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## Interaction of voluntary activity and functional electrical stimulation in the upper extremity as a method for short-term alteration of corticospinal excitability and force control

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**INTERACTION OF VOLUNTARY ACTIVITY AND FUNCTIONAL ELECTRICAL STIMULATION IN THE UPPER EXTREMITY AS A METHOD FOR SHORT-TERM ALTERATION OF CORTICOSPINAL EXCITABILITY AND FORCE CONTROL**

by  
**Katherine Maia Gerton**

Repetitive movement training (RMT) is a well-established method for rehabilitating functional movement. However, many stroke survivors are not able to participate in RMT for the necessary duration to produce results due to rapid muscle fatigue or inability to perform the desired movement at all. Often, functional electrical stimulation (FES) is applied passively, as a rehabilitative therapy, to stroke subjects who are unable to participate in RMT. The effects of voluntary contraction and FES are not well understood for the upper extremity following a stroke. This experiment was designed to elucidate the mechanisms of functional and neurophysiological changes associated with combining FES and voluntary movement vs. the effects of each intervention alone in healthy subjects, with a within-subjects single day design.

Eleven right-handed, neurologically healthy subjects participated in a series of three experimental sessions. The testing conditions were voluntary movement alone (VOL), functional electrical stimulation alone (FES), and voluntary movement supplemented by functional electrical stimulation (VOL+FES). Subjects were evaluated for changes in maximum force and force control before and after each session. Corticospinal excitability was evaluated using transcranial magnetic stimulation (TMS) at five time points throughout each session. There were no significant changes pre-post or between conditions for the maximum force or the force control. FES alone was found to immediately and significantly reduce corticospinal excitability; that reduction continued

through the post measurement. Both VOL and VOL+FES increased corticospinal excitability pre-post, although not significantly. At the post measurement, both VOL and VOL+FES were significantly larger than FES, although not different from each other. These results indicate that adding voluntary movement to functional electrical stimulation may serve to increase corticospinal excitability while allowing the subject to participate in meaningful rehabilitative movements.

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AND FORCE CONTROL**

**by  
Katherine Maia Gerton**

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*“Never half-ass two things, whole-ass one thing”—Ron Swanson, Parks and Rec*

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## LIST OF DEFINITIONS

ADL	Activities of Daily Living
TMS	Transcranial Magnetic Stimulation
MEP	Motor Evoked Potential
CNS	Central Nervous System
Resting Motor Threshold (RMT)	The lowest intensity required to elicit a MEP response of at least 50- $\mu$ V amplitude in 3 of 6 consecutive trials.
Active Motor Threshold (AMT)	The lowest intensity required to elicit a MEP response of at least 200- $\mu$ V amplitude in 3 of 6 consecutive trials, while the subject maintains a small, isometric contraction.
Hot Spot	The location on the primary motor cortex that produces consistent and large MEPs in the target muscle
Maximum Stimulator Output (MSO)	The maximum intensity with which the TMS simulator is able to deliver pulses, 100%
MEP Amplitude	The size of the peak-to-peak amplitude of the MEP response.
FES	Functional Electrical Stimulation

# CHAPTER 1

## INTRODUCTION

### **1.1 The Problem: Stroke Induced Hemiplegia of the Upper Extremity**

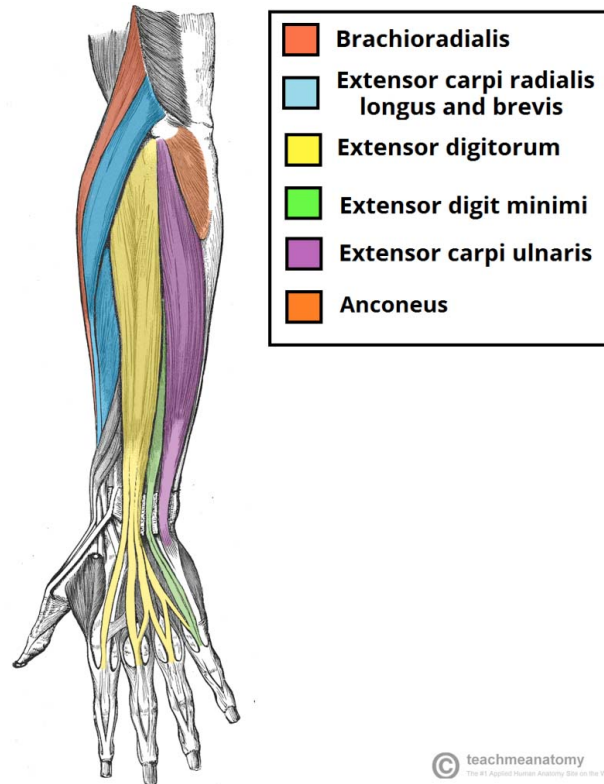
Stroke is the third leading cause of death and the leading cause of long-term disability in the United States, costing over \$33 billion each year in health care and lost productivity [1]. In the U.S. someone experiences a stroke every 40 seconds [1] however, with improved acute care and post-stroke treatment, stroke survivors are living longer while still experiencing the functional disabilities that accompany a stroke. 8 out of 10 stroke survivors experience hemiplegia, the partial to full loss of control over voluntary muscles on one half of the body [2]. While 90% of stroke survivors regain the ability to walk [3], only 50% will regain functional arm use and fewer than 20% will achieve good arm and hand recovery [4].

Most recovery of motor function post-stroke occurs spontaneously during the acute stage, up to 6 months after the event [5]. The level of potential recovery for stroke survivors scales directly with the severity of the stroke [5]. However, even during the chronic stage, significant gains in functional outcomes can be made through rehabilitative therapy [6].

Upper extremity hemiplegia is the most common cause of post-stroke disability [7] and those who are more severely impaired immediately following stroke have a lower potential for recovery [8]. The affected arm commonly develops a flexion synergy, with the elbow flexed and the fingers closed into a fist [9]. Patients may recover to a point where they can generate movements outside of the flexion synergy however, the synergy

and muscle spasticity are significant barriers to producing functional movements [10]. Breaking the flexion synergy in order to produce isolated, volitional movements to open the hand is critical to rehabilitation of unaided reach-and-grab movements necessary for activities of daily living.

Following a stroke, the upper limb is difficult to rehabilitate. One of the sources of this difficulty is the complexity of function of the upper limb. The arm and hand work together to function as a mover, stabilizer, and manipulator to perform daily tasks [11]. This complexity of function is possible because of the multitude of small, specific, overlapping muscles of the forearm and hand (Figure 1.1). This physiological organization makes targeting a specific muscle for rehabilitation difficult and the small size of the muscles means that they fatigue rapidly. Because of this complexity one type of movement or one type of therapy is not sufficient to restore natural movement in all of these tasks. Most upper extremity stroke rehabilitation focuses on retraining the proximal arm muscles as opposed to training hand movements. Training the hand is a much more difficult task than retraining the proximal arm and has a substantially greater impact on improvement of function.



**Figure 1.1** Muscles of the posterior forearm.  
Source: [12]

## **1.2 Functional Outcomes of Repetitive Movement Training and Functional Electrical Stimulation in Current Clinical Practice**

Many stroke patients are unable to perform activities of daily living due to restricted arm movement. Current US health care models prioritize skills for independence and stroke survivors with severe hand impairment are often trained to use compensatory movement, performing tasks with their unaffected limb alone [6]. Any occupational therapy that is implemented rarely causes functional improvements in the ability to perform reach and grasp tasks. This frequently leads to patterns of no-use in the affected limb, characterized by muscle atrophy and increased muscle spasticity [6], making therapies more difficult to implement and any further improvement less likely.

The most pervasive and effective form of rehabilitation therapy is repetitive movement training (RMT). RMT of skilled movements focused on consistently and efficiently achieving a specific goal [13] has been proven to induce long-term functional improvement in arm and hand use [14]–[16]. A two-week course of RMT can induce functional improvements that last for a year [17]. However, many stroke patients are unable to participate in RMT because they do not have the level of motor function to complete the task effectively, or may fatigue too rapidly to participate for the duration required to cause lasting improvement.

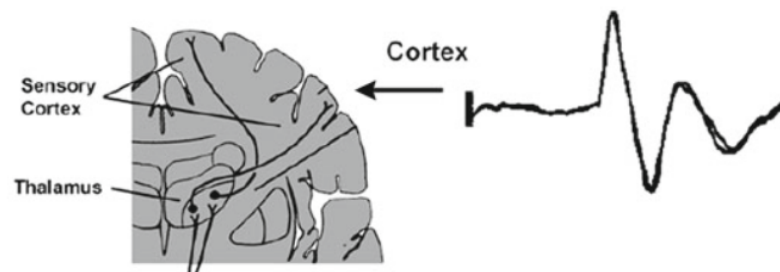
When subjects are excluded from RMT, functional electrical stimulation (FES) can be applied to rehabilitate hand and arm function [18]. Muscle spasticity, the muscle's resistance to passive stretching, is generally worse when a spastic muscle is voluntarily contracted; in stroke subjects, voluntary effort toward a movement can increase muscle spasticity and bring the subject further into the flexion synergy [19]–[22]. FES has been clinically proven to cause physiological improvements in muscle behavior by reducing muscle spasticity [23]. However, the evidence that FES therapy alone can improve functional arm use after stroke is limited and contradictory [24].

The failure of FES to produce lasting improvements in function, like the improvements seen from RMT, arises from several factors, the first of which is that FES is typically applied to the patient at rest [25]–[30]. When the subject is passively resting, FES is treated as a purely sensory phenomenon; the stimulation is not integrated into part of the central motor drive or the motor plan [31], [32]. When the motor cortex is not engaged in sending the commands to move, FES correlates only to an increase in muscle strength without an accompanying improvement in function [30], [33]–[35].

Additionally, while voluntary contraction is more fatiguing than FES at the cardiovascular and nervous system levels, FES therapy is more fatiguing at the ATP consumption level due to unnatural recruitment of muscle fibers [36].

### 1.3 Influence of Repetitive Movement Training and Functional Electrical Stimulation on Corticospinal Excitability

Transcranial magnetic stimulation (TMS) can be used to non-invasively quantify corticospinal tract integrity by measuring changes in amplitude, referred to as corticospinal excitability, and latency, the length of time required for the descending volley to travel from the cortex to the target muscle, of the evoked contralateral muscle contraction, known as a motor evoked potential (MEP). TMS depolarizes the cortex by transmitting an electric field through the scalp and skull. This creates a descending volley of action potentials that travels down the corticospinal tracts and generates a measurable response from the target muscle [37] (Figure 1.2).. MEP amplitude represents the strength of the corticospinal pathway between the cortex and the target muscle [38]. MEPs can be used to evaluate the neurological effect of rehabilitative therapy in that an increase in MEP amplitude following therapy indicates a stronger connection between the brain and muscle while a decrease in amplitude indicates the reverse.

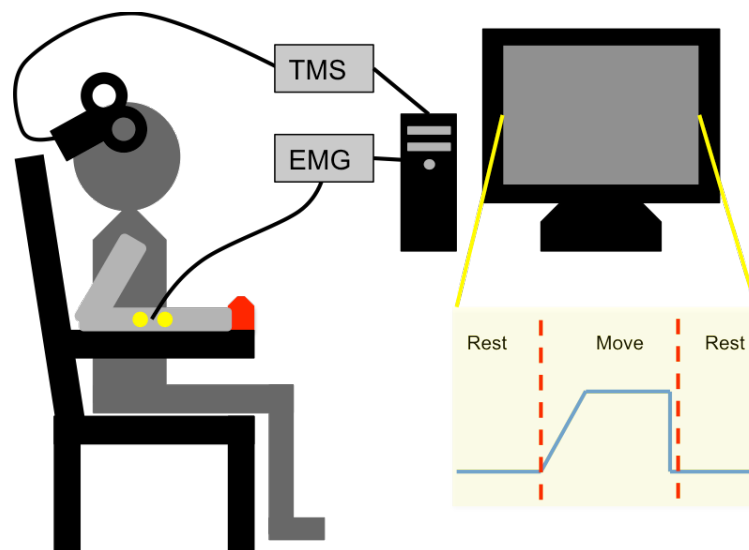


**Figure 1.2** Muscle MEP response to cortex stimulation using TMS.

Source: [37]

TMS outcome measures after stroke vary with the stage of recovery and the degree of motor function [39]. Due to the damage to cortical motor neurons, stroke patients generally have reduced MEP amplitudes and longer latencies than healthy subjects [40]–[42]. When rehabilitating movement following a stroke, increasing corticospinal connections between the damaged cortex and the muscles is key to functional recovery.

