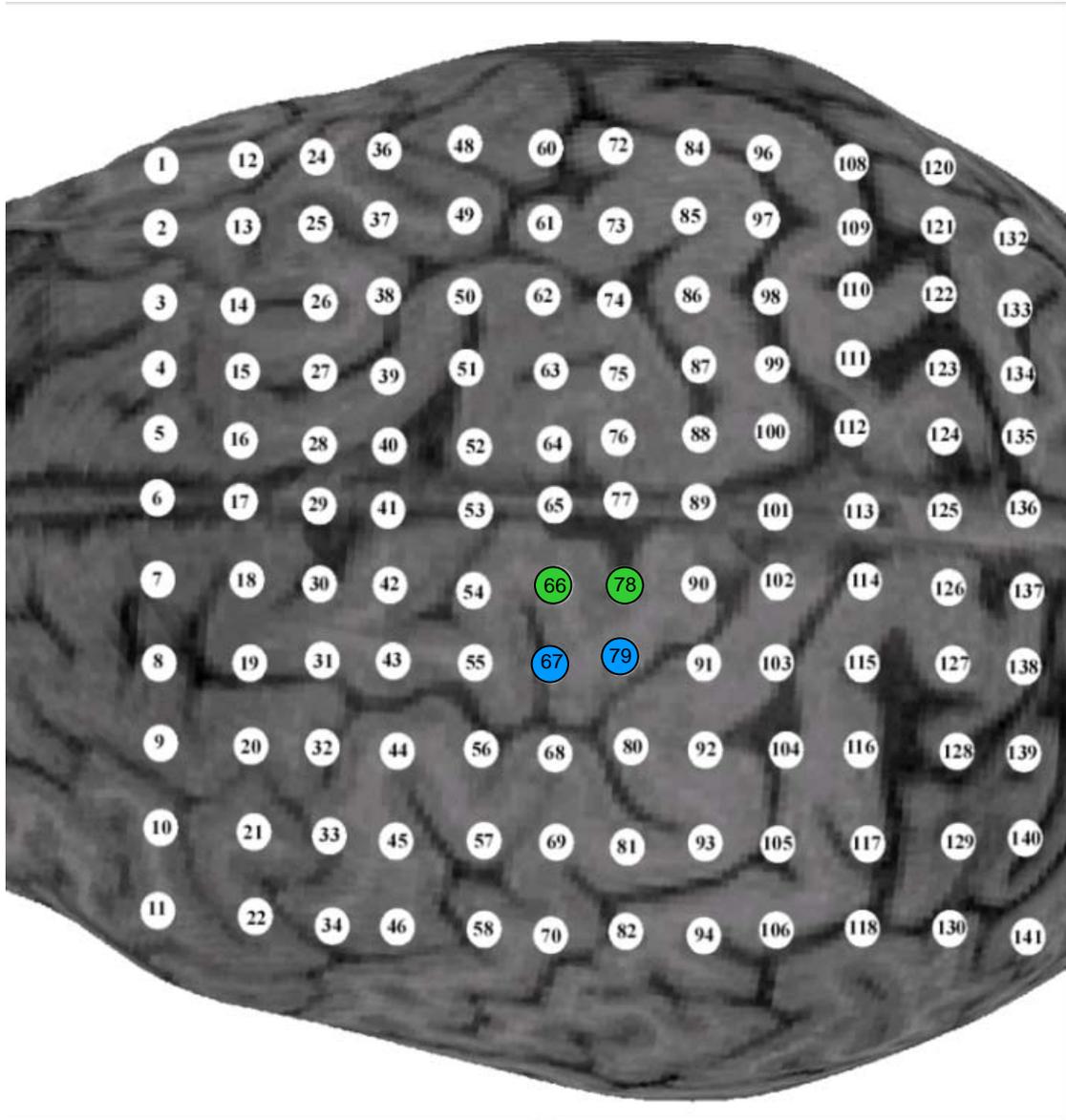


Figure 3-24: SOLMT locations for Participant 10 are shown as three pre-EMST SOLMT locations on the stock brain image (site numbers: 66, 78, and 66 for the first, second and third pre-testing sessions respectively) and are shown in green and three post EMST SOMT locations (site numbers: 79, 79, and 67 for the first, second and third post-testing sessions respectively) are shown in blue.

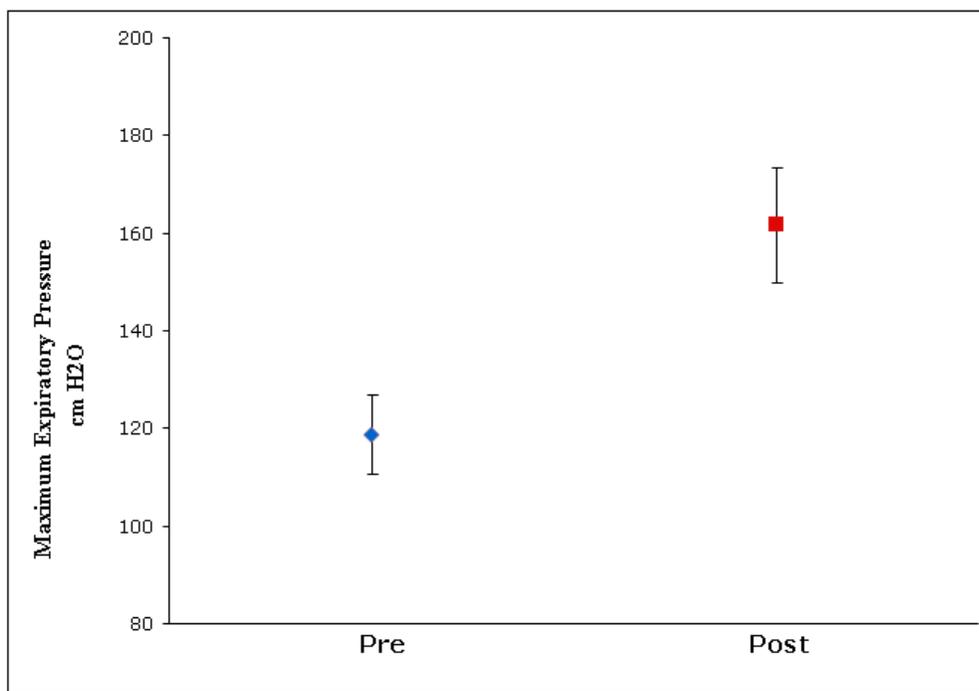


Figure 3-25: Change in maximum expiratory pressure with EMST across participants showed an increase that was found to be statistically significant. Values are mean +/- standard error and the asterisk sign indicates statistical significance.

