ASSESSMENT OF REPETITIVE FACILITATION EXERCISE WITH FMRI-COMPATIBILE REHABILITATION DEVICE FOR HEMIPARETIC LIMBS

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ASSESSMENT OF REPETITIVE FACILITATION EXERCISE WITH FMRI-COMPATIBILE REHABILITATION DEVICE FOR HEMIPARETIC LIMBS

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LIST OF SYMBOLS AND ABBREVIATIONS

Δt_s	Electrical Stimulus Short Latency Response Time Delay
Δt_l	Electrical Stimulus Long Latency Response Time Delay
Δt_m	Magnetic Stimulus Response Time Delay
Δt_o	Time Delay Between the Actuator Input Command and Observable Response
Δt_d	Time Delay Between Mechanical Input Command and TMS artifact
PNF	Proprioceptive Neuromuscluar Facilitation
RFE	Repetitive Facilitation Exercise
fMRI	Functional Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
TMS	Transcranial Magnetic Stimulation
PNS	Peripheral Nerve Stimulation
AF	Augmented Feedback
MCP	Metacarpophangeal
CR	Conventional Rehabilitation
STEF	Simple Test Evaluating Hand Function
IRB	Institutional Review Board
EMG	Electromyogram
FCR	Flexor Carpi Radialis
RMT	Resting Motor Threshold
MEP	Motor Evoked Potentials
NEMA	National Electrical Manufacturers Association
STD	Standard Deviation

SUMMARY

In order for stroke subjects to gain functional recovery of their hemiparetic limbs, facilitation techniques such as the repetitive facilitation exercise, or RFE, have been developed. Currently, there is a lack of understanding of the neural mechanisms associated with these types of facilitation techniques. To better understand the neural mechanisms associated with the RFE a functional magnetic resonance imaging (fMRI) study should be conducted.

This thesis presents experimental results testing the feasibility of implementing an fMRI-compatible actuator to facilitate a myotatic reflex in synchronization with the subject's intention to move their hemiparetic limb. Preliminary data from a healthy individual demonstrated the feasibility of overlapping the long latency component of the afferent myotatic reflex, created by electrical stimulation, with descending nerve impulses, created using transcranial magnetic stimulation, in a time window of 15ms. In addition, a pneumatic actuation time delay due to long transmission line was evaluated. The pneumatic actuator met the timing precision requirement for the rehabilitation device for varying transmission line lengths. Therefore a pneumatic actuation system was chosen for the rehabilitation device.

This thesis will also presents on the design of an fMRI-compatible pneumatic actuator device to excite a stretch reflex response. Initial, experimental results with the device demonstrated that the designed pneumatic device can control the timing of the muscle response with a fixed signal within the required 15ms window required for cortical facilitation, which was found in the previous feasibility study. However, the device was unable to create a long latency reflex observable at the muscle.

Finally, this thesis presents on the capability of the device in creating subthreshold long latency response with precision to overlap with a subthreshold descending nerve impulse, created using transcranial magnetic stimulation. The overlap of the two responses was evaluated by comparing the amplitude of the muscle response with and without the stretch reflex, created by the fMRI-compatible pneumatic actuator device. Varying time delays were analyzed.

CHAPTER 1

INTRODUCTION

1.1 Motivation

Several countries across the world are currently experiencing an aging population and are anticipating increased losses in productivity due to age-related neurological disorders [1]. The United States is one of them; the population of people aged 65 and over in the United States is predicted to reach 15.8% in 2020 and 20% in 2040 [2]. On the global scale, the effects of aging are a more serious problem. For example, in Japan and Italy, the population of people aged 65 and over reached 20% in 2010 and will exceed 30% in 2030.

As the average age of the world population increases due to medical advances, the risk of age-related neurological disorders, such as stroke, also increases. According to the World Health Organization, approximately 15 million individuals suffer from stroke each year worldwide [3]. In the United States, there are approximately 600,000 individuals every year who suffer their first strokes [4]. In Japan, one of the most rapidly aging countries, stroke is one of the most prevalent medical problems with more than 500,000 new stroke patients every year. Nearly one in four men and one in five women age 45 or above can expect to have a stroke if they reach their 85th year. It has been estimated that by 2023 there will be an absolute increase of 30% in the number of patients experiencing their first ever stroke compared with 1983 statistics [5]. Although stroke is a major cause of death worldwide, strokes also cause major motor disabilities in the affected population. As many as 88% of patients that experience an acute stroke experience a motor disability called hemiparesis, or a semi-paralysis of one side of the body [6]. The loss of motor control is highly dependent on the area of the brain that is affected by the stroke. With the loss of motor control of the arms, hands, legs, facial muscles, etc. individuals are not able to perform activities of daily living without assistance [7]. Stroke is the leading cause of serious long-term disability [8]. This long-term loss of motor control can have major socio-economic effects to the worldwide population due to the loss of productivity and greater need for assistance. A study conducted by the American Stroke Association concluded that given the increasing prevalence of stroke as well as the increasing pressures on families to provide care, more research is needed to guide policy and practice in this understudied topic [8].

In order to reduce the loss of worldwide productivity and socio-economic impacts due to stroke, a variety of rehabilitation or facilitation exercises have been developed. Many facilitation techniques were developed in the 1950's – 1960's, such as the Brunnstorm approach [9], proprioceptive neuromuscluar facilitation (PNF) [10], and the Bobath concept [11]. Although these techniques were believed to help hemiparesis individuals gain back motor control, recent studies report that these treatments do not show statistically significant improvements over conventional therapies [12-16].

Despite the lack of evidence, the strength behind recent conventional facilitation exercises is that they take advantage of neural plasticity and sensory neural pathways to help improve the neural connection between the brain and the affected muscle groupings, in contrast with the older approaches, which were designed to normalize muscle tone and improve posture. With the assistance of conventional rehabilitation exercises, it is believed that the unaffected motor cortex is able to reorganize and compensate for the stroke-affected part of the brain. Recent studies indicate that neural plasticity may contribute to functional recovery after stroke [17]. Functional reorganization in the undamaged motor cortex can lead to recovery of hand [18] and finger [19] functions. Rehabilitation exercise could shape subsequent reorganization in the adjacent intact cortex. Consequently, there is a strong need for further scientific study to establish healthcare technologies that may help individuals recover from hemiparesis and maintain their independence.

One such recently developed facilitation exercise that has shown statistical significant motor control improvements [20, 21] is the repetitive facilitation exercise or RFE [20-22], which was proposed by Dr. Kawahira of Kagoshima University in Japan in the late 1990's [20, 23, 24]. This exercise is thought to take advantage of the afferent and efferent neural pathways in the upper and lower limbs. The repetitive facilitation exercise is believed to combine an efferent neural signal, created by the individual's intended motor movement, with the descending component of the long latency response, created by a high velocity stretch of the muscle. This exercise has been studied on hemiparesis individuals as well as an individual experiencing corticobasal degeneration where statistical improvements were observed [22]. The latest result for a person with corticobasal degeneration was also reported in [24]. The group has reported that sessions with this new technique showed better results than conventional rehabilitation sessions [21, 25]. Although portions of the RFE process are understood, the mechanism that is assisting the brain to reorganize and gain back the isolated motor control has not been investigated from a neuroscientific perspective.

1.2 Research Objectives

The ultimate objective of the research is to understand and characterize the neuromuscular mechanisms associated with facilitation techniques designed for functional recovery of hemiparetic limbs. The research includes analysis of a novel facilitation exercise paradigm and implementation with the addition of a robotic device. The specific goal of this project is to establish methods and tools to quantitatively validate a hypothesized physiological mechanism for limb movement facilitation.

The facilitation technique of interest is referred to as the repetitive facilitation exercise, or RFE, which was designed by Dr. Kawahira of Kagoshima University, Japan. The key feature of RFE is that it is designed to take advantage of neural plasticity for functional recovery. The RFE technique utilizes a stretch reflex response to facilitate involuntary movements in the hemiparetic limb. The hypothesized mechanism of RFE is the synchronized voluntary and reflexive activations of motor neurons, which facilitate neural excitations and subsequent motor recovery. Afferent input from peripheral stimulation causes reflexive efferent response, which interacts with descending efferent nerve impulses evoked by the voluntary intent to produce movement, hence facilitating movement.

The central concept behind this project is to design and utilize a robotic device that can meet certain required timing precision for RFE. Such a robotic device would potentially reproduce RFE more reliably, repeatedly, and accurately than human therapists, enabling quantitative assessment of RFE. The robot would also allow for the quantitative analysis of central neural responses to RFE, using functional magnetic resonance imaging (fMRI). Such quantitative analyses would help clarify the neural mechanisms underlying RFE and further improve RFE procedure and assessment by examining the neural responses in terms of their activation area and magnitude.

The specific aims of the project are:

Aim 1: To understand the temporal dynamics of cortical facilitation with controlled afferent stimulation

Aim 2: To design an fMRI-compatible device and confirm fMRI-compatibility

Aim 3: To understand the temporal dynamics of cortical facilitation the fMRI-compatible device stimulates

To achieve these aims, the proposed research will involve (1) analysis of the procedure and sequence of the current manual RFE and development of algorithms implementable with an fMRI-compatible robotic RFE device, (2) quantitative analysis of temporal dynamics of cortical facilitation with afferent stimulation by using sub-threshold transcranial magnetic stimulation (TMS) and supra-threshold electrical peripheral nerve stimulation (PNS), (3) design of an fMRI-compatible device capable of facilitating a stretch reflex with mechanical stimulation, (4) analysis of the mechanically facilitated stretch reflex versus the electrically stimulated stretch reflex, (5) quantitative analysis of temporal dynamics of cortical facilitation with afferent stimulation by using sub-threshold TMS and sub-threshold mechanical muscle tendon stimulation.

CHAPTER 2

BACKGROUND

2.1 Repetitive Facilitation Exercise

In persons with hemiparesis, such as stroke survivors, the upper motor neuron pathways for voluntary movement are often disrupted. For instance, strokes to the middle cerebral artery, lateral striate artery, or the medial striate artery can cause damage to the lateral surface of cortex or to the internal capsule, where the descending axons of the corticospinal tract collect, producing a graded weakness of movement (paresis), or complete loss of muscle activity caused by paralysis (plegia). It is believed that RFE is able to re-establish volitional movement in patient populations by the principles of neural plasticity [26, 27], likely by regaining the activity of the damaged areas or utilizing other intact areas. By synchronizing patients' intent to contract their muscle with peripheral stimulation that reflexively excites the efferent neurons of the muscle, RFE is proposed to establish new functional connections within the brain, allowing stroke survivors to regain motor control of their limbs. RFE is based on the hypothesized mechanism shown in Figure 2.1.

Neuronal signals arising from the person's intention are sent from the prefrontal/premotor cortex to the primary motor cortex. An RFE-trained therapist applies mechanical stimulation by tapping and/or rubbing the agonist muscles so that stretch and superficial reflexes are evoked in synchronization with the patient's intention to move the hemiparetic limb, thus facilitating the activation and subsequent reorganization of neural circuits. In the motor cortex, overlapping of voluntary activation with the long-latency reflex (muscle-brain-muscle) is expected to contribute. Repetition of this process helps the reorganization of neural pathways for voluntary movement.