Repetitive movement training has been consistently shown to increase the corticospinal excitability of the trained muscles (Figure 1.3) [43]. A study by Classen [44] found that repetitive training of a muscle can transiently reorganize the cortex, giving more cortical space to the representation of the practiced movement. Subsequent studies of repetitive movement in the tibialis anterior in the leg [45]–[48] and many muscles of the arm and hand [49]–[51] have shown consistent and significant increases in corticospinal excitability following 20 to 60 minutes of repetitive movement.



**Figure 1.3** A standard TMS experimental setup, recording motor evoked potentials from the muscles of the arm and providing visual feedback of the participant’s movement on the screen.

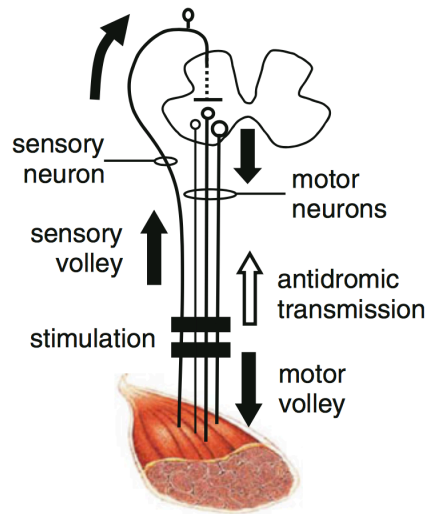


The effects of FES on corticospinal excitability in the upper extremity are less consistent. Corticospinal behavior of arm rehabilitation differs depending on whether the peripheral stimulation is applied over the nerve or over the muscle belly and whether the muscles targeted are flexors or extensors. A study by Mang [52] provided electrical stimulation over the median nerve for 40 minutes and recorded significant increases in the MEP amplitude of the abductor pollicis brevis (APB). Another study by Yamaguchi [50] stimulated the median nerve and found significant increases in MEP amplitude of the wrist flexors, but a decrease in MEP amplitude of the wrist extensors. Even in studies where the FES is applied over the muscle to target flexion, the results are inconsistent. McGie [53] stimulated the muscle belly of the APB and found a decrease in excitability as a result of FES and also found a decrease in excitability as a result of voluntary movement. These results contradict the results of Andrews [54] who also stimulated the muscle belly of the APB but found increases in corticospinal excitability after 20, 40, or 60 minutes of stimulation but a decrease in peripheral excitability. In another study, Barsi [55] trained flexion and extension in a grasping exercise using FES over the muscles but only measured corticospinal excitability over the flexor digitorum profundus (FDP) and found FES to cause an increase in corticospinal excitability while voluntary movement caused a decrease.

While the majority of studies into corticospinal excitability as a result of hand and arm therapy focus on the muscles responsible for flexion, flexion is not the problem in stroke. Stroke patients need to be rehabilitated out of the strong flexion synergy and into control over extension of the hand and arm. The ulnar nerve is difficult to stimulate using surface electrodes and, therefore, most FES for finger and wrist extension is applied over

the motor point of the extensor carpi radialis (ECR) or the extensor digitorum communis (EDC). There have been limited studies on the corticospinal excitability effects of FES based therapy for hand and arm extension. Taylor [49], when studying the ECR, found FES to decrease the corticospinal excitability while voluntary movement increased it. These limited results, coupled with the contradictory results in the flexor muscles make determining the most effective therapy difficult.

**central pathway:** sensory volley recruits motor units through reflex pathways



**peripheral pathway:** motor units recruited by activation of motor axons beneath stimulating electrodes

**Figure 1.4** Schematic of peripheral and central pathways. Motor units are recruited by the electrically evoked motor and sensory volleys initiated by depolarisation of axons beneath the stimulating electrodes. The contribution from the evoked sensory volley is limited by antidromic transmission in motor axons at high stimulation amplitudes (adapted from Collins 2007).

Source: [56]

#### **1.4 Previous Attempts to Combine RMT and FES: Effects on Functional and Neurophysiological Outcomes**

Combining voluntary activity with FES, such that the stimulation is triggered by activation of the target muscle, has been associated with functional improvements in addition to increases in muscle strength [57]. Most of the research into this combined treatment paradigm has been focused on correcting foot-drop in the chronic stroke population [45], [47], [58], [59]. Foot drop is a result of muscle weakness coupled with abnormal timing of muscle contraction throughout the gait cycle [60], that results in an inability to dorsiflex the ankle during ambulation. Functional electrical stimulation to correct foot-drop is most often applied to the common peroneal nerve, but can be applied to the tibialis anterior (TA) directly. Results of voluntarily triggered FES for rehabilitation of foot-drop, regardless of stimulation location, parameters, or duration consistently show increases in MEP amplitude for the TA [61], [62], which imply greater cortical control over those muscles. That increase in control manifests in consistent reports of functional improvements in gait [63], [64].

For voluntarily triggered FES (VOL+FES), the mechanisms that control muscles of the arm are different than the mechanisms that control the muscles of the leg, but the effects on corticospinal excitability are similar. Studies investigating corticospinal excitability as a result of combining voluntary activity and functional electrical stimulation in the upper extremity have begun to show that the combined training paradigm can cause increases in corticospinal excitability. These studies indicate increases in excitability regardless of whether the stimulation was applied over the muscle [49], [53], [55] or the nerve [50], [52] or was targeting flexion or extension. However, these results are limited by the small number of studies investigating the

combined protocol, by the wide variety of stimulation parameters, and varying treatment dosage between studies.

### **1.5 Study Significance**

Functional outcomes of rehabilitation protocols involving FES are inconsistent for upper limb rehabilitation and, for the same treatment protocol in the upper and lower extremity, improvements are less pronounced in the upper extremity [65]. Additionally, the target-specific effect on hand muscles as opposed to the global effect on leg muscles [66], can make effectively rehabilitating the complete upper extremity difficult.

Current clinical therapies favor training proximal arm function and current research into more effective wrist and hand therapies have focused on the muscles responsible for flexion. These strategies have limited ability to cause improvements in the patient's ability to produce fractionated hand movement and engage in the activities of daily living. Determining and implementing the optimal strategy for breaking the flexion synergy and being able to voluntarily elicit finger and wrist extension are much more significant in being able to independently perform tasks.

Therapy involving the combination of FES and voluntary activity may increase participation for patients who are unable to participate in traditional rehabilitation paradigms. This study represents the first systematic investigation of functional and neurophysiological outcomes of voluntary activation and FES based therapy for finger extension. Results of this investigation will enhance our understanding of the effects of FES pulse width on stimulation of the finger extensors.

### 1.4.1 Study Aims and Hypotheses

To maximize upper extremity rehabilitation outcomes we need to understand the underlying physiology and mechanisms of corticospinal excitability changes and physiological changes that are present following a long-term rehabilitation protocol.

We intend to elucidate the mechanisms of functional changes, which are normally seen over weeks of physical therapy, by evaluating each training paradigm in a single day within-subjects experimental design. Perez [67] showed that active involvement skilled task performance increases corticospinal excitability more compared to non-skillful training or the passive training of FES therapy alone. We hypothesize that the combination of FES and voluntary activity in a rehabilitation protocol will cause the greatest increase in MEP amplitude, a measure of corticospinal excitability, and also cause the greatest improvement in functional behavior, measured by fatigue and force control.

**Study Aim 1:** To test the interaction between voluntary contraction and functional electrical stimulation on corticospinal excitability in the upper extremity.

Voluntary drive has been shown to have a consistently excitatory effect on the portion of the primary motor cortex (M1) responsible for controlling that movement; the effects of FES on M1 excitability are less consistent across muscle groups. When FES accompanies voluntary drive, the stimulation is no longer treated only as a sensory phenomenon; instead, it is incorporated into the motor command. We will measure M1 excitability at five time points throughout each paradigm as well as collect motor recruitment curves before and after the session to determine how excitability changes, over time, in response

to each paradigm. We predict that the combination of FES and voluntary contraction will increase corticospinal excitability more than either training alone.

**Study Aim 2:** To test the effect of the interaction between voluntary contraction and functional electrical stimulation on force control and motor fatigue in the upper extremity. FES is known to induce motor fatigue due to the unnatural recruitment of muscle fibers; accompanying FES with voluntary movement should induce more fatigue than either protocol alone. However, the benefit of producing the correct movement, due to the influence of the FES, should produce the most improvement in functional outcomes. We predict that the combination of FES and voluntary contraction will increase force control more than either paradigm alone while inducing the most motor fatigue.

**Study Aim 3:** To compare the effects of narrow pulse-width electrical stimulation (200 $\mu$ s) to the effects of a wide pulse-width electrical stimulation (2ms) on corticospinal excitability in the upper extremity. Several studies have investigated the effect of stimulation frequency on corticospinal excitability and there has been limited investigation into the effect of pulse width on functional measures. However, no studies to date have investigated the effect of altering the pulse width of electrical stimulation on corticospinal excitability in the upper extremity. We predict that altering the pulse width of the electrical stimulation will have no significant effect on corticospinal excitability for each experimental paradigm.

## CHAPTER 2

### METHODOLOGY

#### 2.1 Experimental Set-Up

##### 2.1.1 Participants

Eleven able-bodied participants (5 men and 6 women) completed all 3 experimental sessions. Participants were  $23.7 \pm 4.9$  years of age. Participant demographics are listed in Table 2.1. All participants provided written, informed consent to participate in this study. A medical history and health screening was conducted prior to enrollment to ensure that the subjects had no neurological impairments, were not taking medications known to influence neurological function, and had no other contraindications for TMS (Appendix [68]). All participants self-identified as right-handed and performed all training sessions with their right hand.

**Table 2.1** Participant Demographics for each Experiment

Subject ID	Gender	Age	Experiment Part 1	Experiment Part 2
1	F	24	X	X
2	M	23	X	
3	M	34	X	X
4	F	30	X	X
5	M	19	X	
6	M	24	X	
7	F	19	X	
8	F	19	X	
9	M	21	X	
10	F	24	X	
11	F	23	X	

### **2.1.2 Experimental Set-Up**

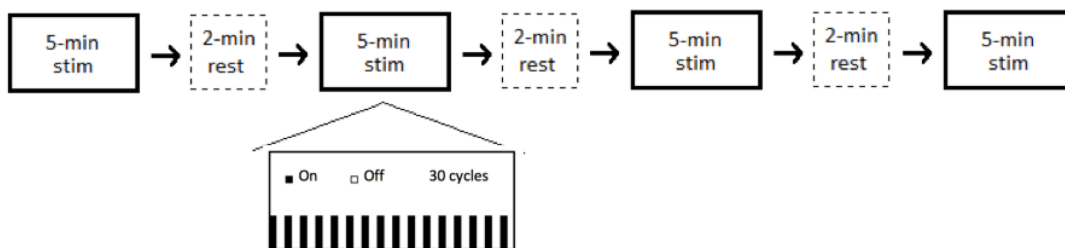
Each of the three experimental conditions, voluntary movement alone (VOL), functional electrical stimulation alone (FES), and voluntary movement supplemented by electrical stimulation (VOL+FES), was conducted in the same way, using the same experimental procedures. Conditions were separated by a minimum of 48 hours to ensure washout of the effects of the previous condition. Conditions were presented in a randomized order to each participant.

Participants were seated comfortably facing a computer screen. During testing, the right shoulder was abducted approximately 30 degrees, and the right elbow was flexed approximately 90 degrees, with the arm and hand rotated such that the right pinky rested on the armrest (Figure 1.3). The left arm was in the same position as the right.

Each intervention consisted of four 5-minute blocks of training, separated by 2 minutes of rest (Figure 2.1). Each block of training was 30 cycles of 5 seconds of activation, followed by 5 seconds of rest. During each 2-minute block of rest, 15 resting MEPs were collected. The training protocol was consistent across interventions and across subjects.

For all conditions, visual cues were presented on a computer monitor, instructing the subject when to contract and when to relax. The visual cue to contract was accompanied by an audible ‘beep’ to reduce the chance of the subject missing the cue. Feedback of the subject’s EMG activity was provided on the screen, with a large dot representing the level of activation. The target activation range was bounded by dashed lines and the dot changed colors from blue to green when the subject was activating within the target range.





**Figure 2.1** Timeline of the training protocol. This figure represents the four cycles of training, shown in Figure 2.3.