Table 3-1: AMT values obtained during the three baseline testing sessions.

<i>Participant ID</i>	<i>Baseline 1</i>	<i>Baseline 2</i>	<i>Baseline 3</i>
1	57	50	58
2	47	43	41
3	55	55	73
4	49	54	55
5	41	41	42
6	58	55	55
7	45	37	41
8	50	50	50
9	48	52	49
10	43	39	41

Table 3-2: The slope parameter values for IO curves obtained using the linear model over the three baseline testing sessions and the average slope and standard deviation measures.

<i>Participant ID</i>	<i>Baseline 1</i>	<i>Baseline 2</i>	<i>Baseline 3</i>	<i>Average</i>	<i>S.D.</i>
1	0.725	0.603	0.858	0.729	0.127
2	0.882	0.881	0.871	0.878	0.006
3	0.743	0.815	0.738	0.766	0.043
4	0.917	0.946	0.779	0.881	0.090
5	0.949	0.902	0.925	0.925	0.024
6	0.934	0.940	0.796	0.890	0.081
7	0.908	0.857	0.927	0.897	0.036
8	0.519	0.812	0.638	0.656	0.147
9	0.813	0.885	0.833	0.844	0.037
10	0.956	0.964	0.855	0.925	0.061

Table 3-3: The slope parameter values for IO curves from sigmoid model over the three baseline testing session and the average slope and standard deviation measures

<i>Subject ID</i>	<i>Baseline 1</i>	<i>Baseline 2</i>	<i>Baseline 3</i>	<i>Average</i>	<i>S.D.</i>
1	0.033	0.091	0.026	0.050	0.036
2	0.058	0.056	0.117	0.077	0.034
3	0.021	0.016	0.042	0.026	0.014
4	0.043	0.033	0.048	0.041	0.008
5	0.043	0.063	0.011	0.039	0.026
6	0.001	0.026	0.003	0.010	0.014
7	0.024	0.006	0.018	0.016	0.009
8	-0.564	0.011	4.878	1.442	2.990
9	0.021	0.017	0.022	0.020	0.002
10	0.029	0.013	0.031	0.024	0.010

Table 3-4: Average values of AMT for motor cortical area corresponding to the lateral abdominal wall muscles obtained from three pre and three post EMST measurement sessions. Note that the post training AMT values are consistently lower than the pre-training AMT values.

<i>Subject ID</i>	<i>Avg. AMT pre-training</i>	<i>Avg. AMT-post training</i>
1	55.00	50.33
2	43.67	39.33
3	61.00	59.67
4	52.67	45.50
5	41.33	40.00
6	56.00	46.67
7	41.00	34.67
8	50.00	47.00
9	49.67	49.33
10	41.00	41.33

Table 3-5: Change in average slope values and standard deviation measures for IO curves using the linear curve fitting equations before and after 4 weeks of EMST.

<i>Subject ID</i>	<i>Avg. slope pre-training</i>	<i>S.D.</i>	<i>Avg. slope-post training</i>	<i>S.D.</i>
1	0.729	0.127	0.808	0.043
2	0.878	0.006	0.869	0.069
3	0.765	0.043	0.787	0.040
4	0.881	0.090	0.970	0.011
5	0.925	0.024	0.954	0.011
6	0.890	0.081	0.869	0.053
7	0.897	0.036	0.914	0.034
8	0.656	0.147	0.894	0.048
9	0.844	0.037	0.825	0.106
10	0.925	0.061	0.892	0.083

Table 3-6: Change in average slope values and standard deviation measures for IO curves using the sigmoid curve fitting equations before and after 4 weeks of EMST.

<i>Subject ID</i>	<i>Avg. slope pre-training</i>	<i>S.D.</i>	<i>Avg. slope-post training</i>	<i>S.D.</i>
1	0.05	0.036	0.03	0.011
2	0.08	0.034	0.07	0.020
3	0.03	0.014	0.04	0.013
4	0.04	0.008	0.01	0.009
5	0.04	0.026	0.03	0.009
6	0.01	0.014	0.01	0.005
7	0.02	0.009	0.03	0.024
8	1.44	2.990	0.02	0.015
9	0.02	0.002	0.02	0.009
10	0.02	0.010	0.03	0.044

Table 3-7: Intensity dependent MEP amplitude response (μV) for all 10 participants labeled below as P#1 to P#10 assessed pre-EMST.

<i>Intensity (% Motor Threshold)</i>	<i>MEP Amp. P #1</i>	<i>MEP Amp. P #2</i>	<i>MEP Amp. P #3</i>	<i>MEP Amp. P #4</i>	<i>MEP Amp. P #5</i>	<i>MEP Amp. P #6</i>	<i>MEP Amp. P #7</i>	<i>MEP Amp. P #8</i>	<i>MEP Amp. P #9</i>	<i>MEP Amp. P #10</i>
90	64.93	29.14	27.80	38.01	13.98	25.65	28.70	53.65	24.43	24.61
100	79.89	52.61	30.49	53.82	22.97	36.05	37.39	52.26	35.18	26.55
110	106.83	81.76	50.17	86.40	31.87	81.62	58.70	125.85	56.49	66.25
120	186.01	296.41	60.95	116.15	75.64	92.54	124.60	263.58	67.18	82.86
130	253.04	351.84	103.18	138.78	132.18	111.38	111.39	352.98	87.52	108.05
140	480.66	687.90	164.11	167.99	190.19	149.33	170.89	366.54	133.57	126.62
150	780.02	792.13	176.09	187.90	249.98	177.44	207.17	522.46	197.68	176.37
160		743.36	222.30	183.51	249.72	202.08	291.99	645.90	239.95	205.17
170		795.34	374.31	201.26	300.67	244.52	316.12	592.47	284.95	192.80

Table 3-8: Intensity dependent MEP amplitude response (μV) for all 10 participants labeled below as P#1 to P#10 assessed post-EMST.