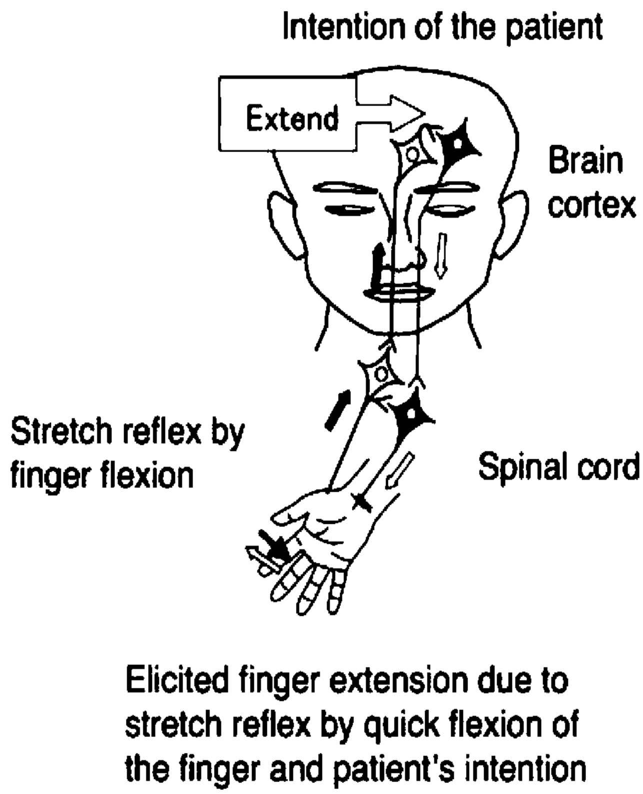
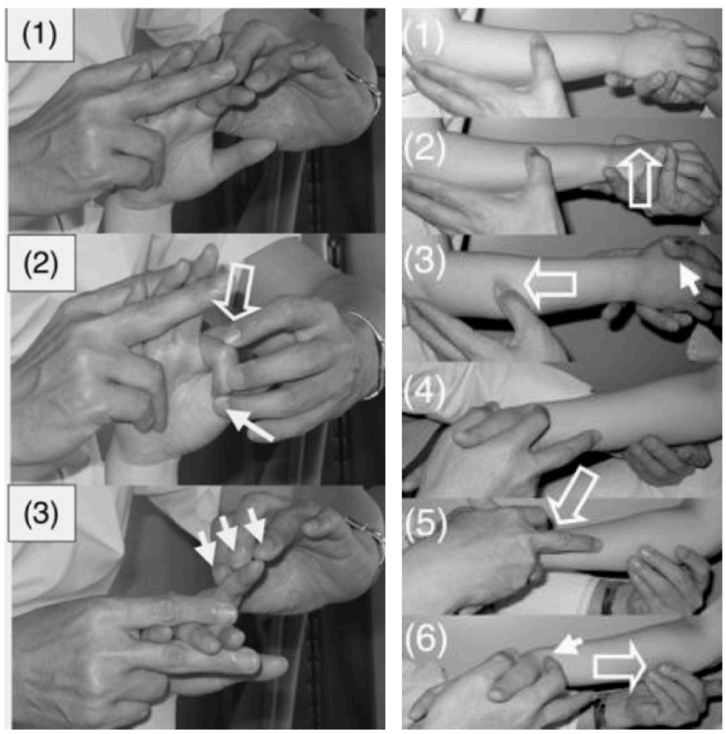


Figure 2.1 [23]: Repetitive Facilitation Exercise (RFE) Hypothesized Mechanism

Figure 2.2 (a) illustrates the procedure to facilitate the extension of the index finger. (1) The other fingers are constrained and allowed minimum movement; the isolated finger is quickly flexed. (2) A therapist flexes the metacarpophangeal (MCP) joint after cueing the patient to extend the finger. (3) Slight resistance against the finger extension is applied during the extension of the finger. The procedure is repeated from (1). Figure 2.2 (b) illustrates the procedure for the forearm to facilitate supination/pronation. (1) A therapist holds the hand of a patient and places the thumb of the other hand on the dorsal aspect of forearm. (2) The therapist quickly pronates the forearm. (3) The therapist rubs the dorsal forearm with the thumb and provides slight resistance against supination. (4) To facilitate forearm pronation, the therapist holds the hand of the patient. (5) The therapist taps the radial side of the wrist for quick supination of the forearm with his/her middle finger. (6) The therapist rubs the ventral aspect of forearm using ring and little fingers. Simultaneous electrical stimulation just below the motor threshold is recommended to further facilitate voluntary movement.



(a) (b)

Figure 2.2 [23]: (a) RFE Procedure for an Isolated Finger; (b) RFE Procedure for the Forearm

Figure 2.3 shows clinical results from an RFE study conducted for 23 inpatient stroke survivors at Kagoshima University hospital. The goal was to compare functional improvements in the upper limb between the use of RFE and conventional rehabilitation (CR). Patients were split into 2 groups, each receiving two 2-week sessions with RFE alternated with two 2-week sessions with CR. One group began treatments with RFE

(RFE Precede) while the other began with CR (RFE Follow). The cross-over design was used to exclude heterogeneity between subjects and show effects of treatment order.

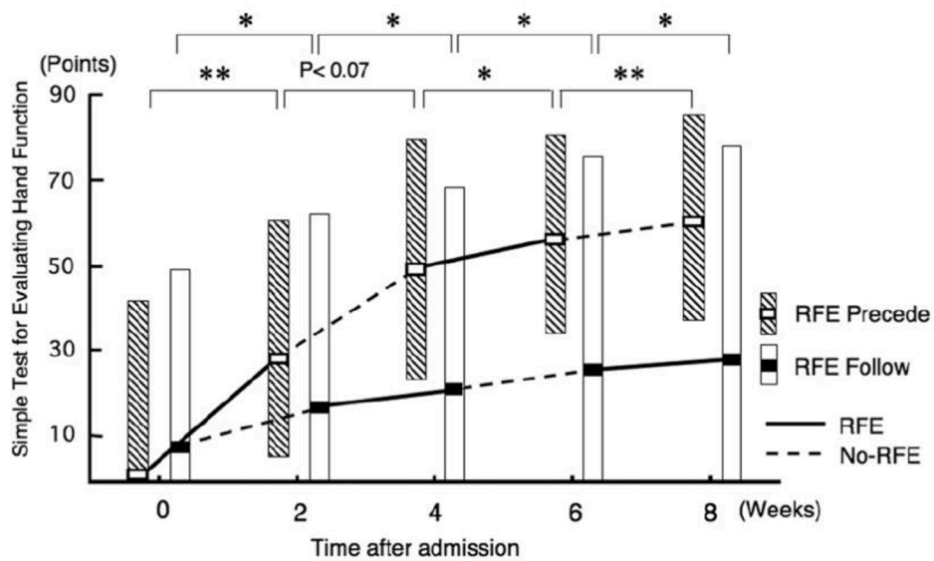


Figure 2.3 [23]: Improvement of the Ability of Manipulating Objects with Hemiparetic Upper Limb by RFE. Data are shown as the median and quartiles. Two 2-week RFE sessions (solid lines) were administered interspserd by two 2-week conventional rehabilitation sessions (broken lines).

Figure 2.3 shows scores for the Simple Test Evaluating Hand Function (STEF) test. The STEF was designed to evaluate upper extremity functions, especially the smoothness of motions objectively and easily in a short time. It consists of 10 subtests, and 10 grades (1-10 points) of each subtest are established in accordance with the time to complete each subtest. Ten subtests are performed with right and left upper extremities respectively. The sum of 10 subtests is 100 points. During the first session of RFE (RFE Precede: weeks 1 and 2; RFE Follow: weeks 3 and 4), both groups gained statistically significant increases in their score. In contrast, the scores during the CR session significantly increased only in the RFE Follow group. Both groups showed small but significant increases for RFE and CR treatments after 4 weeks. Results in the initial 4 weeks suggest that RFE may accelerate and increase the efficacy of rehabilitation treatment in comparison to CR. The latest publication [22] confirmed clinical efficacy in a randomized controlled trial that reveled significantly large impartments in the RFE group than in the control group in both Action Research Arm Test and Fugl-Meyer Arm scores.

2.2 Neural Control of Movement

Neural control of movement is part of the somatic nervous system, meaning an individual has volitional control of it. When an individual wants to contract a muscle and produce a movement, a signal is generated in the brain and is sent from the brain's motor cortex down the descending corticospinal tract neurons to the motor neuron pool within the spinal chord. Here the neural signal crosses a synapse and excites the alpha motor neuron. The alpha motor neuron relays the signal to the muscle, resulting in a contraction [28]. When a muscle contracts, information about the contraction (eg: muscle length, contraction velocity) is sensed by the muscle spindle and relayed back to the spinal cord via the 1a afferent neuron. Within the spinal chord, the 1a afferent synapses onto and further excites the alpha motor neuron [29]. This monosynaptic reflex is called the short latency reflex, and is often assessed by medical practitioners using the tendon tap test [29]. The 1a afferent neuron also projects onto ascending sensory neurons that relay information about the muscular contraction back to the brain. The ascending sensory neurons excite various interneurons within the brain, some of which form excitatory projections onto the descending neurons [30]. It is, therefore, possible to increase the activity of the descending neurons within the motor cortex by stimulating the 1a afferent neuron in the periphery [30]. A muscle contraction that results from cortical excitation due to peripheral mechanical stimuli (muscle stretch, tendon tap, muscle vibration) that excite the muscle spindle or electrical stimuli that excite the 1-a afferent neuron is termed the long latency reflex. A schematic of the described nerve response to electrical stimulation is shown in Figure 2.4, and a schematic of the described nerve response due to mechanical stimulation is shown in Figure 2.5.