**2.1.3.2 Motor Evoked Potentials** Before the training began, the subject's motor hot-spot and resting motor threshold (RMT) were determined. MEPs were elicited with a Magstim Rapid2 magnetic stimulator with a 70mm, figure eight coil (Magstim, Morrisville, NC). All MEPs were recorded from the EDC during TMS of the motor cortex.

To detect the motor hot-spot of the subject's EDC, the coil was held tangentially to the skull with the handle pointing backward and laterally at a 45° angle to the sagittal plane [69] over the approximate location of the hand area of the motor cortex. The optimal stimulus site was determined as the site where TMS, at a suprathreshold intensity, consistently produced the largest MEPs. The BrainSight navigation software (Rogue Research Inc., Cardiff, UK) was used to visualize the brain and virtually mark the location of the hot-spot for all TMS measures throughout the experiment. The hot-spot was located and verified at the beginning of each day of intervention.

Resting motor threshold (RMT) was defined as the minimum stimulus intensity that elicited >3 MEPs of >50 $\mu$ V in 6 consecutive trials [70]. This level was determined by setting the %MSO to +5 from the %MSO used during hot-spot detection and providing 6 stimuli per intensity to the motor hot-spot, separated by -2% MSO. Once a

level was reached where fewer than 3 MEPs had an amplitude of  $>50\mu\text{V}$ , that %MSO was recorded as the RMT.

## **2.2 Experimental Design**

One experiment, with two parts, was conducted under this paradigm. In part 1, the subjects completed three training sessions: voluntary contraction only (VOL), functional electrical stimulation only (FES) and voluntary contraction supplemented by FES (VOL+FES). In the conditions requiring electrical stimulation, the electrical stimulation was applied at 40Hz with a 2ms pulse width. In part 2, a subset of the population from experiment 1 (N=3, 2 female) returned to complete the FES and VOL+FES conditions again, with altered stimulation parameters (Table 2.1). To investigate the effects of altering pulse width on corticospinal excitability, the electrical stimulation was applied at 40Hz with a 200 $\mu\text{s}$  pulse width.

### **2.3.1 Experimental Conditions**

#### **◆ Voluntary Contraction Only**

In the “voluntary” condition (VOL), the subject voluntarily contracted his/her EDC, without FES assistance, in time with the visual cues on the screen. The target was set to 20% of the subject’s maximum voluntary contraction (MVC) of his/her EDC, collected before the start of the training, with the total target window representing 10% to 30% of the MVC. The subject had to maintain the contraction within the target window for 200ms following the “GO” cue before the 5 seconds of “HOLD”ing the contraction; the subject had a maximum of three seconds to achieve the 200ms in the target. If the subject failed to trigger the training for three trials in a row, the training was paused for 2 minutes for the subject to rest. If the subject failed to trigger the electrical stimulation for a second

set of 3 trials in the same block, the training session was stopped. The subject maintained the contraction for 5 seconds, until cued to rest for 5 seconds.

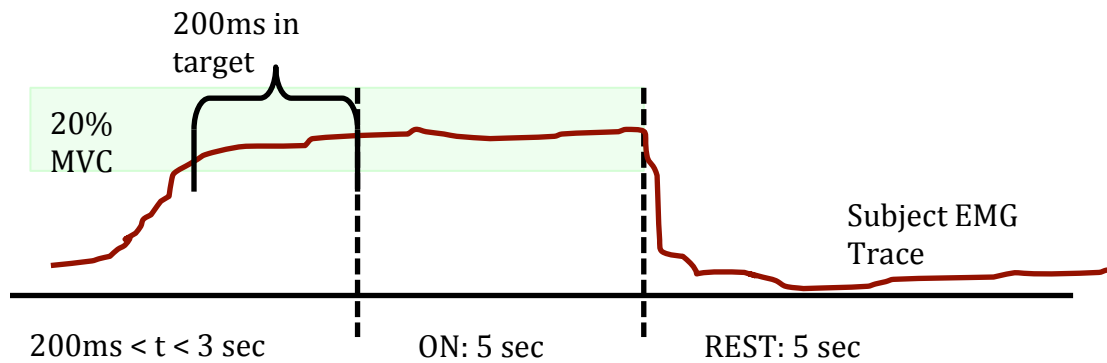
◆ **FES Only**

In the “FES only” condition (FES), the subject was asked to remain completely relaxed for the duration of the training. Disposable, self-adhesive electrodes (VERMED, Buffalo, NY) and a stimulator (Digitimer, Ft. Lauderdale, FL) were used to stimulate the subject’s EDC. The stimulations were applied at 40 Hz with a 2ms pulse width. The stimulation amplitude was determined at the beginning of each session that required FES and was set to the level that elicited functional hand opening without causing pain to the subject. The stimulation was active for 5 seconds, followed by 5 seconds of rest without FES.

◆ **Voluntary Contraction with FES**

In the “voluntary with FES” condition (VOL+FES), the subject voluntarily contracted his/her EDC, without FES assistance, when cued on the screen. When the subject had maintained a contraction within the 10% to 30% MVC window for 200ms, the FES, with the same parameters as the FES only condition, activated. The subject had a maximum of 3 seconds to trigger the electrical stimulation; if the subject failed to achieve 200ms in the target range for three trials in a row, the training was paused for 2 minutes for the subject to rest. If the subject failed to trigger the electrical stimulation for a second set of three trials in the same block, the training session was stopped. The subject was asked to maintain the 20% voluntary contraction that was required to trigger the stimulation, while the FES was active. When cued to rest, the subject relaxed his/her voluntary contraction and the FES turned off. Every first, fifteenth, and thirtieth trial in each block occurred

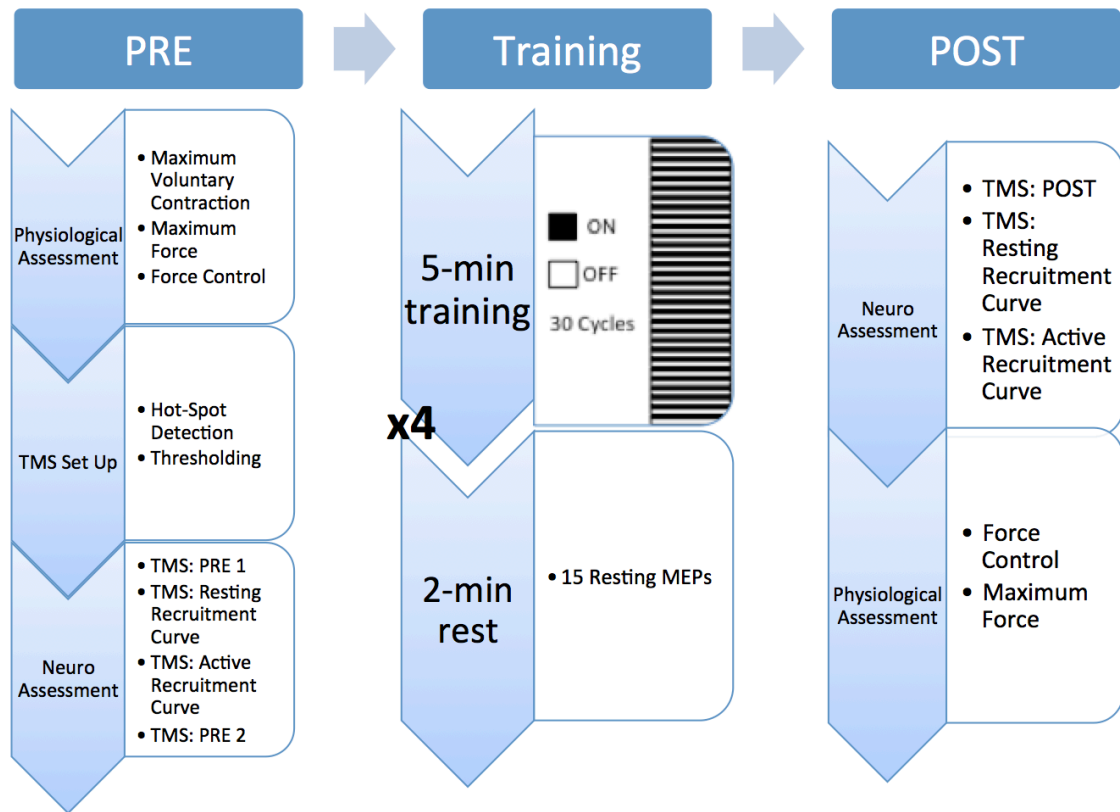
without FES. The subject was informed that some trials might not have FES but were not told at which trials this would occur, so that the experimenter could verify that the subject was voluntarily participating.



**Figure 2.2** Diagram of a single cycle of training during the VOL or VOL+FES condition.

### 2.3 Outcome Measures

All assessments were conducted immediately before and immediately after the intervention. Additionally, 15 resting MEPs were collected during each of the three, two-minute rest periods. Each session was separated by a minimum of 48 hours to ensure washout of any effects from the previous training. For each day of training, assessments were collected in the order shown in Figure 2.3.

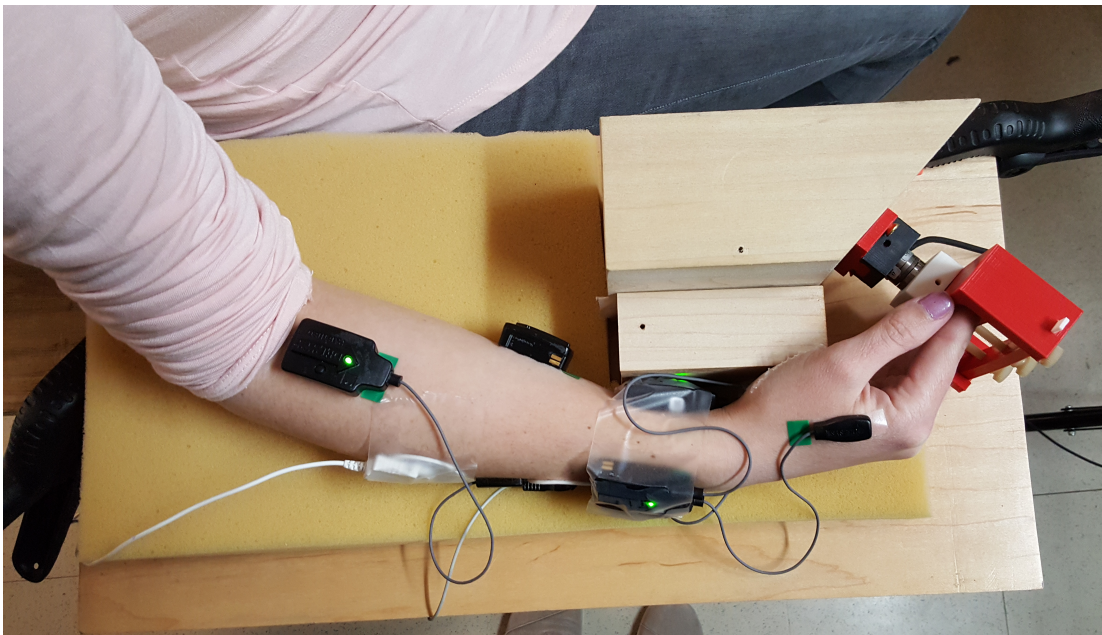


**Figure 2.3** Timeline of a single session. The 7-minute training cycle was repeated four times.

### 2.3.1 Maximum Voluntary Contraction and Maximum Force

The maximum voluntary contraction (MVC) was defined as the EMG activity during maximal effort and was the first measure collected before the experiment. EMG activity was recorded from the EDC, FDI, APB, ADM, and FDS muscles using reusable surface electrodes (Delsys, Natick, MA). The subject was resisted by the experimenter while performing the appropriate movement with maximum effort. MVC was quantified as the mean of the half-second of greatest activity in the rectified EMG signal for each muscle.

Maximum finger extension force was assessed by fixing the subject in a custom designed apparatus made from 3D printed parts and a 6 degree-of-freedom force sensor (ATI, Apex, NC) (Figure 2.4). The subject was asked to open his/her hand, by extending the fingers as strongly as they could, for 5 seconds, followed by 30 seconds of rest, for three trials. The maximum extension force of each trial was calculated as the mean force during the half-second of maximum activity. The maximum extension force was calculated as the mean of the maximum force achieved in each trial.



**Figure 2.4** Subject in the force sensor apparatus, with electrodes recording from five muscles and electrodes delivering FES to the EDC.