<i>Intensity (% Motor Threshold)</i>	<i>MEP Amp. P #1</i>	<i>MEP Amp. P #2</i>	<i>MEP Amp. P #3</i>	<i>MEP Amp. P #4</i>	<i>MEP Amp. P #5</i>	<i>MEP Amp. P #6</i>	<i>MEP Amp. P #7</i>	<i>MEP Amp. P #8</i>	<i>MEP Amp. P #9</i>	<i>MEP Amp. P #10</i>
90	41.57	23.34	25.97	28.09	21.22	24.89	30.3	70.65	29.72	26.25
100	47.29	44.52	29.99	35.175	39.73	40.48	46.23	92.18	40.31	42.57
110	53.37	67.55	55.59	59.11	68.43	64.01	59.71	108.85	62.19	65.88
120	93.43	116.54	50.65	71.49	98.87	78.87	75.51	219.74	71.64	62.24
130	118.63	203.41	143.24	108.4	162.25	98.83	110.92	382.55	100.55	101.38
140	225.49	427.50	179.11	109.72	181.98	135.45	150.56	295.55	130.1	102.01
150	476.94	617.08	332.89	134.16	268.45	142.47	180.03	499.37	171.86	140.58
160		770.32	369.45	149.93	267.14	188.34	193.52	545.78	209.07	155.89
170		789.00	487.07	176.83	295.81	285.93	259.8	581.39	349.3	159.03

Table 3-9: The p-values obtained using 2-tailed paired t-tests comparing intensity dependent MEP amplitude change with training for each of the stimulation intensities used for IO curves. Note that upon making the Bonferroni correction, the p-values for none of the stimulation intensities were below the critical-alpha and were thus found to be non-significant.

<i>Intensity (% Motor Threshold)</i>	<i>t-value</i>	<i>p-value</i>	<i>Critical alpha</i>
120	2.327	0.045	0.0055
140	2.169	0.058	0.0063
150	1.328	0.217	0.0071
110	1.075	0.310	0.0083
130	1.045	0.323	0.0100
160	0.597	0.567	0.0125
90	0.261	0.800	0.0167
100	-0.492	0.634	0.0250
170	-0.509	0.625	0.0500

Table 3-10: Location of the hotspot measured in terms of physical distance from landmark points of vertex and pre-auricular points obtained pre EMST.

<i>Participant ID</i>	<i>Avg. distance from Vertex to SOLMT</i>	<i>S.D.</i>	<i>Avg. distance from SOLMT to pre-auricular point</i>	<i>S.D.</i>	<i>Avg. distance from Vertex (A=anterior; P=posterior)</i>	<i>S.D.</i>
1	2.50	0.00	14.00	0.00	0.00	0.00
2	2.00	0.00	16.50	0.71	2.00	0.00
3	2.00	0.00	14.83	0.29	0.67	1.15
4	2.00	0.00	14.67	0.29	0.00	0.00
5	2.00	0.00	15.67	1.15	0.67	1.15
6	2.00	0.00	15.33	0.76	0.33	0.58
7	1.00	1.00	16.50	0.87	2.00	0.00
8	2.00	0.00	16.17	1.26	0.00	0.00
9	1.75	0.35	16.75	0.35	0.75	1.06
10	2.00	0.00	14.67	0.29	0.33	0.58

Table 3-11: Location of the hotspot measured in terms of physical distance from landmark points of vertex and pre-auricular points obtained post EMST.

<i>Participant ID</i>	<i>Avg. distance from Vertex to SOLMT</i>	<i>S.D.</i>	<i>Avg. distance from SOLMT to pre-auricular point</i>	<i>S.D.</i>	<i>Avg. distance from Vertex (A=anterior; P=posterior)</i>	<i>S.D.</i>
1	2.17	0.29	13.33	0.29	0.00	0.00
2	2.00	0.00	16.33	0.29	0.00	0.00
3	2.00	0.00	14.83	0.29	0.00	0.00
4	1.50	0.71	16.25	0.35	0.00	0.00
5	2.00	0.00	14.50	0.00	0.33	0.58
6	2.00	0.00	15.00	0.50	0.67	0.58
7	1.67	0.58	16.17	0.58	1.33	0.58
8	1.67	0.29	16.67	0.76	0.67	1.15
9	2.17	0.29	15.00	0.50	0.00	0.00
10	1.67	0.58	14.00	0.00	1.00	1.00

Table 3-12: Change in average MEP values for all participants before and after 4 weeks of EMST.

<i>Participant ID</i>	<i>Avg. MEP pre-training</i>	<i>Avg. MEP post-training</i>
1	140	165
2	174	247
3	100	153
4	109	145
5	104	117
6	112	162
7	106	130
8	145	188
9	98	178
10	99	131

CHAPTER 4 DISCUSSION

This study provides three main findings – 1) AMT (active motor threshold) and IO (input output) curves obtained using the parameters described here are reproducible across sessions, 2) AMT for lateral abdominal muscle group is smaller following four weeks of EMST (expiratory muscle strength training), and 3) EMST does not cause a significant change in slope for IO curve.

The reproducibility of measures of cortical excitability for abdominal muscles provides the opportunity to explore the underlying mechanisms specifically in localization of anatomical locations along the neuraxis where the adaptive changes occur in response to different training programs focusing on expiratory muscles. Additionally, this methodology can potentially be used to study the changes in cortical excitability parameters with progression of any disease processes affecting corticospinal pathways to abdominal muscles.