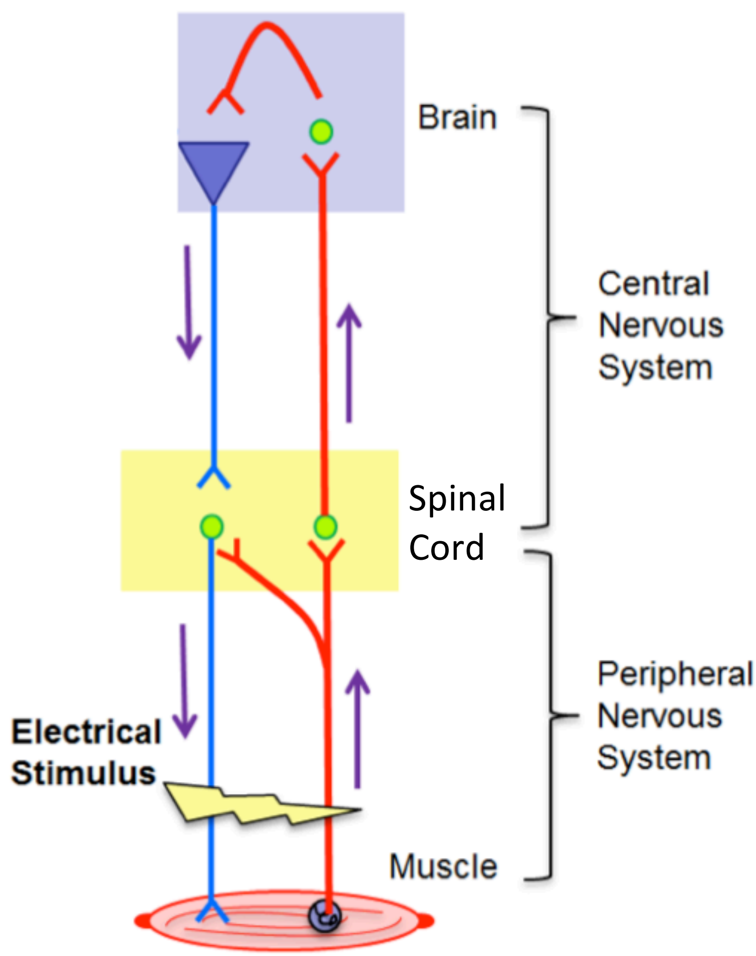


Figure 2.4: Nerve Response Due to Electrical Stimulation

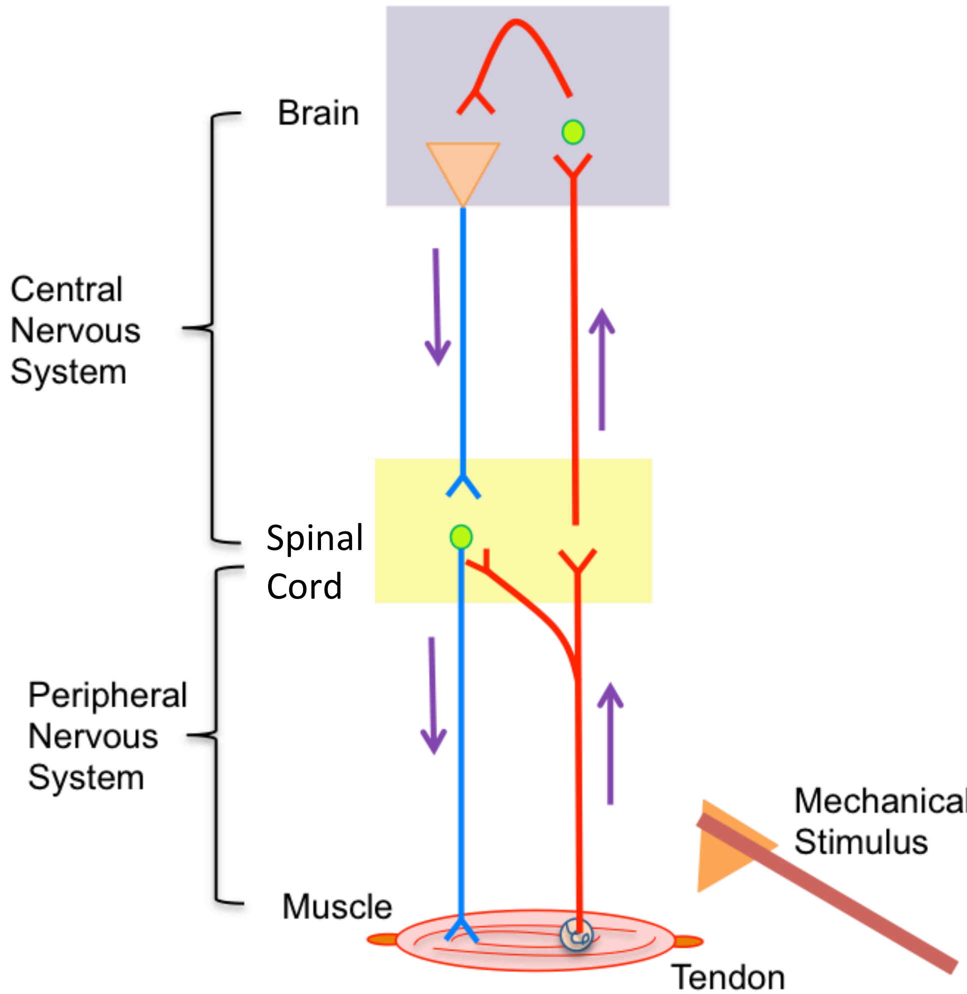


Figure 2.5: Nerve Response Due to Mechanical Stimulation

2.3 Transcranial Magnetic Stimulation

In this study, it is necessary to produce a subthreshold response, originating from the brain, along the flexor carpi radialis muscle. A voluntary subthreshold response refers to when a neural signal, created in the brain, is too weak to contract the muscle or muscles. Since healthy subjects have no interference between their brain and isolated muscle, they are capable of contracting their muscle when asked, this is also known as a voluntary suprathreshold response. However, since stroke subjects have areas of the brain that no longer receive oxygen, they can no longer produce voluntary suprathreshold responses along certain muscles. Instead, stroke subjects produce a weak neural signal, also referred to as a voluntary subthreshold response, which can no longer contract the muscle or muscles. In order to replicate the subthreshold voluntary response (observed in stroke subjects) with healthy subjects, Transcranial Magnetic Stimulation (TMS) will be used (Figure 2.6).

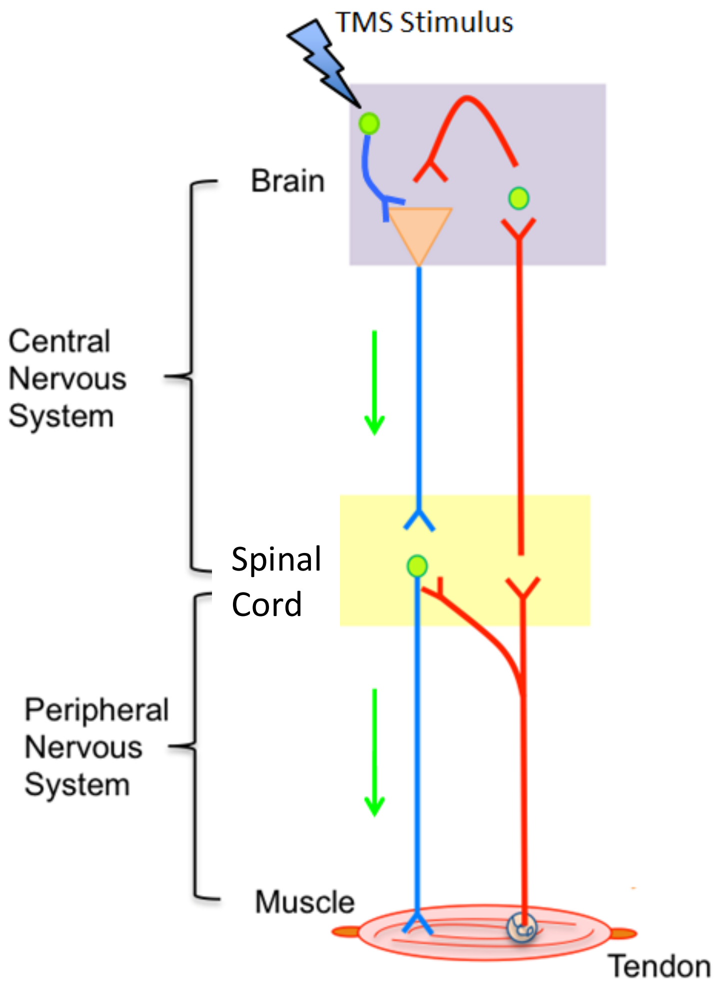


Figure 2.6: Nerve Response Due to Transcranial Magnetic Stimulation

TMS causes a depolarization or hyperpolarization of neurons in the brain. This causes activity in specific or general parts of the brain with little to no discomfort. TMS creates a weak electric current using a quickly changing magnetic field to induce activity in the brain [31]. Altering the strength of the magnetic field can easily change the strength of activity in the brain. Once finding the necessary magnetic field strength to induce a threshold muscle response, the magnetic field can easily be lessened to create a subthreshold response similar to a stroke subject.

TMS will be used in this study to evoke a subthreshold response in healthy subjects. This subthreshold response is similar to a stroke subject's response when asked to try and move a certain isolated muscle or grouping of muscles.

CHAPTER 3

OVERLAP OF TMS & ELECTRICAL STIMULATION

3.1 Study Rationale

The goal of this research is to build a fully automated RFE rehabilitation device. To help understand and characterize the neuromuscular mechanisms associated with this facilitation technique, fMRI images will be collected during the RFE rehabilitation. In order to perform the RFE inside the fMRI, a rehabilitation device that is fMRI-compatible will need to be designed in the future. Before design, however, the neuromuscular mechanism associated with the RFE must be characterized and understood.

Since neural plasticity is heavily dependent on synchronous neuronal depolarization, the timing of the RFE device's mechanical stimulus must be very tightly controlled. The peripheral stimulation (muscle stretch) excites various brain regions, some of which synapse onto and excite the descending neurons in the motor cortex. A map of the brain regions excited by RFE is necessary in order to know which brain regions must remain intact in a patient for the rehabilitation technique to work. An understanding of the temporal dynamics of cortical facilitation with peripheral stimulation will dictate the pacing of the rehabilitation training, itself.

In order for RFE to result in neural plasticity, the patient's intent to contract their muscle must coincide with the afferent stimulation induced depolarization of the descending corticospinal tract neurons that lead to the muscle. A clear understanding of the temporal dynamics of cortical facilitation with afferent stimulation is therefore necessary.

3.2 Experimental Arrangement

The feasibility of cortical facilitation with afferent stimulation and the temporal dynamics of this facilitation were demonstrated in one (N=1) 24 year old, healthy, 5’5”, 115lb female subject with approval of the Institutional Review Board (IRB) committee at Georgia Institute of Technology. Afferent stimulation was delivered to the 1a afferent neuron via transcutaneous electrical stimulation.

The subject lay supine on a bed, with their arms by their sides and the right forearm supinated. Surface bipolar electromyogram (EMG) was measured from the flexor carpi radialis (FCR) muscle of the right hand with two Ag-AgCl electrodes (E224A, IVM, Healdsburg, CA, USA) placed over the FCR muscle belly, spaced 2cm apart. A reference electrode (T716, Bio Protech Inc, Wonju si, Gangwon-do, S. Korea) was placed at the medial epicondyle of the right arm (Figure 3.1). The EMG was differentially preamplified 300 times and bandpass filtered between 15 and 2000Hz (Y03-000, MotionLabs, NY, USA). EMG data was sampled at 5000 Hz with an analog-to-digital converter (Power 1401, Cambridge Electronic Design Ltd, Cambridge, UK) and data acquisition software (Signal 5.0, Cambridge Electronic Design Ltd, Cambridge, UK). A running visual feedback of the raw EMG was provided to the subject to ensure relaxation of the arm muscle.

Transcutaneous bipolar electrical stimulation of the median nerve at the cubital fossa was performed using two spherical stimulating electrodes, separated by 2cm, connected to a constant current stimulator (S88-SIU5-CCU1, Grass, Natus Neurology, Middleton, WI, USA). A 1 ms square wave stimulus was used [32]. The short latency reflex was defined as the peak-to-peak amplitude in the 12 to 30ms window following electrical stimulation. The long latency reflex was defined as the peak-to-peak amplitude in the 45 to 70ms window following electrical stimulation [30, 33].

Figure 3.1: Subject's Arm with EMG and Electric Stimulating Electrodes

Transcranial magnetic stimulation (TMS) of the left primary motor cortex was performed using the Magstim 200 stimulator (Magstim Co, Wales, UK) connected to a figure-of-eight stimulating coil (Magstim second generation double 70 mm remote coil, Magstim Co, Wales, UK), by way of a bistim module (Figure 3.2). The figure-of-eight coil was held tangent to the head with the handle pointing posteriorly at an angle of ~45º to the sagittal plane [34]. The resting motor threshold (RMT) of the FCR was defined as the lowest TMS intensity that produced motor evoked potentials (MEP) greater than 50µV peak-to-peak amplitude in the 12 to 50ms window following TMS, in five out of ten consecutive stimulations [35, 36]. The coil location with the lowest FCR RMT was termed the FCR hotspot and was stored with a TMS navigation system (NDI TMS Manager, Northern Digital Inc., Waterloo, Ontario, Canada) for repeatable placement of the coil.

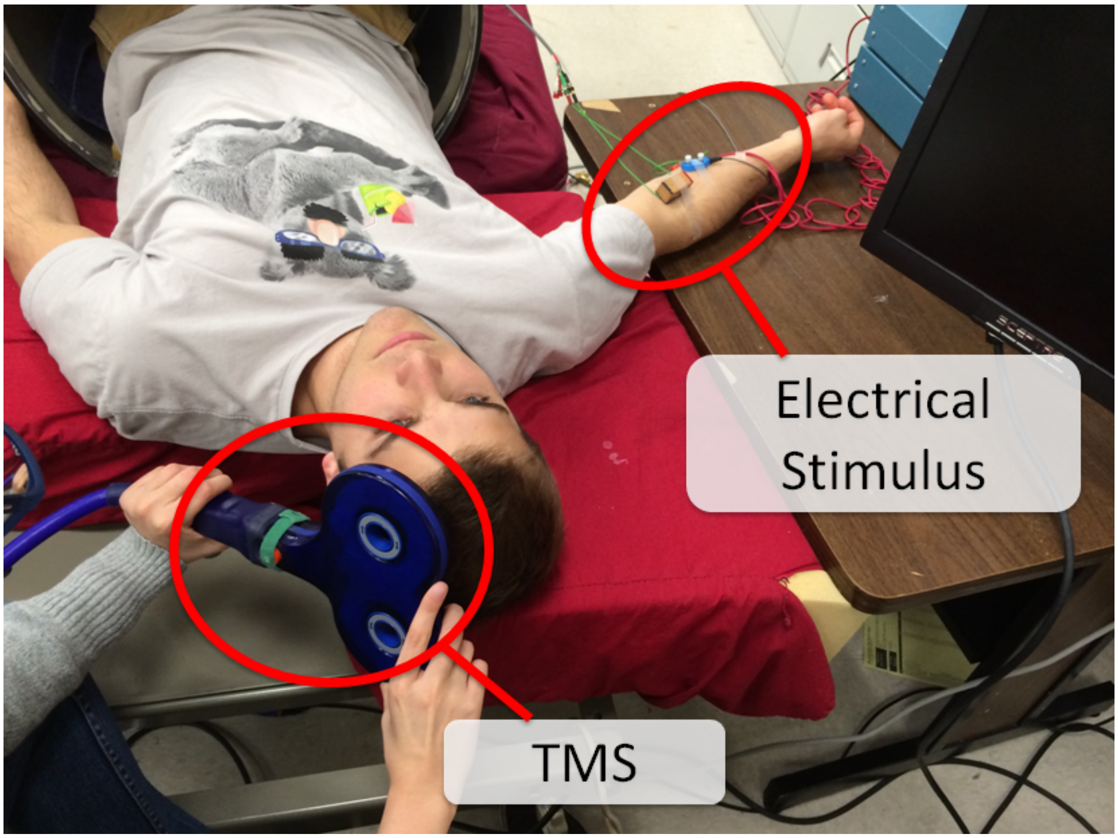


Figure 3.2: Subject with TMS and Electric Stimulating Electrodes

3.3 Procedure

Facilitation of cortical activity with afferent stimulation was investigated by conditioning subthreshold (90% RMT) TMS with electrical stimulation (Figure 3.3). The delays of the short and long latency reflexes were approximated from suprathreshold electrical stimulation as 12 and 45ms, respectively for the individual (Figure 3.4). The delay of the TMS MEP was approximated from suprathreshold TMS as 15ms (Figure 3.4).