### **2.3.2 Force Control**

Sine wave tracing was used to assess force control. With the subject still in the force sensor apparatus from the maximum force trials, subjects were presented with four force tasks. Each subject was presented with a practice task to familiarize him or herself with the mechanism of control. The signal scrolled from the bottom to the top of the screen such that finger extension corresponded to the peak of the signal on the right of the screen

and finger flexion corresponded to the peak of the signal on the left of the screen. This orientation was used such that controlling the trace was more intuitive for their hand position.

Following a practice task each subject performed three sine-wave traces [71]. The sine traces occurred at three frequencies, 0.5, 1.0, and 1.5 Hz with a DC component of 20% max force and an amplitude of 10% max force. These parameters constrained the subject to control the force only in extension, between 10 and 30% of their max force. The order in which the subject performed the sine trace was randomized at the beginning of each trial, with the same order presented pre and post training, with the straight-line trace always being performed last. Each trace consisted of 2 seconds of DC, followed by 30 seconds of signal oscillating between 10 and 30% max force, followed by 2 seconds of DC again. Each second was followed by 1 min of rest.

### **2.3.3 Motor Fatigue**

Straight-line tracing was used to assess motor fatigue. With the subject still in the force sensor apparatus from the force control sine wave tracing, subjects were presented with a single fatigue task. The extension force required to match the presented line was set to 20% of the subject's maximum force. The signal consisted of 2 seconds to achieve the target force, followed by 60 seconds of signal, followed by an additional 2 seconds that were removed for analysis.

### **2.3.4 Resting MEPs**

Resting MEPs were collected as a measure of corticospinal excitability at five time points throughout each session. TMS stimulation was delivered over the EDC hot spot at 120% RMT with 4 seconds between pulses. The PRE and POST collections consisted of 20 MEPs while the collections between training blocks consisted of 15 MEPs.

### **2.3.5 Recruitment Curves**

The recruitment curve describes the input-output properties of the corticospinal system, or how MEP size is affected by changes in TMS intensity [72]. MEPs were evoked and recorded at stimulator intensities ranging from 90% to 140% of the subject's RMT. Each level was separated by 10% of the subject's RMT. If 10% RMT was between whole numbers, the value was rounded to the nearest whole percent. If the subject's RMT was at a level such that 140% RMT was above 100% MSO, the recruitment curves were collected up to 130% RMT.

For the resting recruitment curve, there were a total of 60 stimulations, with 10 stimulations applied at each intensity. The inter-stimulus interval was 4 seconds. The subject remained at rest for the duration of collecting the recruitment curve.



**Table 2.2** The Resting Motor Threshold and Resting Recruitment Curve Percent Stimulator Intensity (%MSO) for each Subject during the VOL Condition

Subject ID	RMT	Resting Recruitment Curve (*RMT)					
		<i>0.9</i>	<i>1.0</i>	<i>1.1</i>	<i>1.2</i>	<i>1.3</i>	<i>1.4</i>
1	44	39	44	49	54	59	64
2	77	69	77	85	93	100	~
3	66	59	66	73	80	87	94
4	56	49	56	63	70	77	84
5	50	45	50	55	60	65	70
6	75	67	75	83	91	99	~
7	50	45	50	55	60	65	70
8	64	58	64	70	76	82	88
9	56	51	56	61	66	71	76
10	62	56	62	68	74	80	86
11	55	49	55	61	67	73	79

For the active recruitment curve, there were a total of 36 stimulations, with 6 stimulations applied at each intensity. The inter-stimulus interval was 5 seconds. The subject triggered the TMS stimulus by contributing between 5 and 15 percent of his/her MVC. When the target was reached, a stimulus was triggered and the subject was cued to relax. The number of stimulations per intensity was reduced from 10 to 6 and the inter-stimulus interval was increased from 4 to 5 seconds to reduce the potential for pre-training fatigue and so that they could successfully complete the recruitment curve following the training.

## 2.4 Analysis

### 2.4.1 Data Analysis

Data was analyzed for changes in functional measures between pre- and post-intervention as well as changes in corticospinal excitability between pre-, during-, and post-intervention.

#### 2.4.1.1 Functional Measures

##### ◆ **Maximum Force**

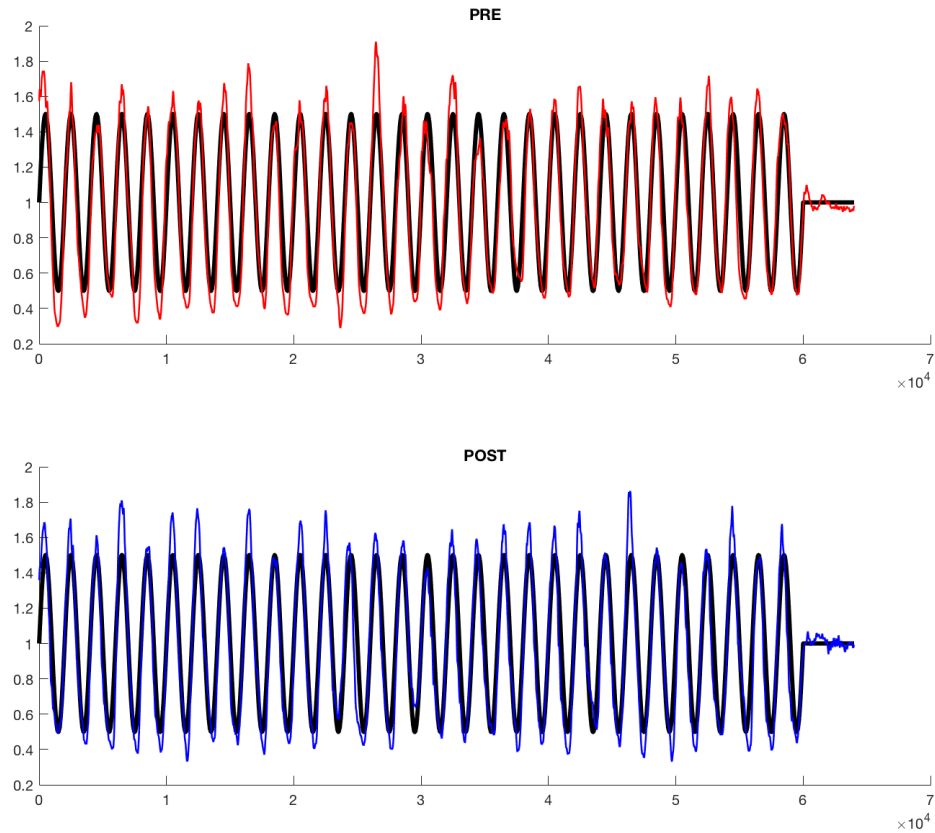
The maximum extension force was calculated as the mean force during the half-second of maximum activity averaged across three trials. For all activities involving force, the calculated maximum force from the pre-intervention time point measurement was used. Maximum force was calculated again at the end of the session.

##### ◆ **Force Control**

Tracking accuracy was measured by the root mean square error (RMSE) of the trace.

$$RMSE = \sqrt{(target - force)^2} \quad (2.1)$$

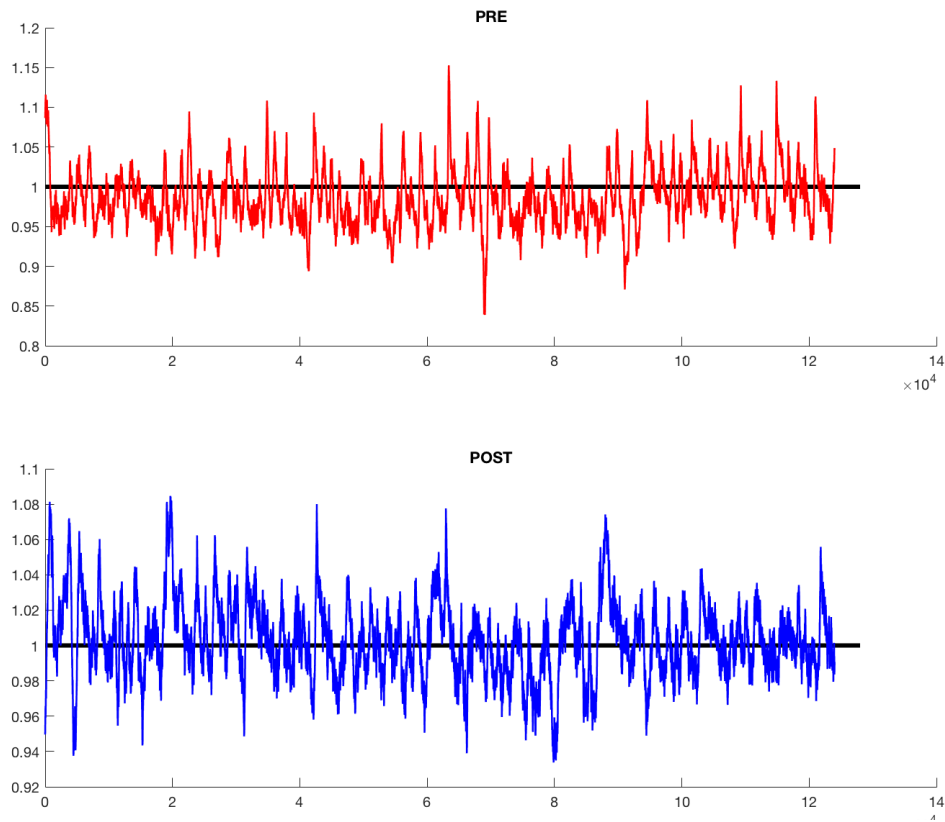
RMSE accounts for both differences in phase and differences in amplitude between the target and applied forces. An RMSE measurement closer to zero indicates a more accurate tracing of the presented signal.



**Figure 2.5** Representation of the force applied by a single, representative subject performing the 1.0Hz signal trace task before and after the VOL+FES condition. The force data has been normalized to 20% pre-intervention MVC. Top: Pre-intervention. Bottom: Post-intervention.

### ◆ Motor Fatigue

To evaluate fatigue between pre- and post-intervention, the coefficient of variation of produced force was used. The subjects were asked to trace a straight line at 20% of their pre-intervention maximum force for 64 seconds. The coefficient of variation measures the standard deviation of the subject's force trace around the target trace, with the beginning and ending 2 seconds removed from the analysis. This measure has been used in several previous studies as a method for evaluating motor fatigue by fluctuations in the subject's applied force [73], [74], [75], [76]. Decreases in force fluctuations are typically interpreted as an increase in fatigue.



**Figure 2.6** Representation of the force applied by a single, representative subject performing the fatigue task before and after the VOL condition. The force data has been normalized to 20% pre-intervention MVC. Top: Pre-intervention. Bottom: Post-intervention.

#### 2.4.1.2 Neurophysiological Measures

##### ◆ MEP Amplitude and Stimulation Removal

Changes in CS excitability were assessed by comparing the mean amplitudes of the MEPs collected before, during, and after the intervention sessions across the group. MEPs were measured as the peak-to-peak amplitude of the evoked motor response in the extensor digitorum communis (EDC).

To ensure that inadvertent background muscle contractions did not influence MEP amplitudes, MEPs were removed from the analysis if the peak-to-peak amplitude was

below 50 $\mu$ V or was greater than 2 standard deviations from the mean of each set of MEPs.

#### ◆ Recruitment Curves

The recruitment curve describes the input-output properties of the corticospinal system, or how MEP size is affected by changes in TMS intensity [72]. In the recruitment curve, there is no MEP at low stimulation intensities, a steep increase in average MEP amplitude at the resting motor threshold (RMT) and then a plateau to a saturation level at higher intensities. Initially, the peak-to-peak value amplitude of each MEP was measured for all stimuli. The pre- and post-intervention stimuli were averaged for each TMS intensity, 10 stimulations per intensity, and fitted with the Boltzmann sigmoidal function [77] (Equation 2.2).

$$MEP(x) = MEP_{min} + \frac{MEP_{max}}{1 + e^{\frac{S50-x}{K}}} \quad (2.2)$$

From this function a relationship was determined between stimulation intensity and peak-to-peak amplitude of the MEPs. The MEPmax is the maximal motor response that is obtained while the S50 and slope represent the threshold and gain, respectively, of the corticospinal neurons and motoneuron pool. [61]. Decreases in corticospinal excitability can be marked by a rightward shift of the recruitment curve, a decrease in the curve slope, or a decrease in MEPmax, or all of the above. Increases in corticospinal excitability are marked by the opposite: a leftward shift of the curve, an increase in slope, or an increase in MEPmax, or all of the above.