Comparison with Previous Studies Examining Abdominal Muscle Representation

The present study obtained SOLMT (site of lowest motor threshold) using a stereotaxic software system wherein the exact physical location of the coil placement during stimulation is not obtained. In order to understand the data obtained from this study in comparison to that reported by previous studies, the physical location of SOLMT was measured for each participant with respect to the vertex or Cz in the international EEG electrode placement system with lateral component as well as any anterior or posterior component.

Forester (1936) documented in his functional representation of the motor cortex, the abdominal muscles to be located just medial to the diaphragm representation. Maskill et al. (1991) reported the diaphragm to be located 3cms lateral and 3cm anterior to the vertex. Walker (1997) found that the representation for RA (rectus abdominis) muscles is located just medial

and posterior to the diaphragm. The SOLMT for lateral abdominal wall muscles in the participant pool was located around the vertex and ranged within 0-2.5 cm (average = 1.925, s.d. = 0.374) laterally and 0-2 cm (average = 0.675, s.d. = 0.754) anterior or posterior with respect to the vertex. These findings are comparable to those reported by Plassman and Gandevia (1989) who using TES (transcranial electrical stimulation) concluded the cortical representation for the oblique muscles to be just at the vertex or within 2cm lateral to it. Even though the location for lateral abdominal musculature has been investigated in a previous study using TES (Plassman & Gandevia, 1989), this is the first study to document cortical representation for this muscle group using TMS.

No previous studies have reported the IO relationship or a precise methodology to ascertain the AMT in lateral abdominal muscles using TMS. This is the first study to investigate the input output characteristics of the abdominal muscle representation over a wide range of stimulation intensities and to measure the slope parameter for IO curves. The importance of using well-defined parameters (stimulation intensity, MEP amplitude, and criterion number of MEPs above a specified level) for the determination of motor threshold for a given muscle has been emphasized in the literature (Rossini et al., 1994; Sharshar et al., 2003). However, previous studies that have reported lateral abdominal wall muscle response to TMS (Demoule et al., 2003) have not attempted to provide such a precise definition for responses from this specific muscle group. Demoule et al. (2003) primarily focused on the diaphragm responses to TMS but additionally measured responses from the lateral abdominal wall muscles. In this present study, AMT for lateral abdominal wall musculature was defined as the lowest stimulation intensity (% MSO or % maximum stimulator output) that resulted in lateral abdominal MEP peak-to-peak

amplitude of 50 μ V in 6 out of 10 consecutive stimulations provided. Therefore, this definition can now be used to compare findings from future studies.

Facilitation was achieved by setting the EMST trainer at 20 % maximum expiratory pressure for each participant and having them initiate blowing through it when the participants reached the end expiratory level in order to control for the effects of lung volume at task initiation (see further discussion on facilitation task under methodological issues in this section). TMS was presented approximately 2 seconds after initiation of the blow. For purposes of controlling background contraction levels the participants in this study blew through a pressure threshold trainer that was more comfortable for them than measuring gastric pressures, which may have provided a slightly more accurate estimate of the expiratory muscle activity (Man et al., 2003; Man et al., 2005). This method of obtaining background contraction is also likely to be better tolerated by different patient populations including those with respiratory and neurological disorders (Sharshar et al., 2003). Also, from other unpublished work from our laboratory, it is known that use of an EMST trainer results in activation of the abdominal muscles. However, it is very likely that other expiratory muscles were also active during facilitation process and may have contributed to the EMG signal.

Reproducibility Measures

Reproducibility of TMS measures was determined using repeated measures ANOVA in the present study and no significant difference was found between the three baseline measures as well as the three post-training measures for either the AMT or IO curve slopes. However, some studies have advocated the use of intraclass correlation or ICC as a more suitable measure for test-reliability determination as it provides an index of degree of association and agreement between pre and post testing scores (Malcolm et al., 2006; Portney & Watkins, 2000). ICC gives

a measure of the proportion of variance that can be ascribed to each independent variable within a given data set. The use of an ANOVA to determine test-retest reliability has been criticized by Malcolm et al. (2006) as ANOVA “does not address the degree of association and agreement between each factor separately and for each individual subject”. Thus, the question arises as to how ICC analysis would impact the results of this study. ICC analysis was performed and it was found that AMT data for the lateral abdominal wall muscles demonstrated good test-retest reliability (for three pre-EMST measures, $ICC = .889$ and for three post EMST measures, $ICC = .971$) whereas the IO curve data demonstrated poor test-retest reliability (for pre-EMST measures $ICC = -.500$ and for post EMST measures $ICC = .354$). In the light of these findings it can be argued that AMT may be a more stable or reproducible measure and this could have contributed to easier detection of a smaller degree of change with EMST. On the other hand, the large degree of intra subject variability suggested by the ICC measure is associated with the IO curve slope and may have made it harder to detect adaptive change in response to EMST. However, it should be noted that even in FDI (first dorsal interosseus) which is one of the most widely reported skeletal muscles in the TMS literature, there is documentation of variable reliability using the ICC measure ranging from moderate (McDonnell et al., 2004) to good (Malcolm et al., 2006). Therefore, it is indicated that with greater intra-individual variability in the IO curve slope, multiple baseline measures should be obtained to assess this variability before introducing a training intervention. Also it is expected that a larger training-induced change is required in order for it to be detected.