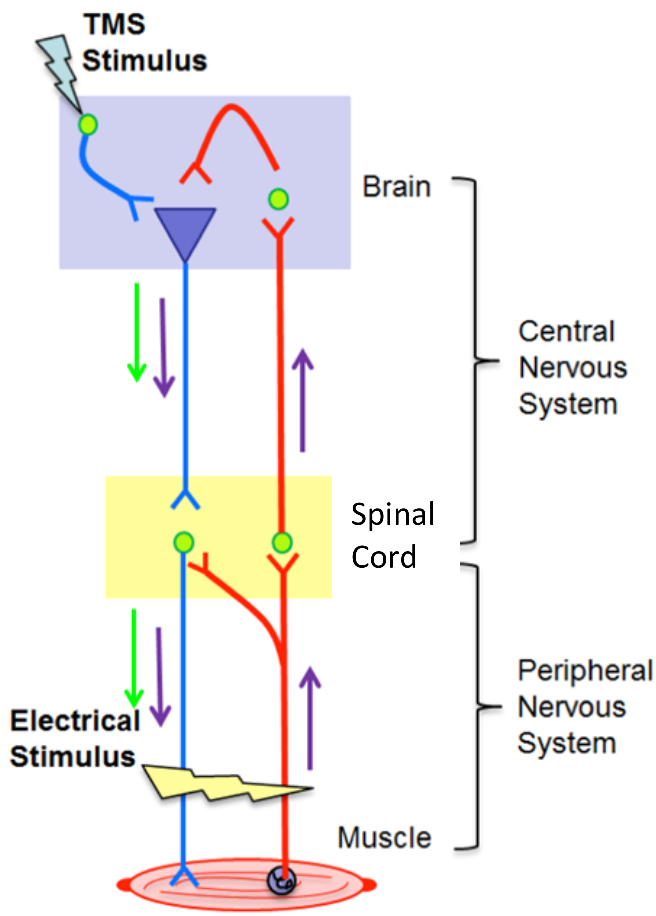


Figure 3.3: Nerve Response Due to Electrical and Transcranial Magnetic Stimulations

In order to overlap the (90% RMT) TMS with the observed 12ms delay short latency response from the suprathreshold electrical stimulation, subthreshold TMS was applied 7, 5, and 3ms before suprathreshold electrical stimulation. Similarly, to overlap the (90% RMT) TMS with the observed 45ms delay long latency response from suprathreshold electrical stimulation, subthreshold TMS was applied 25, 30, 35, and 40ms after the suprathreshold electrical stimulation. Time delays and intervals were selected based on the observed 15ms TMS delay, 12ms short latency delay, and 45ms long latency delay collected during the first part of the study using suprathreshold TMS and suprathreshold electrical stimulation individually. Similar delays and intervals were also used in previous studies [30]. Intensity of electrical stimulation was chosen to elicit a submaximal response on the ascending limb of the stimulus response relationship for the short and long latency reflex.

Twelve responses were collected at each interstimulus interval and for the individual stimulations. The first two responses were discarded as potential startle response. The remaining ten responses were trigger averaged. The peak-to-peak amplitude of the conditioned responses was compared to the sum of the peak-to-peak amplitudes of the individual TMS and electrical stimulations.

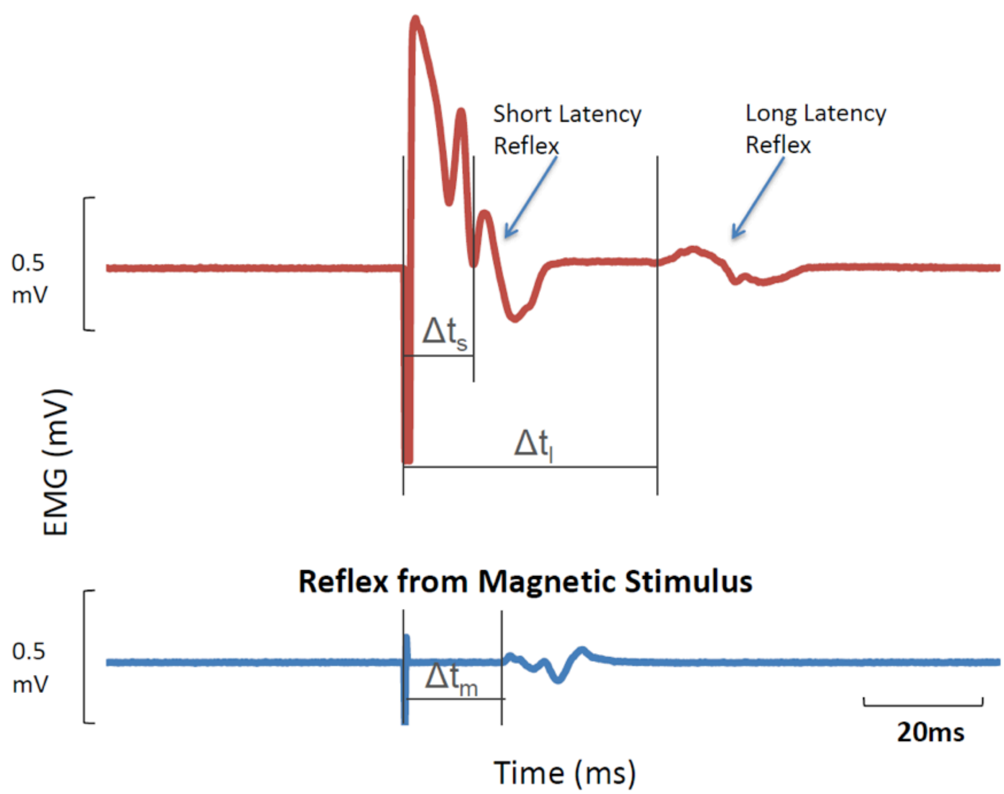


Figure 3.4: Time Delays of Electrical and Magnetic Stimulus

3.4 Results

The peak-to-peak amplitudes of the short and long latency reflexes used for facilitation of the subthreshold TMS were 0.356 and 0.128mV, respectively. The peak-to-peak amplitude of the MEP in response to subthreshold TMS was 0.016mV.

Conditioning the subthreshold TMS with the short latency reflex did not produce any appreciable increase in the overall evoked muscle activity (Figure 3.5). The percent difference of the conditioned response from the sum of the individual short latency reflex and subthreshold TMS was 1.1, -0.1, and -4.7% at the 7, 5, and 3ms interstimulus intervals.

Conditioning the subthreshold TMS with the long latency reflex resulted in a pronounced increase in the overall evoked muscle activity, and this increase was evident across a wide temporal range (Figure 3.6). The conditioned response was 202, 765, 378, and 4.1% greater than the sum of the individual responses at interstimulus intervals of 40, 35, 30, and 25ms, respectively.

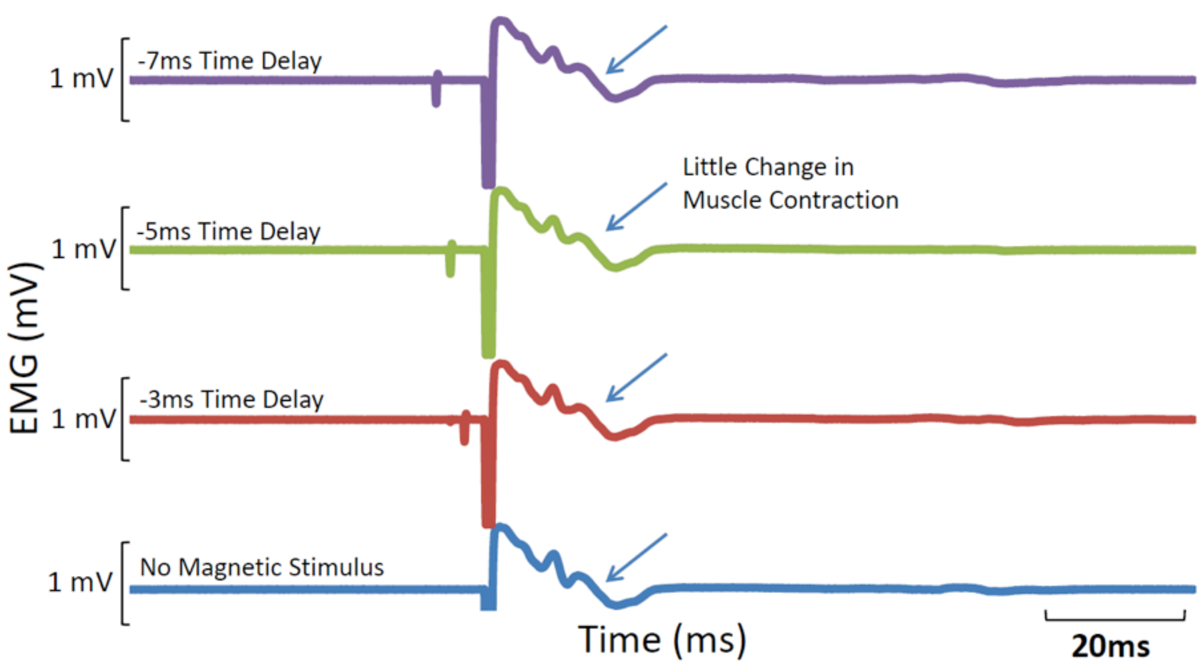


Figure 3.5: Conditioning Subthreshold TMS with Short Latency Reflex

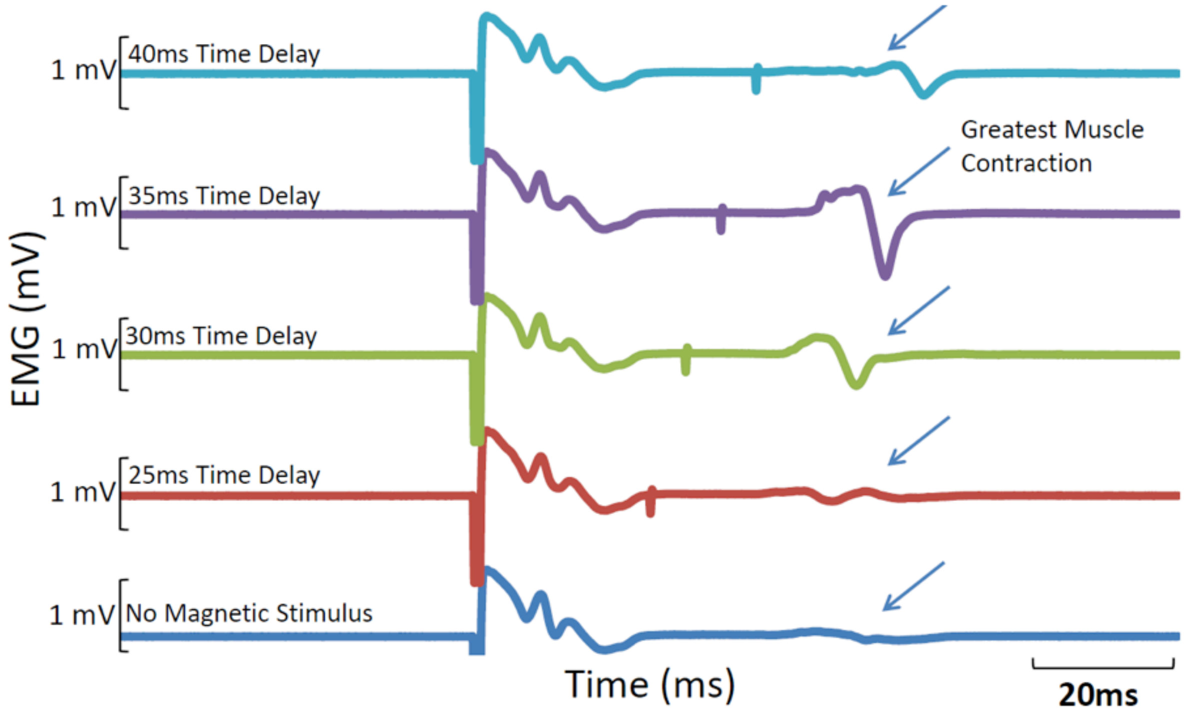


Figure 3.6: Conditioning Subthreshold TMS with Long Latency Reflex

3.5 Discussion

The motor response to subthreshold TMS was substantially facilitated with the long latency reflex, only, and the facilitation was evident across a wide temporal range.