## 2.4.2 Statistical Analysis

Statistical significance for all tests was set at  $P < 0.05$ . Significant results were followed by a *post hoc* test with Tukey's correction, at 95%, to avoid errors associated with multiple comparisons. Analyses that use "condition" as a factor used the three levels: voluntary movement alone (VOL), functional electrical stimulation alone (FES), and voluntary movement paired with FES (VOL+FES).

### 2.4.2.1 Functional Measures

#### ◆ **Maximum Force**

A 2-way, repeated measures ANOVA was performed on the maximum extension force with the factors "condition" (three levels) by "time" (two levels: PRE and POST). The maximum extension force used for evaluation was the mean of the three trials at each time point.

#### ◆ **Force Control**

A 3-way, repeated measures ANOVA was performed on the accuracy, measured by RMSE, of the force trace, with the factors "condition" (three levels) by "time" (two levels: PRE and POST) by Frequency (three levels: 0.5 Hz, 1.0 Hz, 1.5 Hz).

#### ◆ **Motor Fatigue**

A 2-way, repeated measures ANOVA was performed on the coefficient of variation of the extension force with the factors "condition" (three levels) by "time" (two levels: PRE and POST).

### **2.4.2.2 Neurophysiological Measures**

#### **◆ Normalization of MEPs**

A one-way, repeated measures ANOVA was conducted on the MEPs recorded at time “PRE” across conditions. Lack of statistically significant differences ( $p > 0.05$ ) between the PRE measurements for each condition would verify that subjects began each session with similar basal excitability. Additionally, following verification of similar basal excitability, all following statistical evaluations on MEPs were conducted on MEPs that had been normalized to the PRE measurement of each subject per each condition, referred to as the MEP ratio.

#### **◆ PRE-POST MEPs**

A one-way, repeated measures ANOVA was performed on the normalized MEP amplitude with the factors “condition” (three levels). Significant results were followed with a two-sided, one-sample t-test to determine whether the normalized MEP amplitude was significantly different from 1.

#### **◆ MEPs Over Time**

Due to an equipment error during one session for Subject 2, MEPs for BLOCKs 1 and 2 were not collected. Therefore, for the analysis of MEPs over time, this subject’s data was not included in any of the three conditions. The subjects included in the analysis of MEPs over time are N=10 (4 male, 6 female).

A 2-way, repeated measures ANOVA was performed on the normalized MEP amplitude with the factors “condition” (three levels) by “time” (four levels: BLOCK1, BLOCK2, BLOCK3, POST). The time-point “PRE” was excluded from this analysis

because it is the value used for normalization such that “PRE” has an MEP ratio of 1 with a standard deviation of zero.

◆ **Resting Recruitment Curves**

The three parameters analyzed for significance were the MEPmax, MEPhalfmax (S50) and the slope (K) of the fitted sigmoid. The pre-intervention values were compared using three 1-way repeated ANOVA with “condition” as a factor (three levels). A 2-way, repeated measures ANOVA was performed on each of the three parameters of the sigmoidal fit with the factors “time” (two levels: PRE and POST) and “condition” (three levels). MEPs of the recruitment curves were not normalized to any value.

Active recruitment curves were collected but not included in this analysis.



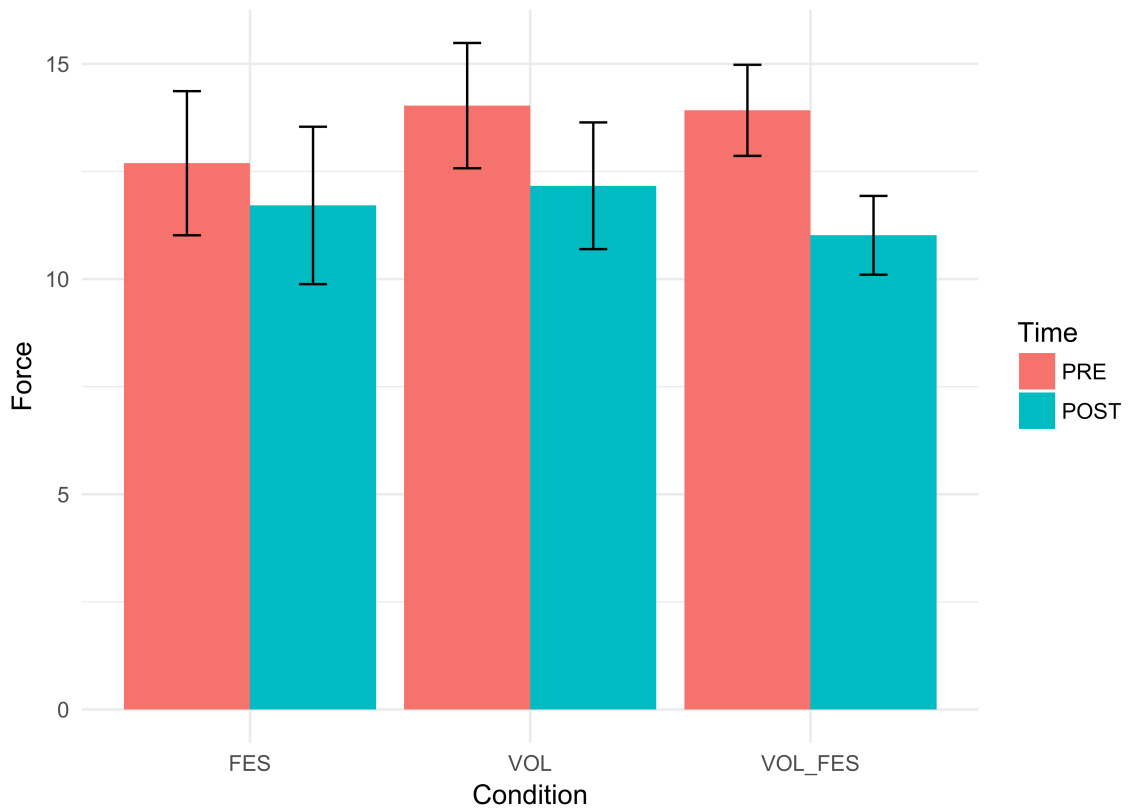
## CHAPTER 3

### RESULTS

#### 3.1 Functional Outcomes

##### 3.1.1 Maximum Force

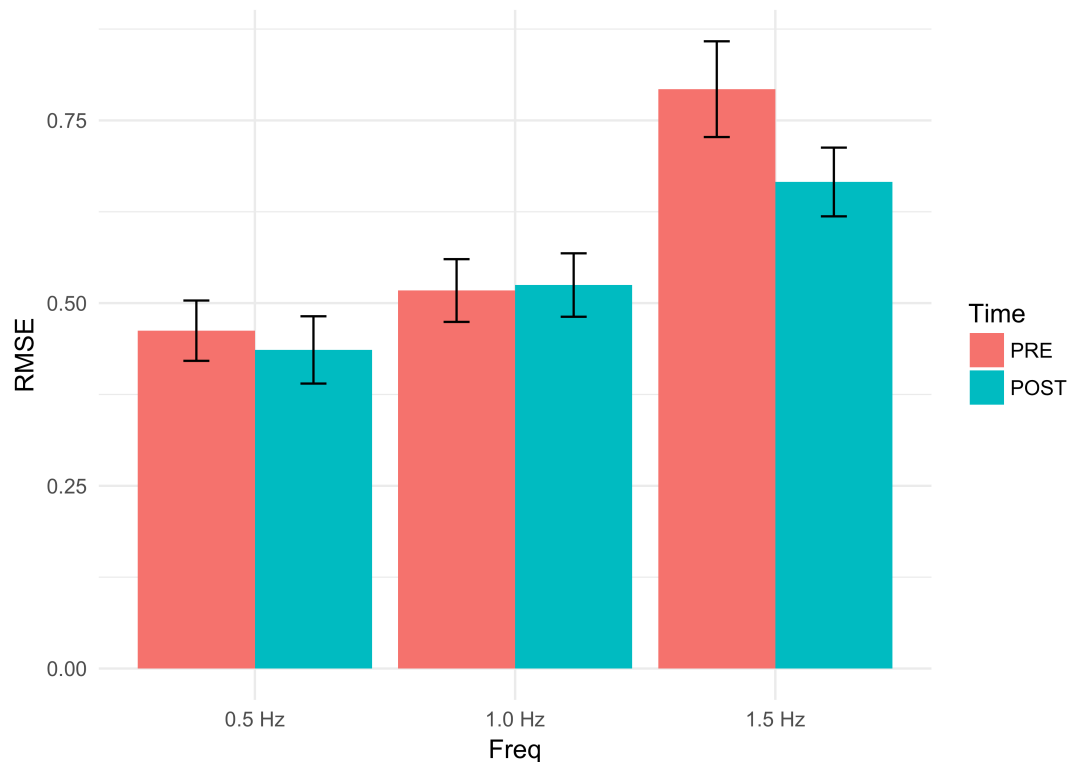
To evaluate the changes in the maximum extension force produced by a subject, a 2-way, within subjects ANOVA was conducted with factors “condition” (three levels) and “time” (two levels: PRE and POST). Neither the effect of “condition” [ $F(2, 30) = 0.247$ ;  $P = 0.782$ ], the effect of “time” [ $F(1, 20) = 3.199$ ;  $P = 0.0787$ ], nor the interaction [ $F(5, 60) = 0.269$ ;  $P = 0.7650$ ] were significant.



**Figure 3.1** Three-trial average magnitude of maximum finger extension pre- and post-intervention with FES delivered with 2ms pulse width. Data averaged across the group ( $n = 11$ ; error bars = 1 SE).

### 3.1.2 Force Control

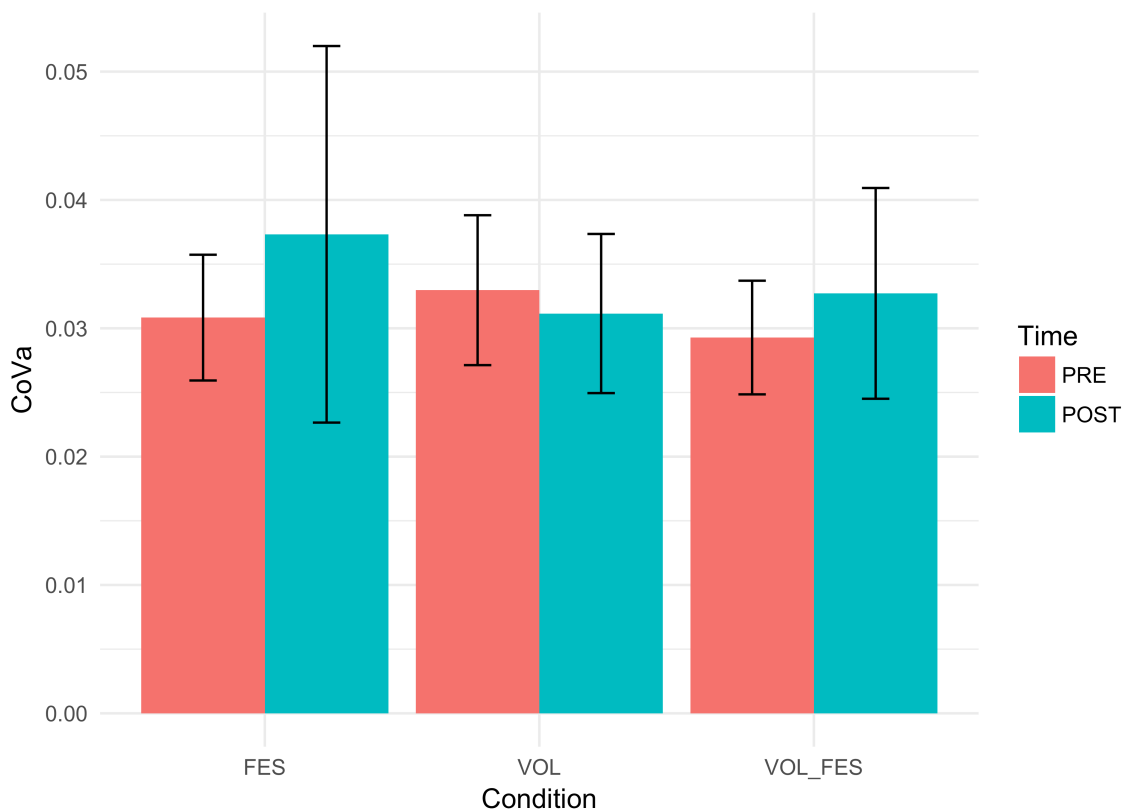
A 3-way, within subjects ANOVA was conducted with factors “condition” (three levels), frequency (three levels: 0.5 Hz, 1.0 Hz, 1.5 Hz) and “time” (two levels: PRE and POST). Frequency was significant [ $F(2, 195) = 20.048$ ;  $P = 0.000^{***}$ ] while neither the effect of “condition” [ $F(2, 195) = 1.70$ ;  $P = 0.186$ ], nor the effect of “time” [ $F(1, 196) = 1.677$ ;  $P = 0.197$ ] were significant. None of the interaction terms were significant. Although frequency was determined to be significant, this analysis was not followed with post-hoc analyses because neither of the training-related parameters (“condition” and “time”) was significant.