EMST Program Effects and Putative Mechanisms

Changes within the central nervous system have long been thought responsible for performance changes that accompany strength training. Literature in the area of exercise and muscle physiology has many references to changes in strength that occur before myogenic changes like hypertrophy (Komi, 1986; Moritani & deVries, 1979; Narici, Roi, Landoni, Minetti, & Cerretelli, 1989; Plautz, Milliken, & Nudo, 2000), including increased EMG signal amplitudes (Aagaard, et al., 2000; Moritani & deVries, 1979, Narici et al., 1989; Sale, 1989), strength gains with imaginary contractions (Herbert, Dean, & Gandevia, 1998; Yue & Cole, 1992; Zijdwind, Toering, Bessem, Van Der Laan, & Diercks, 2003), and cross-training induced increased strength in the limb contralateral to the trained limb (Hortobagyi, Lambert, & Hill, 1997; Moritani & deVries, 1979; Zhou, 2000). However, findings from direct investigations addressing changes in neural drive have been conflicting. Some twitch interpolation studies indicate that strength training does not change individuals' ability to activate muscle, as healthy young adults are able to commonly activate the muscles fully without training (Davies, Parker, Rutherford, & Jones, 1988; Gandevia, 2001). Other studies claim to show increased activation with strength training in young as well as old individuals (Knight & Kamen, 2001; Reeves, Narici, & Maganaris, 2004; Scaglioni et al., 2002). Also, an animal study with rats has shown that strength training does not change the cortical motor representation for the trained limb muscle (Remple et al., 2001). Contrary to these initial findings, comparison of H-reflex and V-wave responses during maximal contraction following strength training has indicated an increase in alpha-motoneuron excitability associated with increased neural drive from the cortex (Aagaard et al., 2002).

Initial reports from both human and animal work documenting impacts of strength training have proposed that progressive training paradigms do not influence cortical motor maps as well

as cortical excitability parameters (Carroll et al., 2002; Jensen et al., 2004; Remple et al., 2001). However, recent works by Griffin and Cafarelli (2006) and Beck et al. (2007) have shown increased cortical excitability following progressive isometric and ballistic strength training programs for the lower limb muscles. Beck et al. (2007) found an increase in MEP recruitment with ballistic strength training in the lower limb muscles and Griffin and Cafarelli (2006) reported increased MEP amplitude with progressive strength training as early as 6 days from initiation of training. In the present study a significant reduction in the AMT was found following 4 weeks of EMST. This decrease in AMT with EMST is a novel finding in the lateral abdominal muscle group and has not been previously reported for any skeletal muscle with strength training. A reduction in AMT may indicate an increase in cortical excitability of excitatory interneurons and corticospinal neurons in the motor representation and could serve as an indication for reduced excitability threshold of slow and fast propagating pyramidal neurons (Chen, 2000; Rossini & Rossi, 2007) corresponding to the lateral abdominal musculature. The reduction in AMT may also indicate increased strength of corticospinal projections (Chen, 2000).

In this study, a reduction in AMT was produced across participants following EMST. This indicates a possible functional and/or structural change within the central nervous system circuitry. Functional and structural changes within the cortex have previously been documented in response to skill training (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Kleim, Barbay, & Nudo, 1998; Kleim et al., 2000; Nudo, Jenkins, & Merzenich, 1996; Plautz et al., 1999). Neuroplastic changes occurring within the cortex in response to skill training are varied and have been documented in animal models as changes in cortical representations, synaptogenesis, changes to neuron structure, protein synthesis as well as gene expression changes (Hyden & Lange, 1983; Kleim et al., 2002; Kleim et al., 1998; Kleim, Lussnig, Schwarz, &

Greenough., 1996; Nudo et al., 1996). The modification in structural components that likely underlie the change in functional properties of the corticospinal pathways is the connectivity within the cortical, subcortical, and spinal structures. At the level of the cortex, increased strength of intracortical synapses is likely due to increased synapse number as has been reported with skilled training paradigms (Kleim et al., 1998; Rioult-Pedotti et al., 1996; Withers & Greenough, 1989). In addition, structural adaptive changes within the cerebellum include increased volume of astrocytes per purkinje cell (Kleim, Markham, Vij, Freese, Ballard, & Greenough, 2007).

Kleim et al. (2002) have documented that following skill training, functional reorganization occurs within the motor cortex and is co-localized with the intra-cortical synaptogenesis. Thus, one possible explanation for the reduced AMT measured in the present study could be the increase in cortical synapses most likely within the expiratory muscle representation in the motor cortex.

At the level of the brainstem, the VRG-E connectivity to the premotor cortex, motor cortex, cerebellum, hypothalamus, and pons as well as abdominal motoneurons at the lumbar level of the spinal cord, indicate a strong possibility of adaptive modifications within the VRG-E in response to EMST. Neuroplastic changes within the brainstem circuitry controlling respiration have been associated with exposure to hypoxia, hypercapnia, and exercise (Mitchell & Johnson, 2003; Morris et al., 2003). Such modifications in the brainstem output have been linked to alterations in firing rates and patterns of firing synchrony (Lindsey, Morris, Shannon, & Gerstrin, 1997; Morris, Shannon, & Lindsey, 2001). Other potential mechanisms underlying respiratory plasticity include changes in number and strength of synaptic connections and unmasking of silent synapses within the brainstem (Mitchell & Johnson, 2003). It is conceivable that some

adaptive changes are occurring within the brainstem with EMST. These adaptations may be associated with changes in motor patterns for coordination of respiration during EMST which may persist after the training is terminated.

In addition, increases in V-wave and H-reflex amplitudes following strength training likely indicate an increase in corticospinal drive and increased spinal alpha-motoneuron excitability (Aagaard et al., 2002). It is possible that the present finding of decreased AMT may be attributable to contributions from increases in spinal alpha-motoneuron excitability and potentially an increase in synaptic density at the spinal level. Finally, the present study findings of decreased AMT can be explained in the light of changes within the cortex but without any comparative data from TES, paired-pulse TMS or peripheral stimulation the contribution of spinal cord circuitry that may have resulted consequent to EMST cannot be ruled out.

Of the strength training studies discussed in this paper, all had a small number of participants. There were 8 participants in Carroll et al. (2002) and Jensen et al. (2004) studies and 10 participants were strength trained in the study by Griffin and Cafarelli (2006) and there were 10 participants in the present study who were strength trained. Therefore, a clearer picture of strength training induced changes in corticospinal excitability may emerge with future studies employing a larger sample size and may thus clarify differences between muscle groups in terms of sites of cortical and spinal excitability changes with strength training as have been implied by Griffin and Cafarelli (2006).