3.5.1 No Facilitation Due to Short Latency Reflex

A subthreshold intensity of TMS was chosen to ensure assessment of cortical (rather than spinal) facilitatory interactions of the afferent stimulation. Subthreshold TMS excites some intracortical interneurons and brings the descending corticospinal tract neuron closer to threshold 7ms after the stimulus, but did not create a significant increase in descending corticospinal tract volleys [37]. The electrical stimulation used in this demonstration study is analogous to the mechanical stretch reflex; it excites the afferent fibers originating from the muscle spindle [29].

While the intestimulus intervals of 3-7 ms were chosen for short-latency reflex based on the literature [30], the actual effective interval may vary depending on subjects. While the current results are in favor of supporting the absence of facilitation for short-latency reflex, the results from one subject do not necessarily exclude the possibility for such facilitation in other subjects and interstimulus intervals. Further studies with additional subjects and intestimulus intervals are warranted to provide more conclusive interpretation on this matter.

3.5.2 Long Latency Reflex Facilitates Subthreshold Cortical Activity

The increase in the motor response due to conditioning of the subthreshold TMS with the long latency reflex is comparable to other studies [30], and suggests an interaction of the two stimulations. By itself, the subthreshold TMS excites some intracortical interneurons and brings the descending corticospinal track neurons closer to threshold, but not enough to cause a descending volley [29]. The long latency reflex has a cortical component; it excites the descending corticospinal tract neurons [30]. When the subthreshold TMS encounters depolarized corticospinal tract neurons it increases the descending neurons' activity and results in a greater motor response.

Subthreshold TMS was substantially facilitated by the long latency reflex across a wide temporal range of 15ms for the individual. This can be due to the temporal dynamics of either the subthreshold TMS or afferent electrical stimulation. The duration of cortical facilitation due to afferent stimulation is clinically relevant, as this determines the temporal range for the RFE therapy technique. The results were demonstrated in only one subject, therefore the 15ms temporal range may be wider or narrower for other subjects depending on their cortical facilitation characteristics.

3.6 Conclusion

The neuromuscular mechanism associated with the repetitive facilitation exercise is most likely the long latency response of a stretch reflex. The long latency reflex resulted in cortical facilitation across a wide temporal range of 15ms in one subject. In order to facilitate the repetitive facilitation exercise using a robotic device, the device must meet a timing precision requirement of at least 15ms.

CHAPTER 4

TIME DELAY VARIANCE OF A PNEUMATIC ACTUATOR

4.1 Study Rationale

An fMRI-compatible RFE rehabilitation device with a pneumatic tendon hammer is proposed to study the neural mechanisms of RFE in an fMRI environment. fMRI-compatible pneumatic actuating rehabilitation devices have already been implemented [37], however no device has been developed to study the temporal dynamics of cortical facilitation with afferent stimulation. The pneumatic actuator tendon hammer will stretch the muscle by hitting its tendon. The temporal dynamics of cortical facilitation due to the tendon hammer tap will be studied with the aid of transcranial magnetic stimulation (TMS) in chapter 7.

A crucial part of the described RFE is the application of an external load onto the tendon of the flexor carpi radialis muscle, which facilitates an afferent stimulation. In the temporal dynamics of cortical facilitation with afferent stimulation experiment, described in chapter 3, it was determined that the timing of the long latency component of the afferent stimulation with the cortical facilitation is a crucial component in manipulating temporal dynamics. Therefore, the actuation system that will be utilized in the rehabilitation device must achieve at least a 15ms level of precision in terms of activation time. Since the rehabilitation device must be fMRI-compatible a pneumatic actuation system has been proposed to facilitate afferent stimulation. However, before developing an fMRI-compatible device the precision of the proposed pneumatic system must be analyzed to ensure the system meets the 15ms timing precision determined in chapter 3.

4.2 Experimental Arrangement

The quality of the pneumatic actuation system was tested by placing a pneumatic cylinder against a fixed wall and measuring the time difference between the input command to the system and the desired force output. An fMRI-incompatible Bimba stainless steel pneumatic actuator with a bore size of 3.175cm and cylinder length of 25.4cm was used during the experiment. Two pressure sensors (SSI Technologies 100PSIA 1/8NPT 4.5V) were located at the front and rear chambers of the pneumatic actuator cylinder. Actuator chambers were pressurized with air provided by a reservoir tank, maintained at 170kPa (24.6psi), and a 4-way spool valve (Festo MPYE-5-1/8-LF-010-B). A load cell (Omega-Dyne LCM703-50 S/N.M150390) was coupled to the end of

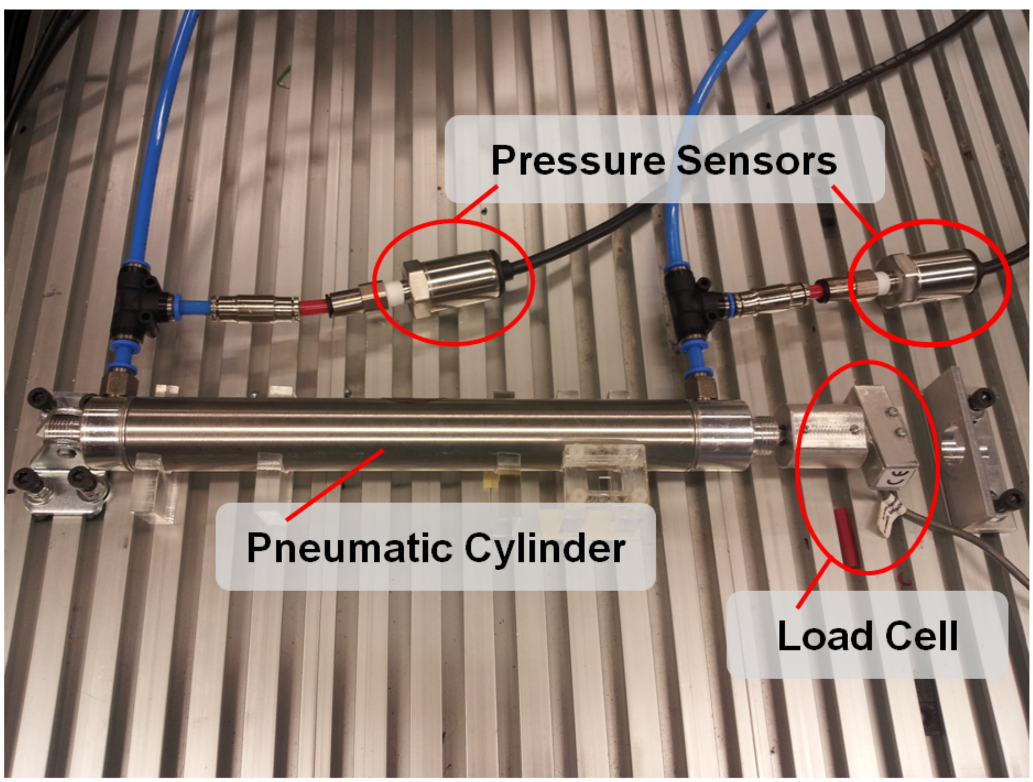


Figure 4.1: Pneumatic Actuator Experimental Setup

the actuator rod to measure the force exerted onto the fixed wall. The outputs from the load cell and pressure sensors were collected by a National Instruments USB-6221 data acquisition device. The actuator cylinder was constrained from movement and the actuator rod was restricted to actuate 2.5cm with the load cell coupled to the end of the rod, as can be seen in Figure 4.1.

4.3 Procedure

During the experiment, on/off signals were sent to the spool valve to induce a push/pull sequence on the actuator rod. These inputs caused the rod to either output an observed 70N force onto the fixed wall or retracted the rod back into the cylinder. Three hose lengths were tested during the experiment: 2, 5 and 7.25m. The range of tested hose lengths were chosen considering the needs of an fMRI-compatible device (5m to 7.25m) and a possible clinically used rehabilitation device (1m to 2m). A total of 50 push/pull cycles were completed in two sets for each hose length. Each cycle lasted a period of 20 seconds: 10 seconds with an input that charges the rear chamber to push the rod toward the wall and 10 seconds with an input to retract the rod back charging the front chamber and discharging the rear. The period of cycles was selected large enough to let the system reach to its steady state before the next input command is given.

4.4 Results

The target force magnitude of 38N was selected because it is the known median peak tap force required to excite normoreflexic, or normal response to tendon tap, individuals [38]. The difference between the time of input command and the instant at which the actuator force achieved the desired output force of 38N was measured for 100 repetitions for each transmission line length configuration. The magnitude of the mean time delay, standard deviation, and total range of the data set for each transmission line is shown in Table 4.1.

Table 4.1: Pneumatic Actuator Time Variance for Varying Transmission Line Lengths

Hose Length (m)	Mean Delay (s)	STD (s)	Range (s)
2	0.206	0.0029	0.016
5	0.275	0.0025	0.013
7.25	0.332	0.0042	0.019

4.5 Discussion

In order for the fMRI-compatible rehabilitation device to facilitate cortical activity with afferent stimulation, the pneumatic actuator must maintain a high level of precision with respect to the timing of the output force. The stainless steel actuator studied achieved a time delay standard deviation of desired force output below 5ms for each transmission line length. The best precision observed was a standard deviation of less than 1% of the average time delay for the 5-meter long transmission line. This result was not expected. The 2-meter transmission line length was expected to have a smaller standard deviation since there is less transmission line friction. One possible explanation in the larger standard deviation with the 2-meter transmission line length would be possible changes in cylinder dynamics. Changing out the line lengths may have caused the cylinder to be altered slightly causing greater stiction in the cylinder.

Not surprisingly, the magnitude of the time delay increased as the transmission line length increased. The measurements observed in the described experiments did not yield conclusive data on the relation between the time delay variance and the line length. The change in hose length should not have affected the magnitude of the mean delay as much as it did. The time delay due to the hose length is equal to the length of the hose divided by the speed of sound [39]. Therefore, the 2, 5, and 7.35m hose lengths should have only affected the mean time delay by 5.8, 14.5, and 21.1ms, respectively. However, the mean time delays between the three different hose lengths ranged from 206ms to 332ms, a 126ms difference between hose lengths. One possible explanation in the large range would be possible varying cylinder dynamics. Varying friction in the cylinder may have caused the large range in mean time delay.

4.6 Conclusion

Across a wide temporal range of 15ms the long latency reflex resulted in cortical facilitation, as determined in chapter 3. In order for the fMRI-compatible rehabilitation device to substantially facilitate the motor cortex, the proposed pneumatic system must achieve a force output with a timing variance less than 15ms.

The time delay standard deviation for each transmission line length was below 5ms. Therefore, the proposed pneumatic actuation system meets the timing precision requirement for the rehabilitation device for each transmission line length 68.2% of the all the trials (hence 1 standard deviation). Although this does not capture all trials, overlapping of the stimuli is still possible 68.2% of all trials. As can be seen in Table 1, the time delay range for each hose length was near 15msec. The time delay range could possibly decrease by further studies with improved actuators with less stiction of the rod and less friction in the cylinder. Developing a pneumatic actuation system with a time delay range less than 15ms will improve temporal synchronization of the afferent stimulation with the patient's intent at the cortical level.

CHAPTER 5

DESIGN OF FMRI-COMPATIBLE HEMIPARESIS REHABILITATION DEVICE

In order for the device to meet the requirements of the study, the device required fMRI-compatibility, an adjustable design so individuals of various statures could utilize the device, and a synchronized time delay between the individual's voluntary neural signal and the long latency component induced by a mechanical stimulus.

In the previous feasibility studies described in chapters 3 and 4, it was concluded that the long latency reflex excited by an electrical stimulus resulted in cortical facilitation across a temporal range of 15ms. It was also concluded that the proposed pneumatic actuation system met the timing precision requirement for the rehabilitation device at varying transmission line lengths. Therefore a pneumatic actuation system may be used in an fMRI-compatible robotic device to facilitate cortical activity.

5.1 fMRI-Compatible Device

Since fMRI images are collected utilizing strong magnetics, the images can easily be distorted by the presence of magnetic materials and electrical currents within the fMRI laboratory. Hence, no sensors or metals could be implemented into the design of the rehabilitation device. The fMRI-compatible requirement therefore restricted the device design so no sensory information could be collected and relayed to control the device.

A schematic of the fMRI setup and the proposed pneumatic system is shown in Figure 5.1. The fMRI to be used for image collection is between 5 to 7 meters apart from the fMRI control room. Between the control room and the fMRI there is a barrier which allows the usage of fMRI-noncompatiable materials to be used in the control room. Thus, the design's air valves and controls will be stored in the control room and the pneumatic transmission lines will relay the on/off mechanical actuation to stimulate a long latency response in the subject.