**Figure 3.2** Magnitude of the root mean square error (RMSE) during tracing of various frequency sine waves in finger extension, pre- and post-intervention with FES delivered with 2ms pulse width. Data averaged across the group ( $n = 11$ ; error bars = 1 SE).

### 3.1.3 Coefficient of Variation

A 2-way, within subjects ANOVA was conducted with factors “condition” (three levels) and “time” (two levels: PRE and POST). Neither the effect of “condition” [ $F(2, 30) = 0.411$ ;  $P = 0.665$ ], the effect of “time” [ $F(1, 20) = 0.784$ ;  $P = 0.379$ ], nor the interaction [ $F(5, 60) = 0.269$ ;  $P = 0.665$ ] were significant.



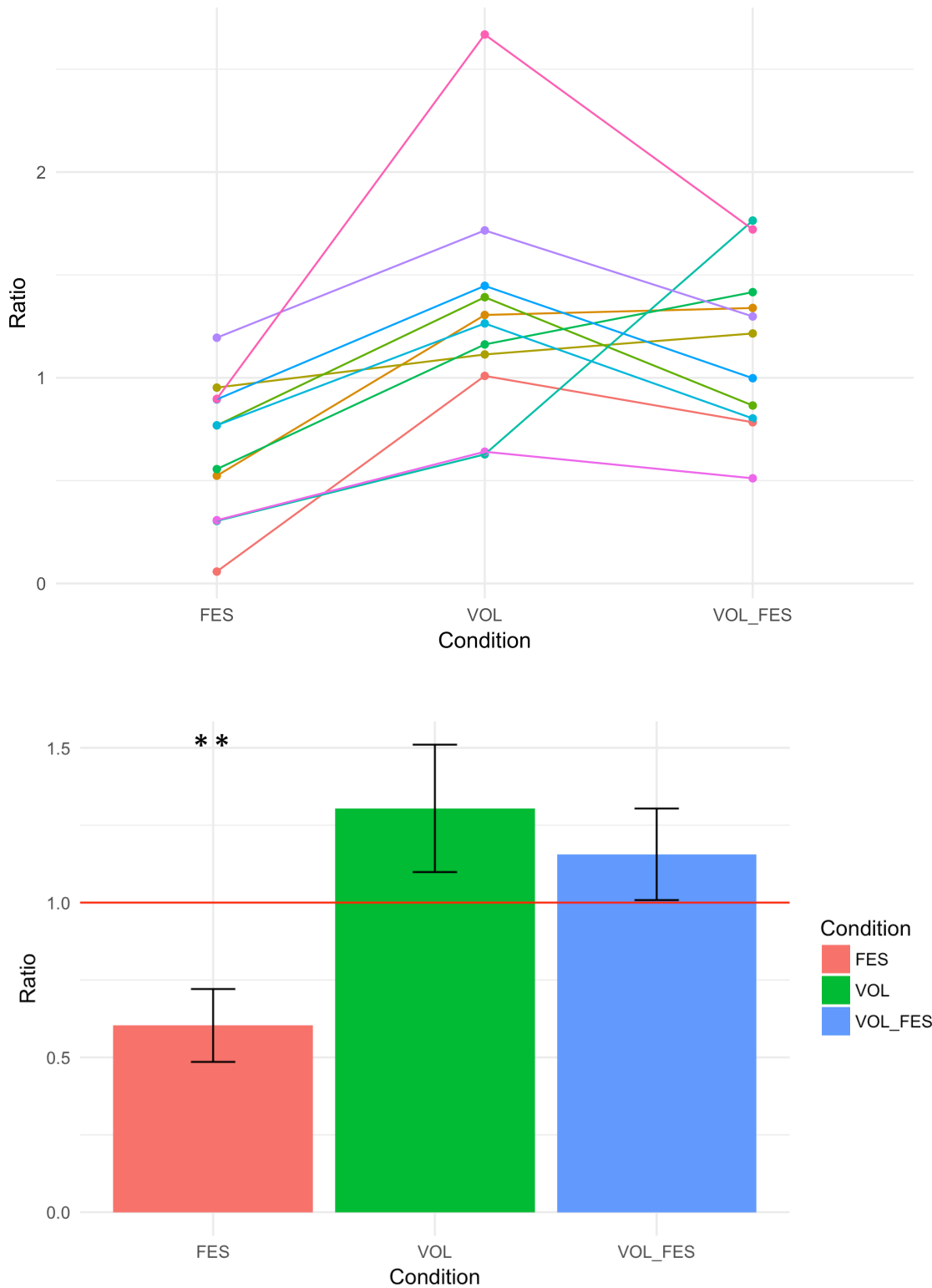
**Figure 3.3** Magnitude of the coefficient of variation (CoVa) during isometric finger extension, pre- and post-intervention with FES delivered with 2ms pulse width. Data averaged across the group ( $n = 11$ ; error bars = 1 SE).

## 3.2 Neurophysiological Outcomes

### 3.2.1 MEPs Pre- to Post-Intervention

A 1-way ANOVA was performed to test for group-wise differences between the pre-intervention MEP measurements. The effect of “condition” was not significant [ $F(2, 30) = 1.498$ ;  $P = 0.24$ ] meaning that the pre-intervention MEPs were not different across the conditions. Because the conditions were not different before each intervention, the subsequent statistics were performed on MEPs that had been normalized to their pre-intervention measurement, referred to as the MEP ratio.

The changes in MEP amplitude between pre- and post-intervention were evaluated using a 1-way ANOVA on the post-intervention MEP ratio with the factor “condition” (three levels: VOL, FES, VOL+FES). The effect of “condition” was significant [ $F(2, 30) = 6.482$ ;  $P = 0.00458^{**}$ ]. This analysis was followed with 3, one-sample t-tests to determine whether the post-intervention MEP ratio was significantly different from 1, the normalized pre-intervention MEP amplitude. The t-test revealed that the MEP ratio for the FES condition was significantly reduced from the pre-intervention measurement [ $t = -3.3563$ ;  $P = 0.007288^{**}$ ] while the VOL [ $t = 1.8116$ ;  $P = 0.1001$ ] and VOL+FES [ $t = 1.2919$ ;  $P = 0.2255$ ] conditions did not show significant increases from the pre-intervention measurement. The FES MEP ratio decreased from the pre- to post-intervention measurement by  $45 \pm 11\%$  while VOL increased by  $30 \pm 18.5\%$  and VOL+FES increased by  $15.5 \pm 13.5\%$  (Figure 3.4).



**Figure 3.4** Motor evoked potential (MEP) amplitudes from extensor digitorum communis pre- and post-intervention with FES delivered with 2ms pulse width. Top: Individual responses, each line is a single subject. Bottom: Data averaged across the group (n = 11; error bars = 1 SE; \*, p < 0.05, \*\*, p < 0.01).

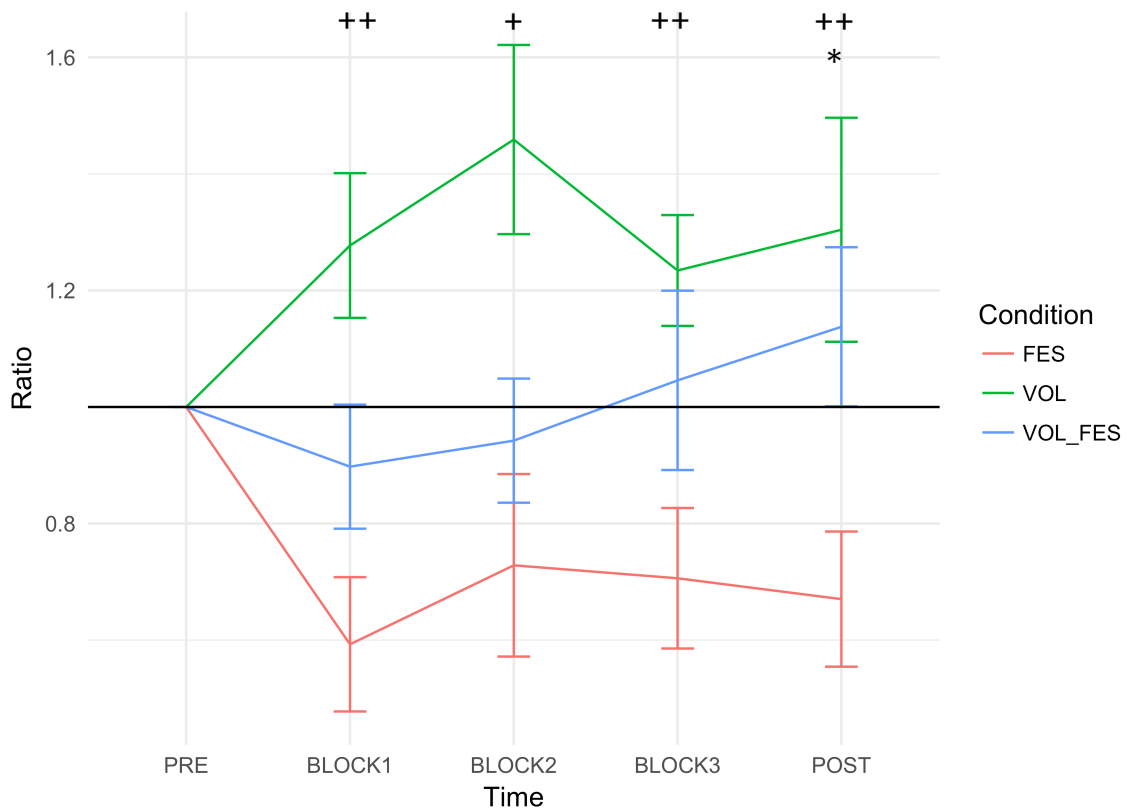
### 3.2.2 MEPs Over Time

To evaluate the changes in MEP amplitude a 2-way, within subjects (N=10) ANOVA was conducted with factors “condition” (three levels) and “time” (four levels: BLOCK 1, BLOCK 2, BLOCK 3, POST). The “PRE” time point was not included in this analysis because it was the normalization value and, thus, had a value of 1.0 with a standard deviation of 0. The effect of “condition” on MEP ratio was significant [ $F(2, 135) = 4.886$ ;  $P = 0.00894^{**}$ ], while the effect of “time” was not significant [ $F(4, 132) = 0.315$ ;  $P = 0.868$ ] and neither was the interaction [ $F(2, 135) = 1.222$ ;  $P = 0.291$ ]. The values of the MEP ratio at each time point are presented in Table 3.1.

Following the ANOVA, because “condition” was the only significant factor, the data was separated into its time points and a Tukey *post-hoc*, at 95% was conducted within each time block. This evaluation reveals how the MEP ratio is affected by each condition in relation to the other conditions at each point in time. In BLOCK 1, VOL was significantly different from FES ( $P = 0.00583^{**}$ ) while VOL+FES was not different from FES ( $P = 0.213$ ) or VOL ( $P = 0.246$ ). In BLOCK 2, VOL was still significantly different from FES ( $P = 0.0157^*$ ) while VOL+FES was not different from FES ( $P = 0.527$ ) or VOL ( $P = 0.164$ ). In BLOCK 3, VOL was still significantly different from FES ( $P = 0.00238^{**}$ ) while VOL+FES was not different from FES ( $P = 0.0736$ ) or VOL ( $P = 0.342$ ). Following the intervention, at time “POST”, VOL remained significantly different from FES ( $P = 0.00483^{**}$ ); additionally VOL+FES was significantly different from FES ( $P = 0.0332^*$ ) although it was not different from VOL ( $P = 0.714$ ).

**Table 3.1** Averaged MEP Ratio Values for the Five Experimental Time Points are Presented for each of the Three Conditions.