Methodological Issues

Control of various methodological variables is extremely important in studies using EMG measures. This was ensured for electrode placement by using indelible ink to mark the recording site for the sEMG electrode on the lateral abdominal wall which was maintained throughout the course of the study. Also, it was ensured that the coil was always held at a 45 degree angle with

respect to the rostral-caudal skull axis and was positioned at a tangent to the scalp at each stimulation site as proposed by Kleim et al. (2007).

Signal Contamination

In theory, surface electrodes placed on skin can pick up signals from any muscle in the body via a phenomenon called cross-talk (Demoule et al., 2003). Demoule and colleagues (Demoule et al., 2003) have demonstrated this in terms of sEMG signal from the diaphragm which showed signal contamination from other inspiratory muscles in a sub-group of the study participants. Demoule et al. (2003) examined the cross-talk effect by using multiple electrode placement sites (over inspiratory and expiratory muscles namely serratus anterior, pectoralis major, and transverses abdominis) and through comparison of signals obtained from surface and needle electrodes placed in these sites. Therefore, it is theoretically possible that signal contamination could have occurred in the sEMG signals obtained from the participants in the present study. However, the small variability in response latencies across participants indicates that this was less likely and not significant. Also, signal contamination is likely a bigger concern in case of diaphragm muscle whose anatomy makes it harder to obtain its recordings using sEMG. Surface recordings from abdominal muscles on the other hand are relatively easier to obtain given the easy recruitment and large size of this muscle group. In addition, all TMS responses were obtained while the participants were actively expiring through the trainer which was accompanied by a mechanical indicator of abdominal compression (indicated by respiratory inductive plethysmography). None the less it should be noted that signals obtained in this study were from the lateral abdominal wall which likely means that in addition to external oblique muscle the signal may have gotten contributions from internal oblique and possibly even transverse abdominis.

Electrode Placement

It has been shown that removal and replacement of the electrodes can result in decreased reliability of TMS measures (McMillan, Watson, Walshaw, & Taylor, 1998). This difference in test-retest trials has been attributed to the electrodes being placed over different motor unit populations which in turn can affect the target cortical motor area response (Malcolm et al., 2006). In order to minimize the effects from electrode removal and replacement for each of the testing sessions, precise markings of the electrode placement were made with indelible ink. However, it is possible that slight placement changes caused by electrode replacement and or change in skin conductivity across different testing days could have affected the reliability results.

Central Muscle Fatigue

Repeated abdominal muscle contraction for facilitation purposes during TMS measures can arguably impact MEP response characteristics in the latter parts of each testing session. Sharshar and colleagues (Sharshar et al., 2003) have documented the possibility of central muscle fatigue with repeated facilitation efforts in the diaphragm. In spite of the fact that a small sustained background contraction (20% maximum expiratory pressure) was used for the present study it is possible that central fatigue might have occurred in the later portion of the experimental sessions and has been documented in the limb musculature (Smith, Martin, Gandevia, & Taylor, 2007; Sogaard, Gandevia, Todd, Peterson, & Taylor, 2006; Taylor & Gandevia, 2008). One method for assessment of central fatigue following submaximal contractions is perceived effort (Taylor & Gandevia, 2008). In the present study, none of the participants reported perceived fatigue in the abdominal region at the end of the TMS testing sessions. However, a systematic evaluation of the impact of the facilitating sub-maximal

contractions of the abdominal muscles on MEP amplitude was not conducted and therefore the contribution of some central fatigue cannot be ruled out.

Afferent Input

Komori and colleagues (Komori, Watson, & Brown, 1992) have documented that the peripheral afferents become involved from the very initiation of muscle contraction and influence various aspects of motor performance. There was likely some voluntary load compensation and cortical facilitation that resulted from blowing through a pressure release valve of the EMST trainer and caused an increase in MEP amplitudes compared to rest condition that was not tested in this study. Also, it should be noted that the present study design did not allow for distinguishing sensory feedback effects from pyramidal pathway activation effects. However, all of the study participants were required to maintain the same level of muscle contraction in a sustained manner during TMS presentations for all three baseline and three post-training sessions. Therefore, it is unlikely that the peripheral afferents played a prominent role in the post EMST changes in MEP characteristics.

Other Expiratory Muscles

It is important to acknowledge that there are other muscles including the rectus abdominis and internal intercostals and some back muscles that contribute to the expiratory process during active expiratory tasks such as cough and loud speech. None of these additional participating expiratory muscles that work synergistically with the lateral abdominal wall muscles were tested in this study. Therefore, this work represents only a portion of the motor origin of the motor responses involved in active expiration.

Other Cortical Excitability Measures

In addition to the measures used in this study, cortical excitability can also be quantified by measurement of area of motor map representation. However, it has been documented in upper

limb muscles that area of motor representation is related to MEP amplitude and should therefore provide similar reproducibility findings (Kamen, 2004; Lim & Yiannikas, 1992; Maccabee, Amassian, Cracco, & Cadwell, 1988).

Contributions from Ipsilateral Projections

Abdominal motoneurons receive corticospinal projections from the medial portion of the motor cortex located close to the central fissure (Penfield & Boldrey, 1937; Tsao et al., 2008). Thus, given the abdominal muscle representation it is likely that the current spread while using TMS stimulates abdominal representations in both hemispheres resulting in excitation of the opposite motor cortex (Fujiwara et al., 2001; Strutton et al., 2004; Tsao et al., 2008). Ziemann et al. (1999) have proposed that ipsilateral pathways activated with TMS are likely from ipsilateral polysynaptic projections from the same motor cortex. Based on MEP latency differences obtained from contralateral and ipsilateral abdominal muscles, Tsao et al. (2008) have recently proposed use of scalp sites that are 2cm lateral to vertex in order to minimize contributions from ipsilateral projections from the opposite hemisphere. The SOLMT in some of our participants was located between 0cm and 2cms from the vertex. As no EMG data was obtained from the left abdominal wall muscles in this study, we cannot rule out the contribution of uncrossed pathways from the opposite (right) hemisphere to the MEP data. SOLMT measurement comparisons between pre and post training sessions did not yield significant differences. Thus, it can be deduced that the physical location of the SOLMT did not change with EMST. Lack of change in SOLMT location with EMST indicates that cortical excitability and not abdominal muscle representation within the motor cortex was altered in response to EMST.