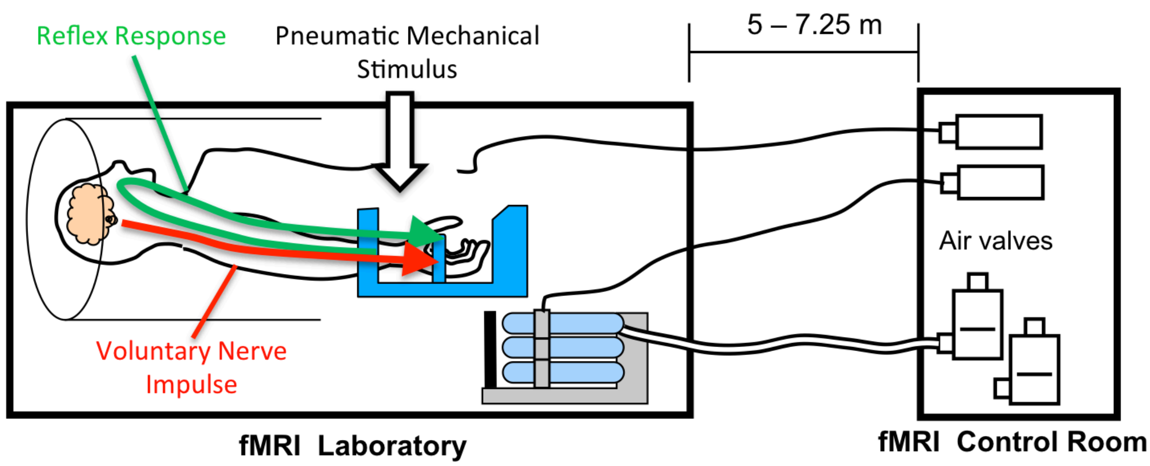


Figure 5.1: fMRI Schematic of Pneumatic Rehabilitation Device

Non-magnetic pneumatic actuators were implemented into the design of the device along with non-magnetic pneumatic fixtures and transmission lines. All materials used in the construction of the device are poly-based.

5.2 Adjustable Design

In order to observe a repeatable long latency response along the flexor carpi radialis, the mechanical stimulus must strike each individual's supine wrist along a narrow area to induce a rapid stretch of the muscle tendon. The location of the tendon varies depending on the physique of the subject; therefore the device required a wide positioning range of the pneumatic actuator to ensure a rapid stretching of the muscle.

The positioning range of the rehabilitation device is shown in Figure 5.2. The arch support of the device allows the angle of the actuator to change in the y-z plane based on the positioning of the individual's hand during facilitation. For varying subject arm lengths, the arch support and armrest were built to translate along the x-direction of the base. Once the angle of the actuator is set, the pneumatic actuator may also translate in height so the medical hammer tip touches the arm of the subject. For fine adjustments, the actuator may also rotate to ensure the actuator is striking the tendon in the correct location. Positioning of the device is set once all clamps on the device are in their locked position.

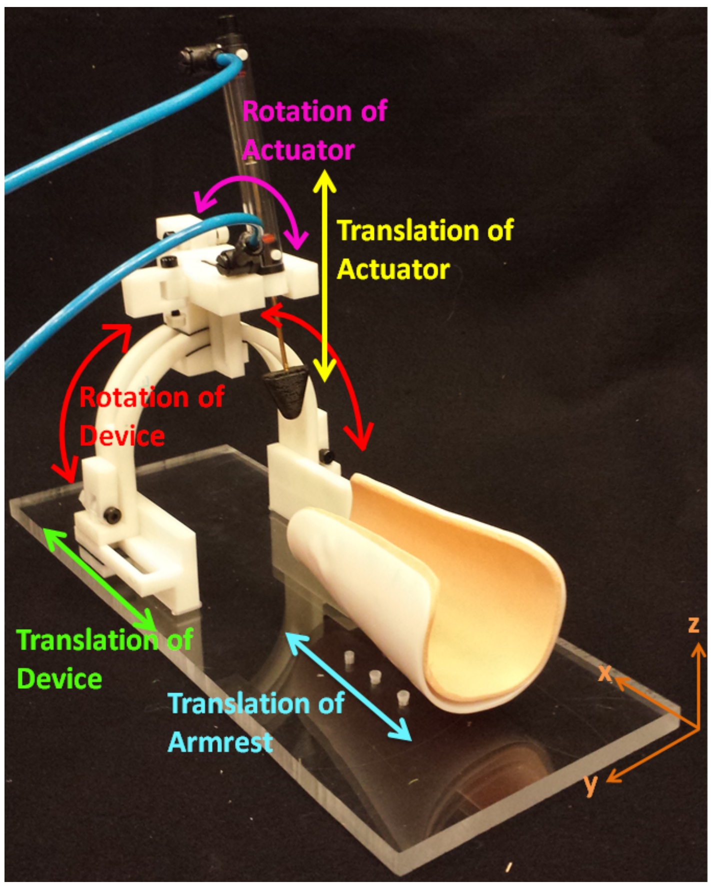


Figure 5.2: Pneumatic Rehabilitation Device Positioning Range

Each individual's response to a mechanical stimulus is also force dependent. The population's reflexive response ranges from hyper-, normo-, and hyporeflexic. The median peak tap force for eliciting a reflexive response is 12.8N, 38.0N, and 85.2N, respectively for hyper-, normo-, and hyporeflexic individuals [38]. Therefore, the rehabilitation device was designed to have the capability to change peak actuation force for each subject.

5.3 Time Controllable Design

The neural pathways of the human body vary between individuals. Major contributing factors include differing conductivity of nerves, varying cross sectional areas of nerves, and changes in lengths of the neural pathways. These variations lead to different observed latencies in the short and long latency responses from the same stimulus [40-42].

Also, the short and long latency responses may vary among trials within an individual. A significant loss in the detectability of the short and long latency responses may occur if the stimulation presentation rate is either set at too high or too low of a frequency [43]. Hence, the rehabilitation device has the capability to change stimulation rate for each individual.

5.4 Evaluation of Device fMRI-Compatibility

In order to confirm the fMRI-compatibility of the rehabilitation device, an imaging test was completed. The device was brought to the fMRI machine (Siemens Trio 3T) at the Center of Advanced Brain Imaging at Georgia Institute of Technology. The affect of the device on image quality was analyzed by comparing fMRI images of a phantom object with and without the device. The device was first placed in the fMRI and images were collected of the phantom object. The rehabilitation device was then removed and fMRI images were again collected of the phantom object. Placement of the rehabilitation device and the image area of interest can be seen in Figure 5.3.

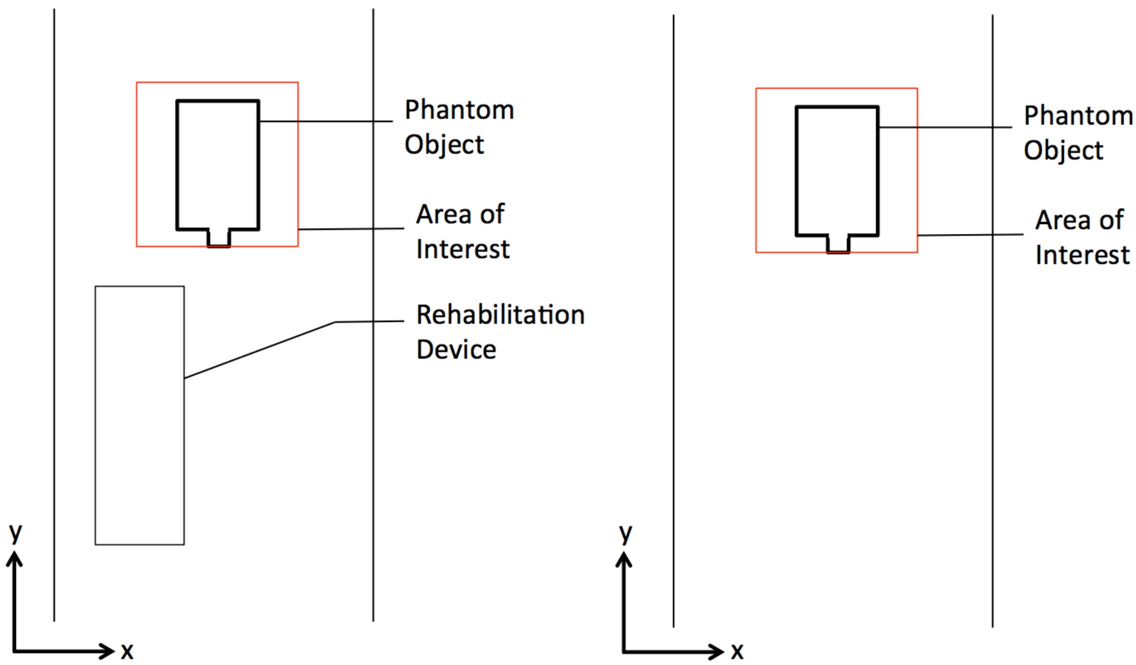
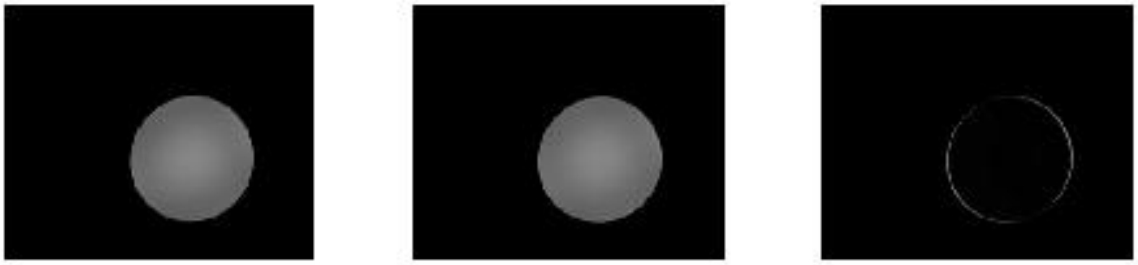


Figure 5.3: Placement of Rehabilitation Device and Phantom Object in fMRI

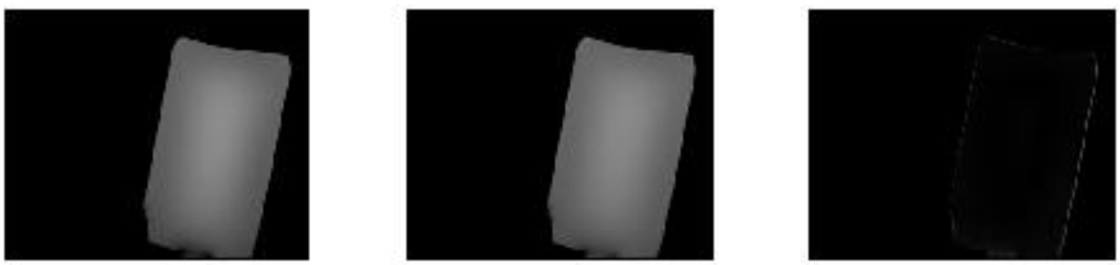
To find image distortion due to the rehabilitation device, the captured fMRI images were analyzed with direct pixel-to-pixel absolute difference analysis according to NEMA (National Electrical Manufacturers Association) requirements. According to NEMA, in order for a device to be considered fMRI-compatible, it must achieve a maximum distortion or absolute difference under 10% [44].

Analysis was completed by comparing the distortion of three coupled images from the x-y, x-z, and y-z planes of the phantom device which can be seen in Figures 5.4, 5.5, and 5.6, respectively. The figures show the original image with the device (a), the original image without the device (b), and the absolute difference between the two images (c).



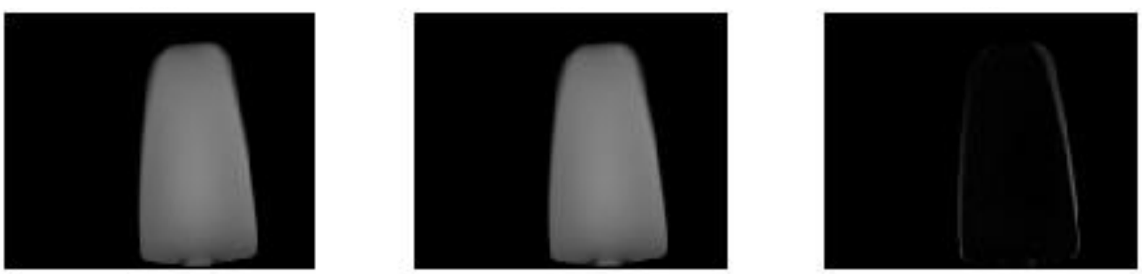
(a) (b) (c)

Figure 5.4: Distortion Analysis of the Phantom Object in the X-Z Plane



(a) (b) (c)

Figure 5.5: Distortion Analysis of the Phantom Object in the X-Y Plane



(a) (b) (c)

Figure 5.6: Distortion Analysis of the Phantom Object in the Y-Z Plane

Based on image (c) obtained for each plane, the percentage difference was calculated to compare the pixel-to-pixel absolute difference between the two original images (a) and (b). The results are shown in Table 5.1.