Condition	PRE Mean±SD	BLOCK 1 Mean±SD	BLOCK 2 Mean±SD	BLOCK 3 Mean±SD	POST Mean±SD
<b>VOL</b>	1.00±0.00	1.2771±0.393	1.4589±0.513	1.2342±0.301	1.3041±0.608
<b>FES</b>	1.00±0.00	0.5927±0.364	0.7283±0.495	0.7061±0.381	0.6703±0.367
<b>VOL+FES</b>	1.00±0.00	0.8976±0.337	0.9422±0.337	1.0457±0.154	1.1376±0.432



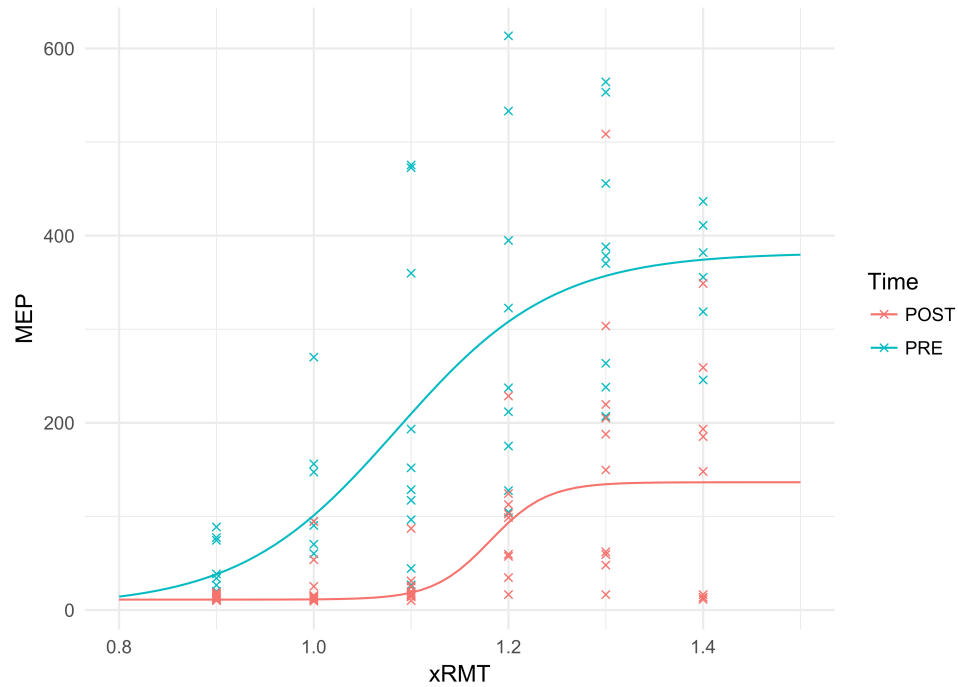
**Figure 3.5** Motor evoked potential (MEP) ratio from extensor digitorum communis across the 5 experimental time points with FES delivered with 2ms pulse width (n = 10; error bars = 1 SE; Significance Codes: + VOL vs. FES, \* VOL+FES vs. FES, # VOL vs. VOL+FES; \* p<0.05, \*\* p<0.01).

### 3.2.3 Resting Recruitment Curve

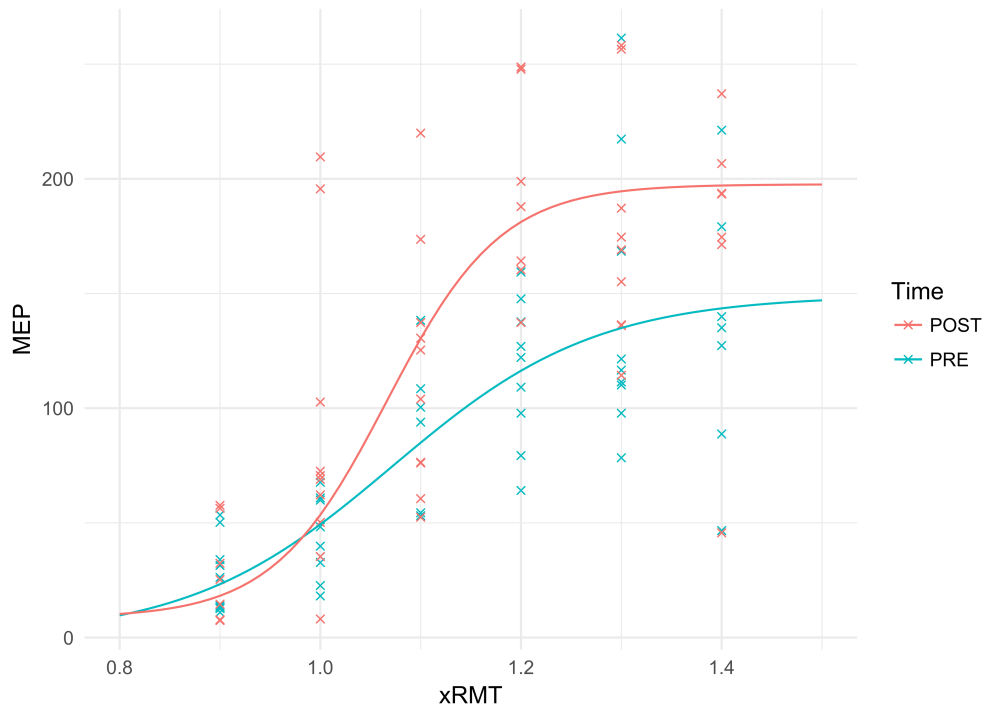
A 1-way ANOVA was performed to test for differences between the parameters extracted from the sigmoidal fit in the pre-intervention measurements. The effect of “condition” was not significant for MEPmax [F(2, 30) = 0.556; P = 0.574], S50 [F(2, 30) = 0.314; P=0.733], or the slope [F(2, 30) = 1.729; P=0.195] meaning that at baseline the parameters were not different across the conditions. The sigmoidal curve-fit for representative subjects in each of the three conditions are shown in Figures 3.6, 3.7, and 3.8.

The effects of time and condition were quantified for the input-output relationship from the pre- and post-intervention curve-fit parameters. The effect of “time”, “condition” and the interaction were not significant for any of the parameters. For MEPmax, the interaction between the two factors was not significant [F(2, 63) = 0.2331; P = 0.106], nor was the effect of “time” [F(1, 64) = 0.741; P = 0.393] and “condition” [F(2, 63) = 0.659; P = 0.521]. For S50, the interaction between the two factors was not significant [F(2, 63) = 0.597; P = 0.554], nor was the effect of “time” [F(1, 64) = 0.867; P = 0.356] and “condition” [F(2, 63) = 1.192; P = 0.311]. For the slope, the interaction between the two factors was not significant [F(2, 63) = 0.900; P = 0.4.12], nor was the effect of “time” [F(1, 64) = 1.7222; P = 0.273] and “condition” [F(2, 63) = 0.876; P = 0.422].

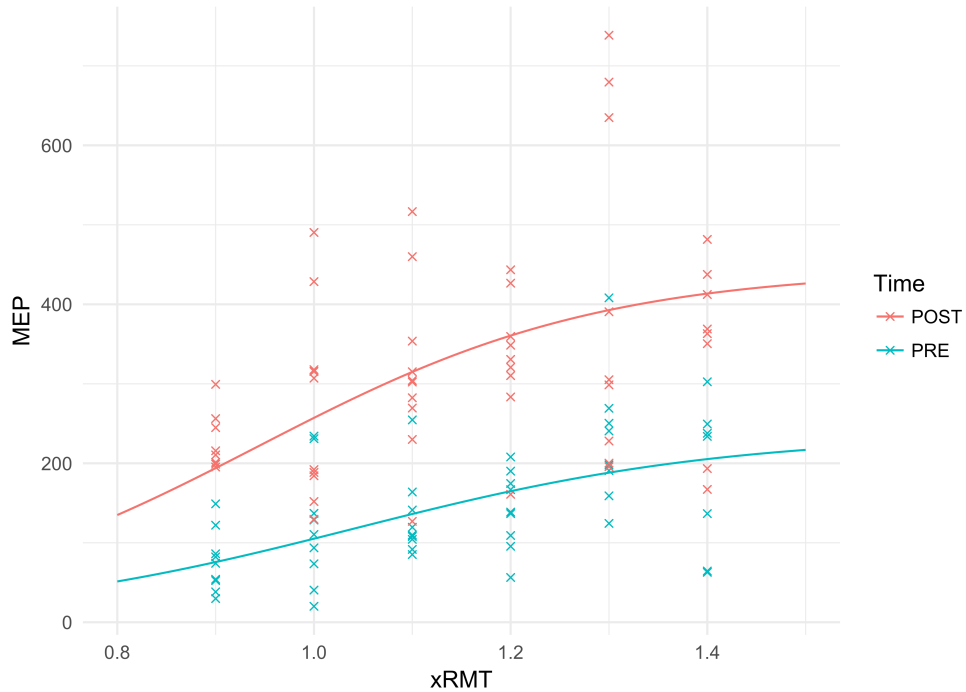




**Figure 3.6** Changes in motor output after training. EDC MEP recruitment curve pre- and post-intervention for a representative subject of the FES. All shown are curves fitted using Boltzman sigmoidal function. The curve was fit through the average of the ten stimuli of per percent of resting motor threshold (RMT).



**Figure 3.7** Changes in motor output after training. EDC MEP recruitment curve pre- and post-intervention for a representative subject of the VOL. All shown are curves fitted using Boltzman sigmoidal function. The curve was fit through the average of the ten stimuli of per percent of resting motor threshold (RMT).



**Figure 3.8** Changes in motor output after training. EDC MEP recruitment curve pre- and post-intervention for a representative subject of the VOL+FES. All shown are curves fitted using Boltzman sigmoidal function. The curve was fit through the average of the ten stimuli of per percent of resting motor threshold (RMT).

## **CHAPTER 4**

### **DISCUSSION**

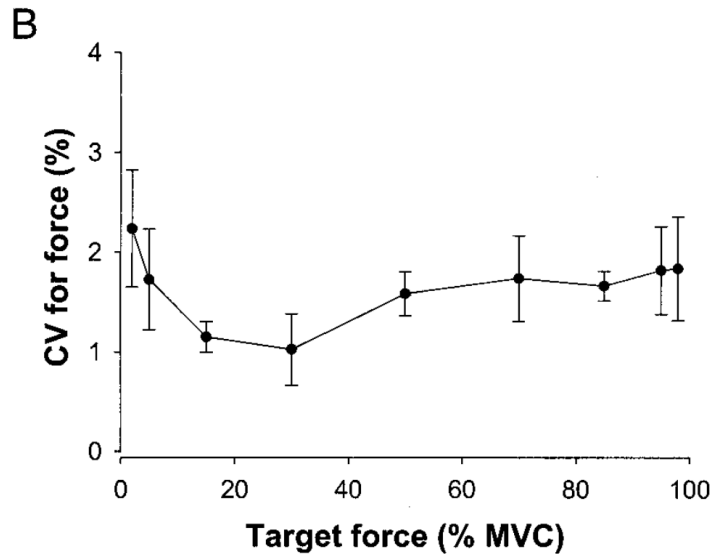
In this study, we investigated the effect of pairing voluntary movement with muscle located electrical stimulation for hand opening. No significant changes were seen in functional behavior following any of the three interventions. Contrary to our hypothesis, voluntary activation supplemented by FES did not cause a larger increase in corticospinal excitability than voluntary contraction alone. Increases in corticospinal excitability for the EDC, although not significant, were seen for both voluntary movement and voluntary movement supplemented by FES while significant decreases in EDC excitability were seen for FES alone.

#### **4.1 Functional Outcomes**

It is unlikely that a single day intervention would cause improvements in the functional behavior of healthy controls. For the measures of force control, determined by the RMSE of each subject's signal traces, there was no difference in improvement, at any tracing frequency, for any condition. The three frequencies of the traces were chosen such that the subject had to engage different control mechanisms to perform the task. The 0.5Hz trace is "feedback" control while the 1.5Hz trace is predictive, or "feed forward", control and the 1.0Hz trace is right on the edge between the two control mechanisms. Subjects were given the opportunity to practice the task once, before beginning the measurements, on each day of training. The subjects who performed best prior to any training or intervention were the subject who regularly engaged in athletic activities such as volleyball or tennis; these sports require better control over the muscles of the arm and

hand than activities of daily living for healthy controls who are not active in sports. It is likely that any subject improvement in force control seen in this study is directly related to the increasing familiarity with the task.