Motor Facilitation Task

As noted earlier, using a low intensity background muscle contraction can lower MEP response variability and reduced motor threshold (Darling et al., 2006) and was useful in the

present study given high motor thresholds for abdominal muscles (Tunstill et al. 2001). It is important to acknowledge that abdominal muscles are involved in varied and complex functions such as speech, cough, vomiting, and postural maintenance. These different tasks share common central control mechanisms but also are thought to be regulated by different synaptic inputs for specific expiratory tasks (Puckree et al., 1998). Further, many studies report changes in facilitation patterns based on facilitation task used during TMS stimulation in various skeletal muscles (Ackermann, Scholz, Koehler, & Dichgans, 1991; Datta, Harrison, & Stephens, 1989; Gandevia, McKenzie, & Plassman, 1990; Tunstill et al., 2001). In case of the abdominal musculature, Tunstill et al. (2001) reported that facilitation using a valsalva maneuver resulted in smaller MEP responses when compared to those obtained during a voluntary trunk flexion task. In the present study, the facilitation task used required the participants to blow through the EMST device which was the same device that was employed during the 4 weeks of EMST. Therefore, it is likely that use of a different facilitation task such as valsalva maneuver or trunk flexion would have yielded different outcomes.

Implications for Swallow Rehabilitation

The act of swallowing requires precise coordination with respiratory events (Brussard & Altschuler, 2000; Larson, Yajima, & Ko, 1994) as swallowing is usually initiated and terminated during the expiratory phase of respiration with brief apneic period (Selley, Flack, Ellis, & Brooks, 1989; Smith, Wolkove, Colacone, & Kreisman, 1989). Brainstem networks that control respiration and swallowing include ventral respiratory group neurons that are associated with repetitive rhythmic muscle activity and are commonly labeled as central pattern generators (Brussard & Altschuler, 2000). The central pattern generator for swallowing includes a network of premotor neurons that are involved in sequencing the motoneuron activity during the pharyngeal and esophageal phases of swallowing (Brussard & Altschuler, 2000). Also, the premotor neurons

in the swallowing central pattern generator are located within the medulla in the solitary tract nucleus (Jean, 1984; Kessler & Jean, 1985) and have connections with multiple sites within the brainstem and other sites in the central nervous system. In addition, there is evidence for projections from swallow premotor neurons to swallow related muscles (Jean, 1984; Kessler & Jean, 1985). This anatomical location and overlap with the respiratory control centers in the brainstem indicates a potential meeting ground for control of swallowing, respiration and airway protective mechanisms such as cough (Brussard & Altshuler, 2000).

Neuromuscular disorders such as Parkinson's disease are commonly accompanied by compromised performance of both the respiratory as well as the swallow function (Lim, Leow, Huckabee, Frampton, & Anderson, 2008). Due to the close proximity of the respiratory and swallowing central pattern generators in the medulla, it is possible that interventions such as EMST that specifically target respiratory muscles have a positive impact on the performance of swallowing musculature. In fact, improvements in cough effectiveness demonstrated by a significant increase in cough volume acceleration and decrease in penetration-aspiration have been documented with EMST in individuals with Parkinson's disease (Pitts, Bolser, Rosenbek, Troche, & Sapienza, 2008). In terms of mechanistic underpinnings, it is important to note that subglottal pressure generation is important for healthy swallowing function (Gross, Mahlmann, Grayhack, 2003; Sapienza & Wheeler, 2006). The increased expiratory pressure generation ability has been documented with EMST which likely aids in improving swallow function by potentially modifying the swallow motor program (Sapienza & Wheeler 2006).

Future Studies

Future studies should attempt to tease out the specific location of neuroadaptive changes underlying the increased muscle strength documented with EMST. Incorporation of additional techniques such as paired pulse TMS and peripheral magnetic stimulation can be used to localize

whether the adaptive changes causing reduced AMT are indeed cortical or if the changes occur at a sub-cortical site. Also, In order to evaluate the complete efferent pathway to expiratory musculature, future work should obtain cortical excitability measures from other expiratory muscles especially the rectus abdominis and rib cage muscles.

Age related differences in cortical excitability measures have been reported and are thought to be associated with changes in intracortical circuitry with aging (Matsanuga, Uozumi, Tsuji, & Murai, 1998; Sharshar et al., 2003). The impact of aging was not examined in this study as only young healthy subjects were recruited. In the diaphragm it has been documented that age does not impact the diaphragm muscle response to TMS. However this needs to be tested in the abdominal muscle groups to assess if this holds true for this muscle group as well.

This study can serve as the basis for future work with direct clinical relevance to individuals with motor speech disorders. This preliminary work with healthy individuals has opened doors for investigation of training related adaptations that likely occur in patient populations showing functional improvements in expiratory tasks with rehabilitation. Thus, this methodology can be employed in the future to study changes in corticospinal output to the lateral abdominal musculature in terms of changes in AMT and IO curve characteristics. In the present study no change was found in the IO curve slope with EMST. However, the training induced adaptations within the corticospinal circuitry may vary in specific populations like multiple sclerosis, Parkinson's disease and others including post-stroke as well as spinal cord injury patients experiencing abdominal muscle weakness and compromised expiratory muscle function. Therefore, EMST program and its impact on specific disordered discussed should be investigated further in terms of corticospinal output changes.

In addition, impact of any other training based rehabilitation programs targeting abdominal muscle performance on the corticospinal output can now be examined using the methodology described in this study. Thus, the methodology for assessment of cortical excitability measures presented in this study provides many avenues for future research to explore the mechanistic changes and the nature of neural adaptations accompanying abdominal muscle training in various populations.