Table 5.1: Absolute Percentage Difference Due to Distortion

	Compared to (a) [%]	Compared to (b) [%]
X-Z Plane	5.6592	5.6231
X-Y Plane	5.8475	5.8393
Y-Z Plane	4.5003	4.3545

The maximum distortion or absolute difference found for all image comparison was under 6%, therefore meeting the NEMA requirements to be considered fMRI-compatible.

CHAPTER 6

EVALUATION OF DEVICE PERFORMANCE

6.1 Study Rationale

Although the fMRI-compatible robotic device was designed to facilitate a stretch reflex across the flexor carpi radialis muscle, it is unknown whether or not it can facilitate a long latency response from a stretch reflex. Also the time delay between the start of the pneumatic actuation and the resulting response is also unknown.

Since a mechanical stimulus utilizes a slightly longer neural pathway than an electrical stimulus the long latency response should have a longer latency response or may not appear at all due to output force limitations of the pneumatic actuator [41, 42, 45]. Also mechanically evoked potentials have more temporal dispersion than electrically evoked potentials, so the observed contraction across the muscle (or observed EMG signal) will be of lower magnitude or not observed at all [40]. The decreased excitation, in return, increases the difficulty in stimulating a long latency response.

6.2 Experimental Arrangement

The feasibility and control of facilitating a long latency response with a mechanical stimulus applied by the designed pneumatic actuation device was demonstrated in one (N=1) 24 year old, healthy, 5’5”, 115lb female subject (same subject tested in chapter 3) with approval of the Institutional Review Board committee at Georgia Institute of Technology. The subject was seated comfortably in a chair with their right forearm resting supinated on the padded support of the device. The forearm was restricted from movement while the hand and wrist were unrestricted from movement. Surface bipolar electromyogram (EMG) was measured from the flexor carpi radialis (FCR) muscle of the right arm with one pair of disposable surface electrodes placed approximately 2cm apart over the FCR muscle belly (Figure 6.1). EMG was sampled at 1000 Hz and collected using a Quanser Q8 Terminal Board data acquisition device. The EMG signal was measured using a WavePlus wireless EMG system manufactured by Cometa Systems, which includes preamplifiers in the EMG sensors. The measured signal was lowpass filtered at 80Hz. A running visual feedback of the raw EMG was provided to the subject to ensure relaxation of the arm muscle.

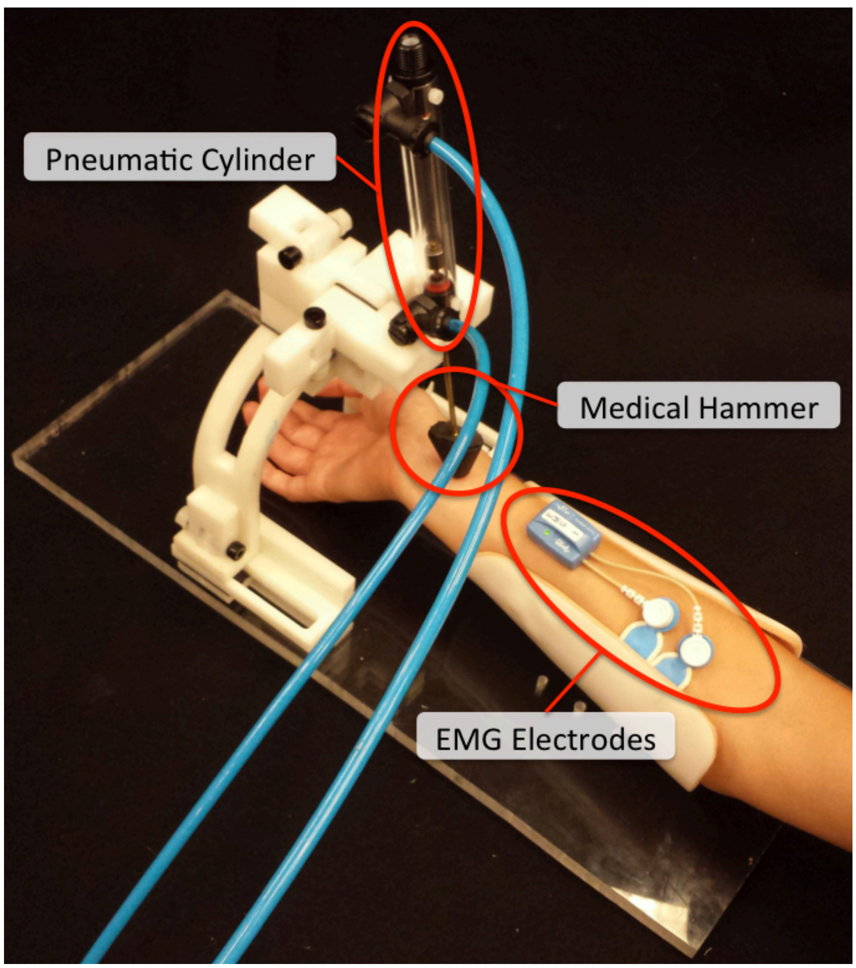


Figure 6.1: Experimental Setup with Pneumatic Actuation Device

High velocity, transcutaneous mechanical stimulation of the FCR tendon approximately 3cm from the wrist was facilitated by the device using a pneumatic actuator with a bore size of 0.93cm and a cylinder length of 7.62cm. A medical reflex hammer stop was placed at the end of the pneumatic actuator (Airpel E9D20U) to help stimulate stretching. A 5s saw-tooth signal was sent to a four-way spool valve (Festo MPYE 5-1) to induce an impulsive push and slow retraction sequence of the actuator rod. A hose length of 7.25m was used during the experiment; chosen considering the fMRI requirements. The output force varied depending on the experiment.

6.3 Mechanical versus Electrical Stimulus Response

6.3.1 Concept

In order to understand the neural mechanism associated with the reorganization of the brain during hemiparesis rehabilitation, it is necessary to overlap a voluntary sub-threshold neural signal with an involuntary long latency reflexive neural signal while an fMRI is collecting brain activity of the individual. The feasibility of overlapping the two signals was demonstrated in [46] using an electrical stimulus to evoke the long latency response. Since an electrical stimulus is fMRI-incompatible, the designed rehabilitation device utilizes a mechanical stimulus to excite an involuntary neural signal. A clear understanding of the differences in mechanical versus electrical long latency responses is therefore necessary to overlap the involuntary neural signal with the voluntary, mechanical stimulated, long latency response in future studies.

6.3.2 Procedure

Facilitation of a long latency response from a mechanical stimulation was investigated. The mechanical stimulus was applied to the subject with a constant reservoir pressure of 416.7kPa (60psi). Tweleve responses were collected. The first two responses were discarded as potential startle responses. The remaining ten responses were trigger averaged. The peak-to-peak amplitude and time delay of the mechanical long latency response was compared to the peak-to-peak amplitude and time delay of the submaximal electrical response reported in chapters 3 and 4. The long latency reflex was defined as the peak-to-peak amplitude in the 45 to 70ms window following mechanical stimulation [30, 33]. To measure the time delay, the start of the stimulus was defined as the time when the observed EMG reached a value greater than 0.05mV.

6.3.3 Results

The mechanically excited stretch reflex achieved a short latency response however a long latency response was not observed. Figure 6.2 compares the mechanically and electrically stimulated responses. Δt_l is defined as the time delay between the start of the observed stimulation and the start of the long latency response due to electrical stimulation, whereas the time delay between the mechanically excited long latency response and the start of the mechanical stimulation could not be measured.

The averaged peak-to-peak amplitude of the mechanically stimulated short latency response was approximately 0.078mV where as the electrically stimulated short latency response was 0.356mV. The mechanically stimulated short latency response was approximately 4.5 times smaller than the submaximal electrically stimulated response.

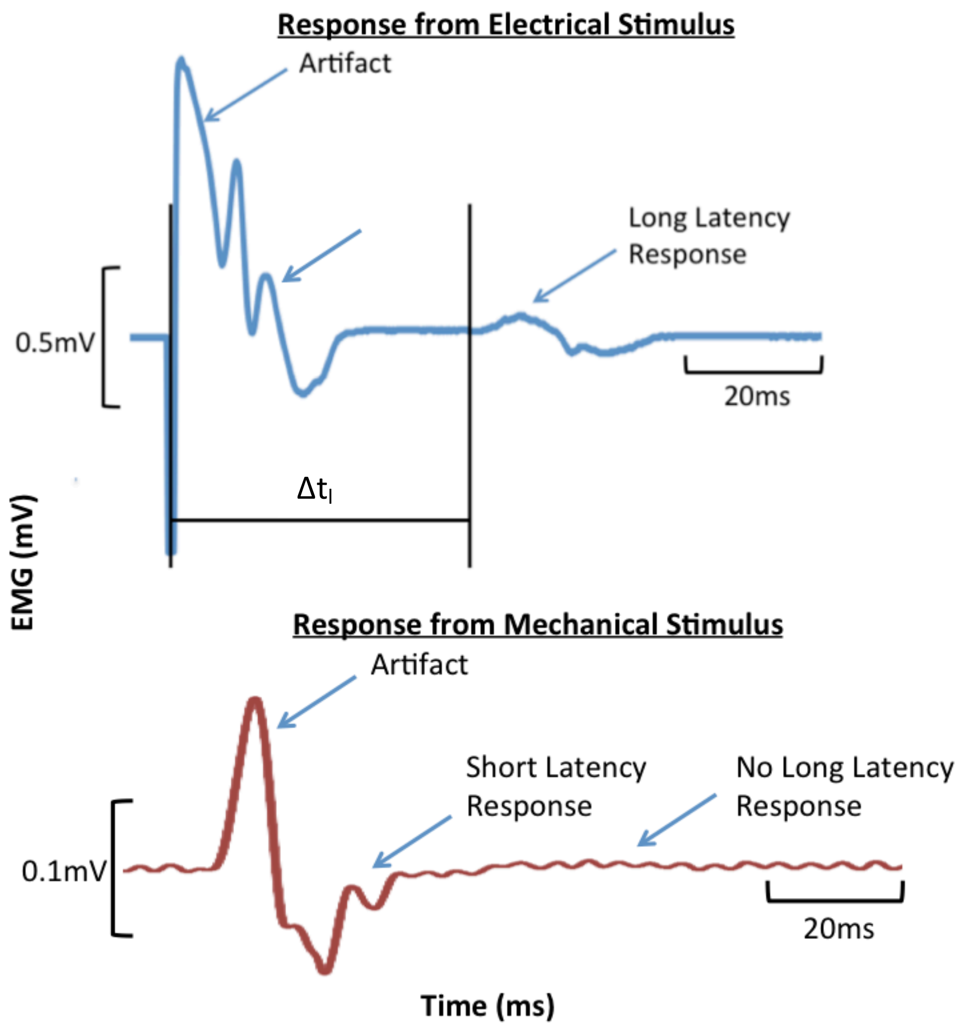


Figure 6.2: Responses from Mechanical and Electrical Stimuli

6.3.4 Discussion

Manipulation of temporal dynamics requires specific timing of the long latency response. In chapter 3, it was determined that manipulation of temporal dynamics is possible with the specific timing of a neural impulse from the motor cortex and the long latency response excited by an electrical stimulus. However, electrical stimulation is not fMRI-compatible therefore a mechanical stimulus was implemented in the device.

As seen from Figure 6.2, the reflexive responses from an electrical and mechanical stimulus are very different. The artifact from the electrical stimulus has an

EMG observed magnitude of 0.96mV. Whereas the artifact from the mechanical stimulus has an EMG observed magnitude of 0.22mV. The averaged peak-to-peak amplitude of the mechanically stimulated short latency response was approximately 0.078mV where as the electrically stimulated short latency response was 0.356mV. These observations may be explained by the fact that the electrical stimulus was applied directly to the median nerve to excite a nerve impulse, where as the mechanical stimulus was applied to the tendon to induce a muscle stretch which then excites a nerve impulse. The electrical nerve impulse is directly stimulating the nerve therefore a greater response was observed.