Coefficient of variation was used as a measure of fatigue because we wanted to investigate the ability of the subject to smoothly and consistently perform a movement. Each condition in this study saw a drop in the magnitude of the maximum force between pre- and post-intervention of approximately 10%. Post-intervention, subjects were asked to perform the task at 20% of their pre-intervention maximum force; this means that the post-intervention task actually required about 30% of the fatigued maximum force. Taylor [73], investigated the effects of fatigue, measured by percent of the maximum voluntary force, on the coefficient of variation of produced force. Applying 30% of the maximum force leads to a reduction in the coefficient of variation and is the lowest point on Taylor's [73] coefficient of variation curve (Figure 4.1). There were no significant differences between the magnitudes of the decreases in maximum force for each condition. Coupled with the decreases but lack of significant differences in coefficient of variation for each condition, this suggests that there is no difference in the amount of fatigue induced by the different interventions.



**Figure 4.1** Fluctuations in index finger force during voluntary contractions performed with first dorsal interosseous muscle. Data consist of those parts of each trial when subjects received no visual feedback. B: coefficient of variation (CV) for force was greatest at low forces, decreased to a minimum at 30% MVC, and then increased to plateau after 50% MVC. Data in are plotted as median  $\pm$  SE for 10 subjects. Source: [73]

## 4.2 Neurophysiological Outcomes

### 4.2.1 MEPs Pre- to Post-Intervention

Part one of the experiment in this study was designed to study the effect of the interaction of voluntary contraction and FES on corticospinal excitability. We found no significant changes in corticospinal excitability for the voluntary contraction, such as the significant decreases seen by Barsi [55] or increases seen by Taylor [49], and no significant increases in corticospinal excitability for voluntary contraction with FES condition, such has been found in previous studies [53], [50], [59], [64]. The magnitude of the increases that were seen for these conditions were comparable to the conditions found by Taylor in the ECR [49], which were significant. Increasing N into the range of 15 or 20 subjects would likely enhance the significance of the results of this study.

The most significant finding of this study is the extent to which FES alone decreases corticospinal excitability and the ability of adding voluntary contraction to the stimulation to erase the negative corticospinal effects of the stimulation alone. The effects of FES were an immediate and persistent reduction in corticospinal excitability. This electrical stimulation had been designed to mimic a voluntary movement, hand opening, and the mimicry is not equivalent to a volitional movement toward the same task. These results imply that receiving passive electrical stimulation for rehabilitation, although it is the current clinical practice, is unable to produce positive connections between the motor cortex and the target muscle. Studies in the past have shown that the cerebellum creates a model of the desired movement [78] and compares it to the movement performed [79]; when these do not match up, the brain seeks to attenuate the error using the somatosensory cortex [78]. This mechanism is important for motor learning of a voluntary skill, but is also believed to play a role in the incorporation of FES into a part of the voluntary drive and the potential mechanism of the increase in excitability seen with voluntary activation supplemented by FES that is not seen in FES alone.

Part two of the experiment in this study was designed to show the effect of pulse width of the peripheral electrical stimulation on cortical excitability. These effects were evaluated by bringing back three of the subjects who participated in the main experiment and retesting the FES alone and VOL+FES conditions using a 200 $\mu$ s pulse width instead of a 2ms pulse width. A 200 $\mu$ s pulse width for electrical stimulation is the most common pulse width used in studies involving FES.

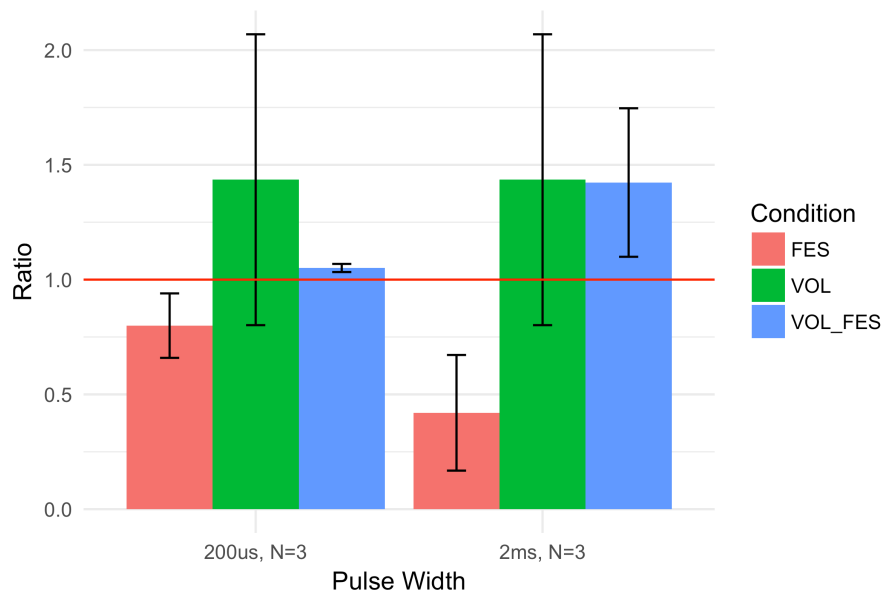
Hindle [80] found short (200 $\mu$ s) and long (1ms) pulse durations to be equally effective in enhancing corticospinal excitability of the TA. However, the widest pulse

width he investigated was 1ms. Previous studies investigating the effects of pulse width on corticospinal excitability in the upper extremity have found no significant differences in the effects induced by short or long pulse widths [46], [66], [80], [81] however, the pulse widths investigated were between 50 $\mu$ s and 1ms. Based on these previous results, it is unlikely that increasing the pulse width to 2ms would yield any significant differences over the more standard 200 $\mu$ s pulse width for electrical stimulation.

In this study, with a pulse width of 2ms, preliminary results from a limited sample size suggest that wider pulse widths may exaggerate the effects seen when FES is applied at a shorter pulse width, although the differences are not wide enough to imply significance (Figure 4.2). The exaggerated effects between the 2ms and 200 $\mu$ s pulse width could be caused by the ability of wider pulse widths to recruit more central pathways as opposed to peripheral pathways [56], [81] (Figure 1.4) or it could be caused by the relative ease with which the 200 $\mu$ s is integrated into native motor commands such that stimulation at 200 $\mu$ s is interpreted by the brain as a less erroneous signal than a 2ms pulse width signal [32]. Alternately, the decrease in excitability as a result of the FES condition between the 200 $\mu$ s and 2ms condition may be merely a result of increased muscle fatigue induced by the longer pulse width [82]. It will be important to collect a larger sample size in experiment 2 to determine whether the differences seen in the EDC for both short and long and very long pulse widths persist and whether or not the difference is significant.

While all 11 subjects in this study were able to tolerate the 2ms pulse width stimulation, several reported it to be uncomfortable. Surface application of FES for muscle stimulation stimulates the pain receptors directly under the stimulation electrodes

in addition to stimulating the target muscles. Applying the stimulation with a  $200\mu\text{s}$  was still able to elicit a functional contraction and the subjects reported that the stimulation was much more comfortable. An important aspect of determining the optimal FES stimulation parameters will be to balance what subjects find comfortable and tolerable with what stimulation parameters elicit the best results. This is particularly relevant when rehabilitating stroke patients, who generally have higher peripheral sensitivity than healthy subjects.



**Figure 4.2** Motor evoked potential (MEP) amplitudes as a pre- to post-intervention ratio from extensor digitorum comunus as a function of pulse width. Each group by pulse width contains the same subjects ( $n = 3$ ; error bars = 1 SE).

#### 4.2.2 MEPs Over Time

Iftime-Nielsen [32] found, during fMRI of similar tasks to the tasks evaluated in this study, that peripheral electrical stimulation alone is treated, by the brain, as an erroneous signal, however, the addition of voluntary drive to the electrical stimulation (VOL+FES condition) allows the FES to become a part of and to enhance the motor command. This



incorporation of the electrical stimulation is seen in the contrast between each of the three conditions. Voluntary contraction alone immediately increases corticospinal excitability and remains elevated throughout the experiment. FES alone immediately and significantly reduces corticospinal excitability and remains significantly reduced to the end of the intervention. However, voluntary contraction with FES causes an immediate decrease in corticospinal excitability but not to the extent of FES alone; at the subsequent time points within the intervention, corticospinal excitability of the EDC steadily increases, to the point where it is almost as elevated as the final measurement for the VOL condition (Figure 3.5). The results from this study solidify the previous results that voluntary participation in a movement is necessary for enhancing corticospinal connections between the motor cortex and the target muscle, results that cannot be achieved through passive electrical stimulation alone.

## **CHAPTER 5**

### **CONCLUSION**

#### **5.1 Study Limitations**

The primary limitation of this study is the application of a 2ms pulse width. The longest pulse width found in the current literature is 1ms. This lack of similar electrical stimulation parameters in similar experimental paradigms limits our ability to draw meaningful conclusions from the results of this experiment.

The second significant limitation of this study is the small sample size. Results of the first experiment would be solidified by increasing the N to between 15 and 20 subjects. Additionally, recruiting more subjects into part 2 of this experiment would help to elucidate the effects of pulse width on corticospinal excitability under this experimental paradigm.

While the design of this study targets the hemiplegic chronic stroke population, no stroke subjects were enrolled in this experiment. A stroke population will almost certainly respond differently to these treatments than a healthy population. Without a stroke population in the study, we are not able to determine the effects these rehabilitation paradigms may have on an affected subject.

#### **5.2 Future Investigations**

Future efforts in this area would focus on increasing the sample size of the healthy population in both experiments. Additionally, those efforts would build a stroke group to compare to the healthy population so that the true effectiveness of these paradigms as a

rehabilitation strategy can be evaluated. A longer term goal would be investigate each experimental paradigm in a longitudinal study, of three times a week for 6 to 8 weeks, comparable to the duration of a clinical rehabilitation paradigm. This longitudinal study would show whether or not the changes in corticospinal excitability caused by a single day of training persist over time. A longitudinal study would also allow for any improvements in functional behavior that would occur as a result of the training to be seen.

### **5.3 Clinical Significance**

This study provided insights into how to engage stroke patients in more useful clinical rehabilitation. For patients with the ability to make some volitional movements, engaging them in making those movements during therapy has a positive effect on corticospinal excitability. This indicates stronger connections between the cortex and the target muscle. However, basing the FES on the subject's recorded muscle effort would allow patients to participate in the therapy even if they are flaccid, or cannot produce visible volitional movement. Additionally, the required target participation can be increased or reduced with patient ability and recovery such that everyone is able to engage in the protocol effectively.

### **5.4 Conclusions**

This study attempted to elucidate the mechanisms of functional improvement and increases in corticospinal excitability that are usually seen over weeks of physical therapy. The increase in corticospinal excitability caused by combining voluntary activity

with functional electrical stimulation has significant implications for rehabilitation in chronic stroke. FES enables the stroke patient to participate in therapy, producing meaningful movements, while the voluntary activation engages their motor cortex such that the neurological connections between the brain and the muscle are enhanced instead of inhibited.

## **APPENDIX**

This appendix contains the subject screening questionnaire that is used to determine whether the potential subject has any contraindications for TMS and whether or not they are medically qualified to participate in a TMS experiment.

## CORTICAL STIMULATION SUBJECT SCREENING QUESTIONNAIRE

- Have you ever been diagnosed with any neurological or psychiatric condition? YES/NO  
-for example, stroke, Parkinson's disease, depression, or other  
If YES, please clarify (nature of condition, duration, current medication, etc).
- Have you had epilepsy/seizures, febrile convulsions in infancy, or recurrent fainting spells? YES/NO
- Does anyone in your immediate or distant family have epilepsy? YES/NO  
If YES please state your relationship to the affected family member.
- Have you ever undergone a neurosurgical procedure (including eye surgery)? YES/NO  
If YES please clarify.
- Have you ever had a head injury? YES/NO  
If YES please clarify.
- Do you currently have any of the following fitted to your body? YES/NO  
-Heart pacemaker, Cochlear implant, Medication pump, Surgical clips, other metal.
- Are you currently taking any unprescribed or prescribed medication? YES/NO  
If YES please clarify.
- Have you had alcohol or recreational drugs in the past 12 hours? YES/NO
- Are you male or female? \_\_\_\_\_ YES/NO  
If you are female, are you pregnant or is there a possibility you may be pregnant?
- Do you have frequent or severe headaches? YES/NO
- Have you ever participated in a TMS study and had any adverse reaction? YES/NO

I, \_\_\_\_\_, confirm that I have read the consent form and completed the above questionnaire. I confirm that I am not taking recreational drugs, have not participated in a TMS experiment earlier today and feel well rested. The nature, purpose and possible consequence of the procedures involved have been explained. I understand that I may withdraw from the study at any time.

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