Furthermore, specific comparisons of this study's findings in healthy subjects and the methodology presented can be used to delineate the differences between how healthy versus diseased populations with injuries/insults at various anatomical locations within the neuraxis adapt with EMST. For example, such studies can provide a better understanding of the potential differences between the adaptive processes underlying individuals with cortical versus spinal level insults. It is very likely that such research could open new avenues to tailor treatment programs for specific populations in accordance with such findings. Finally, this study has provided the basis for future investigations examining the impact of manipulating training dose on duration and cortical excitability changes and their relationships with detraining effects on performance. Thus, effects of changes in duration, intensity, and number of repetitions should all be examined in both healthy as well as specific populations with expiratory muscle weakness.

The present results showed no significant differences for each of the three post-training measures obtained over a period of ten days. This indicates that there was persistence to the changes in cortical excitability for at least up to ten days following EMST. It has been reported that synaptogenesis occurs during late stages of skill training (~7-10 days) and precedes motor map reorganization (Classen et al., 1998; Kleim, Hogg, VandenBerg, Cooper, Bruneau, & Remple, 2004). In addition, there is evidence from the rat model that early removal of a training

stimulus prior to behavioral improvement but before map reorganization, is associated with reduced levels of performance at 30 days following training termination. However, in a group of rats trained for a longer duration (2 weeks) when cortical motor maps have reorganized in response to training, performance levels were high at 30 days from training termination and motor map reorganization was maintained (Hogg, Cooper, Vozar, Vandenberg, & Kleim, 2001; Monfils, Plautz, & Kleim, 2005). Thus, it has been speculated that in the case of skill training, establishment of the skill is accompanied by motor map reorganization. Once cortical representations are modified they seem to exhibit resistance to detraining effects (Monfils et al., 2005). Therefore, it is likely that similar critical time points are in place in the cortical, and potentially the sub-cortical circuitry, for strength training. It is important to explore the detraining effects and their interactions with manipulation of training parameters such as duration of training and number of repetitions used during each training session on cortical excitability measures. If such critical time points do exist and impact neuroplasticity as well as performance following termination of EMST, then such information on accompanying neural adaptations could be used to shape training programs for maximizing benefits.

Conclusions

In summary, this study found that cortical excitability measures of AMT and IO curve slopes for lateral abdominal wall muscles are reproducible across three testing sessions. A four-week EMST program induced changes in cortical excitability parameters demonstrated by a reduced AMT. These outcomes suggest a change in cortical, bulbar and or spinal circuitry in healthy young individuals in response to EMST program.

APPENDIX A
HEALTH QUESTIONNAIRE

Age_____ Height_____ Weight_____

Sex: Male_____ Female_____

Do you currently have or had a history of the following (Put a check mark against all that apply):

____ Strength training in the last 3 months

____ Smoking in the last 5 years

____ Cardiac problems

____ Respiratory or Breathing problems including Asthma

____ Neurological or Neuromuscular disease

____ Stroke

____ Upper or Lower respiratory tract infection in the last 2 weeks

____ Hypertension (If yes, is it controlled with medication: yes____ no____)

APPENDIX B
TMS SCREENING FORM

Coded Name of TMS subject: _____

Your head will be exposed to a magnetic pulse. To maximize safety, please answer the questions below. Please do NOT hesitate to ask any questions you may have regarding below.

Do you have, or have you ever had, any of the following? If YES, please explain on back.

- Y N Metallic hardware on the scalp?
- Y N Cardiac pacemaker?
- Y N Any history of heart disease or heart conditions?
- Y N Implanted medication pumps, intracardiac line, or central venous catheter?
- Y N History of cortical stroke or other cortical lesion such as brain tumor?
- Y N Prior diagnosis of seizure or epilepsy?
- Y N Previous brain neurosurgery?
- Y N Any chance you are pregnant? Date of last menstrual period _____
- Y N Any electrical, mechanical, or magnetic implants?
- Y N Migraine headaches- if YES, are they controlled? _____
- Y N List current medications on back of form (we are interested in medicines that Affect seizure threshold such as tricyclic antidepressants and neuroleptics)
- Y N Any problems swallowing or diagnosis of dysphagia?
- Y N Any history of cancer in your head or neck?
- Y N Unstable medical conditions? _____
- Y N Any body or clothing metal above your shoulders? If so, please remove.
- Y N Any metal on your body (i.e. watch or jewelry, hair holders or pins, eye glasses, Body piercing, wallet, keys) If so, please remove.

I have read and understand all questions in this document. My signature below indicates that I have accurately and completely answered all questions in this document.

SIGNATURE OF TMS SUBJECT: _____ DATE: _____
SIGNATURE OF INVESTIGATOR: _____ DATE: _____

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BIOGRAPHICAL SKETCH

Anuja Chhabra was born on October 4, 1977 in Haryana, India. She spent the first few years of her life in Haryana before moving with her family to Chandigarh, India in 1980 where she spent the next 22 years of her life. She completed her high school education at Carmel Convent School (Chandigarh, India) and MCM D.A.V. College (Chandigarh, India) in 1995. Following this, she continued her education at Post Graduate Institute of Medical Education and Research (Chandigarh, India) in Audiology and Speech Therapy and obtained her bachelor's degree in 1998. Anuja went on to pursue a master's degree in psychology in 2000 from Annamalai University (Tamil Nadu, India). During her graduate education in psychology, Anuja worked part-time as a speech pathologist at a non government organization benefiting children with multiple disabilities (Tamana, New Delhi, India).

Anuja moved to Tucson, Arizona in 2001 to start graduate education in speech pathology and to explore her interest in research. Her education was supported by Graduate Tuition Scholarship from 2001-2003. She discovered her interest in the area of speech physiology and voice through her clinical practicum and while doing her master's thesis. She graduated from University of Arizona in 2003 and following that immediately started her doctoral education at the University of Florida (Gainesville, Florida) with Dr. Christine Sapienza. She received the Graduate Alumni Fellowship to support her doctoral work for the first four years of her doctoral education.

Anuja married her husband Leo Daab in May 2006. Upon completion of her doctoral education, she hopes to continue working in the area of motor speech and voice.