These differences in peak-to-peak amplitudes of the artifact and short latency response may explain the reason no long latency reflex was observed with mechanical stimulation. The mechanical stimulation may not have been great enough to evoke a suprathreshold long latency response. However, since a short latency response was observed, it is possible that the long latency response exists but is not great enough to be observed. The device may be creating a subthreshold long latency response instead of a suprathreshold long latency response as intended. A subthreshold long latency response may be able to facilitate suprathreshold cortical activity if combined with a subthreshold voluntary response however further studies are necessary.

6.4 Reservoir Tank Pressure and Latency of Response

6.4.1 Concept

In chapter 3, it was determined that the timing of the long latency response with cortical facilitation is a crucial component in manipulating temporal dynamics. Therefore, the pneumatic actuation device must achieve a certain level of timing precision in exciting a response. Considering the wide range of forces needed to elicit a reflexive response out of a majority of the population, the device is capable of changing output force. As the force increases the stretch of the muscle will also increase. This repeated increase in muscle stretch will also affect the reflexive response [43]. In order to control the timing of the long latency response, a clear understanding of the relation between the output force and the start of the response is therefore necessary.

6.4.2 Procedure

The time delay between the input command of the pneumatic actuator and the beginning of the EMG observable response (Δt_o) was investigated (Figure 6.3). The mechanical stimulus was applied to the subject as the reservoir pressure was increased by increments of 68.9kPa(10psi) from 137.9 to 620.5kPa (20 to 90psi). At each reservoir pressure, twelve responses were collected. The first two responses from each pressure were discarded as potential startle responses. The time delay between the time of the input command, or valve opening, and the start of the stimulus was collected from the remaining responses. The magnitude of the mean delay, standard deviation, and range of time delay for each pressure were then compared.

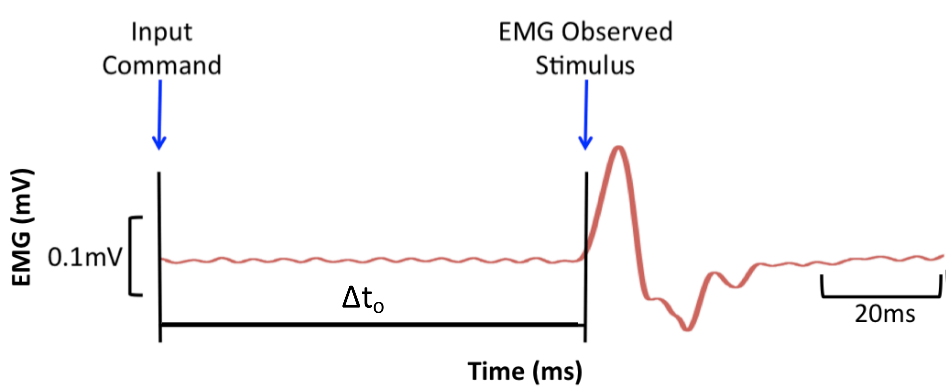


Figure 6.3: Input Command and Stimulus Start Time Delay

6.4.3 Results

The mean delay, standard deviation, and total range for the time delay between the input command and the EMG observable response to the mechanical stimulus is shown in Table 6.1. The start of the stimulus was defined as the time from the input command until the observed EMG reached a value greater than 0.05mV. No response was facilitated at a reservoir pressure of 137.5kPa (20psi) therefore the collected data is not shown.

Table 6.1: Observable Stimulus Time Delay for Varying Reservoir Pressures

Reservoir Pressure (psi)	Mean Delay (s)	STD (s)	Delay Range (s)
30	0.211	0.0120	0.040
40	0.194	0.0119	0.047
50	0.190	0.0101	0.038
60	0.195	0.0092	0.034
70	0.187	0.0094	0.033
80	0.171	0.0063	0.030
90	0.171	0.0066	0.029

6.4.4 Discussion

In order for the pneumatically actuated hemiparesis rehabilitation device to facilitate cortical excitation, the device must control the timing of the involuntary long latency response. According to chapter 3, in order to combine a voluntary nerve impulse sent from the motor cortex with an involuntary nerve reflex, the pneumatic system must achieve a long latency response with an accuracy of 15ms.

The time delay standard deviations for each reservoir pressure were below 12ms. Therefore, the pneumatic actuation system does not meet the timing precision to facilitate cortical excitation at least one standard deviation from the mean delay for each reservoir pressure (hence two-sided standard deviation). However, since mechanically evoked potentials are understood to have more temporal dispersion than electrically evoked potentials [39] and since the timing requirement was a result of an electrical stimulus study, the varying pressures may be able to excite a subthreshold long latency response precise enough to overlap with a cortical excitation.

As can be seen from Table 6.1, as the pressure in the reservoir tank increased the mean delay, standard deviation, and delay range of the EMG observed response from the signal input all decreased. Therefore, at higher reservoir pressures the response is easier to control. The time delay for each reservoir pressure ranged from 29 to 47ms. The time delay range could possibly be decreased by further studies with other pneumatic actuators with less stiction of the rod and less friction in the cylinder.

6.5 Conclusion

The device was unable to evoke a suprathreshold long latency response with the fMRI-compatible pneumatic actuator, however it is hypothesized that the device may be creating a long latency response but is too weak to be observe. Also, at varying pressures the device was unable to achieve the 15ms requirement for cortical facilitation required by electrical stimulation. However since the device is exciting a response using a mechanical stimulus and since mechanically evoked potentials are understood to have more temporal dispersion than electrically evoked potentials [39], the varying pressures may be able to result in a mechanically excited subthreshold long latency response precise enough to overlap with a cortical excitation. In order to evaluate whether or not the device is creating a subthreshold long latency response and in capable of overlapping with a cortical excitation, a TMS study should be conducted with the device.

CHAPTER 7

OVERLAP OF TMS & MECHANICAL STIMULATION FROM DEVICE

7.1 Study Rationale

Although the fMRI-compatible device was able to control the initial stretch response with a fixed signal, it is unknown whether or not the device can create a long latency response from the stretch. In chapter 6, a suprathreshold long latency response was not observed. However, since a short latency response was observed, it is possible that the long latency response exists but is not great enough to be observed. The device may be creating a subthreshold long latency response instead of a suprathreshold long latency response as intended. A subthreshold long latency response may be able to facilitate suprathreshold cortical activity if combined with a subthreshold voluntary response, such as TMS. In order to observe this subthreshold long latency response, a TMS study should be conducted.

In chapter 3, an increase in motor response was observed due to the conditioning of the subthreshold TMS response with the threshold long latency response, and suggested an interaction of the two stimulations. When the subthreshold TMS encounters depolarized corticospinal tract neurons it increases the descending neurons' activity and results in a greater motor response. Though the electrically excited long latency response was at threshold, similar techniques may be applied to assess whether or not the mechanical device is capable of creating a long latency response.

7.2 Experimental Arrangement

The feasibility of cortical facilitation with afferent stimulation from the mechanical device and the temporal dynamics of this facilitation were demonstrated in three (N=3) healthy, right-handed, male subjects with approval of the IRB committee at Georgia Institute of Technology. Ages ranged from 28 to 19 years of age with a mean age of 22.6.

The subjects laid supine on a bed, with their arms by their sides and the right forearm supinated on the padded support of the device. The forearm was restricted from movement while the hand and wrist were unrestricted from movement. Surface bipolar electromyogram (EMG) was measured from the flexor carpi radialis (FCR) muscle of the right hand with two Ag-AgCl electrodes (E224A, IVM, Healdsburg, CA, USA) placed over the FCR muscle belly, spaced 2cm apart. A reference electrode (T716, Bio Protech Inc, Wonju si, Gangwon-do, S. Korea) was placed at the medial epicondyle of the right arm (Figure 7.1). The EMG was differentially preamplified 300 times and bandpass filtered between 15 and 2000Hz (Y03-000, MotionLabs, NY, USA). EMG data was sampled at 5000 Hz with an analog-to-digital converter (Power 1401, Cambridge Electronic Design Ltd, Cambridge, UK) and data acquisition software (Signal 5.0, Cambridge Electronic Design Ltd, Cambridge, UK). A running visual feedback of the raw EMG was provided to the subject to ensure relaxation of the arm muscle.

High velocity, transcutaneous mechanical stimulation of the flexor carpi radialis tendon, approximately 3cm from the wrist, was facilitated by the device using a pneumatic actuator with a bore size of 0.93cm and a cylinder length of 7.62cm. A medical reflex hammer stop was placed at the end of the pneumatic actuator (Airpel

E9D20U) to help stimulate stretching. A 5s saw-tooth signal was sent to a four-way spool valve (Festo MPYE 5-1) to induce an impulsive push and slow retraction sequence of the actuator rod. A hose length of 7.25m was used during the experiment; chosen considering the fMRI requirements. The mechanical stimulus was applied to the subject with a constant reservoir pressure of 413.7kPa (60psi). The short latency reflex was defined as the peak-to-peak amplitude in the 12 to 30ms window following mechanical stimulation. The long latency reflex was defined as the peak-to-peak amplitude in the 45 to 70ms window following mechanical stimulation [30, 33].

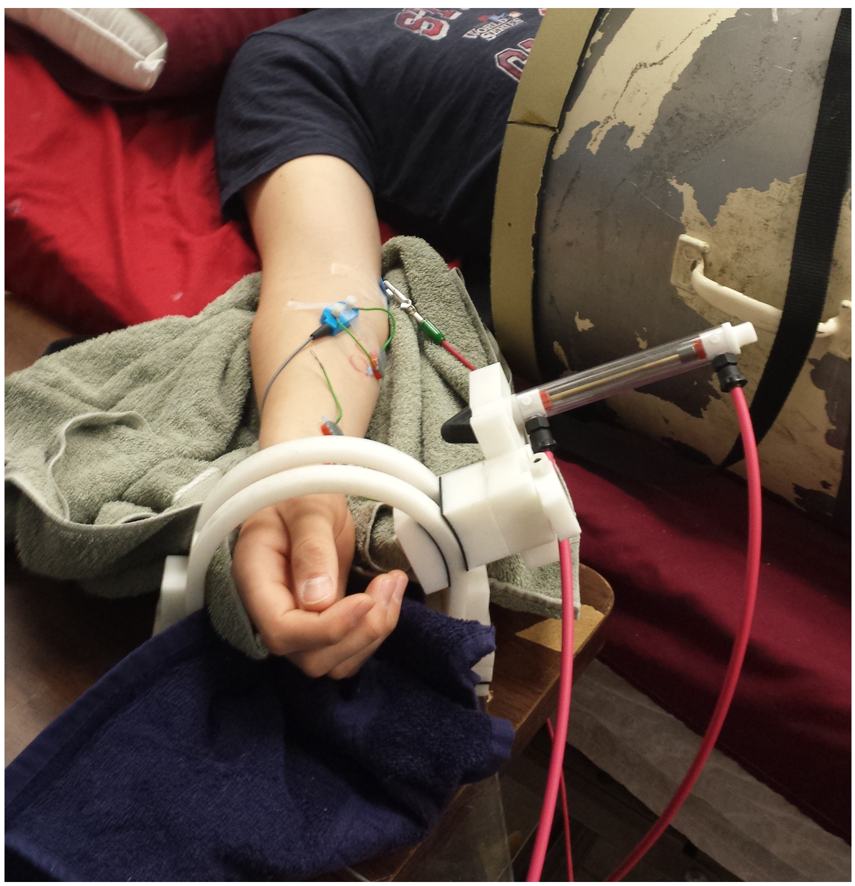


Figure 7.1: Experimental Setup with Mechanical Stimulus Device and EMG Electrodes

Transcranial magnetic stimulation (TMS) of the left primary motor cortex was performed using the Magstim 200 stimulator (Magstim Co, Wales, UK) connected to a figure-of-eight stimulating coil (Magstim second generation double 70 mm remote coil, Magstim Co, Wales, UK), by way of a bistim module. The figure-of-eight coil was held tangent to the head with the handle pointing posteriorly at an angle of ~45º to the sagittal plane [34], as can be seen in Figure 7.2. The resting motor threshold (RMT) of the FCR was defined as the lowest TMS intensity that produced motor evoked potentials (MEP) greater than 50µV peak-to-peak amplitude in the 12 to 50ms window following TMS, in five out of ten consecutive stimulations [35, 36]. The coil location with the lowest FCR RMT was termed the FCR hotspot and was stored with a TMS navigation system (NDI TMS Manager, Northern Digital Inc., Waterloo, Ontario, Canada) for repeatable placement of the coil. Subthreshold TMS was defined at 90% of the resting motor threshold (RMT). An RMT (threshold) response and 90% RMT response for one subject can be seen in Figure 7.3.

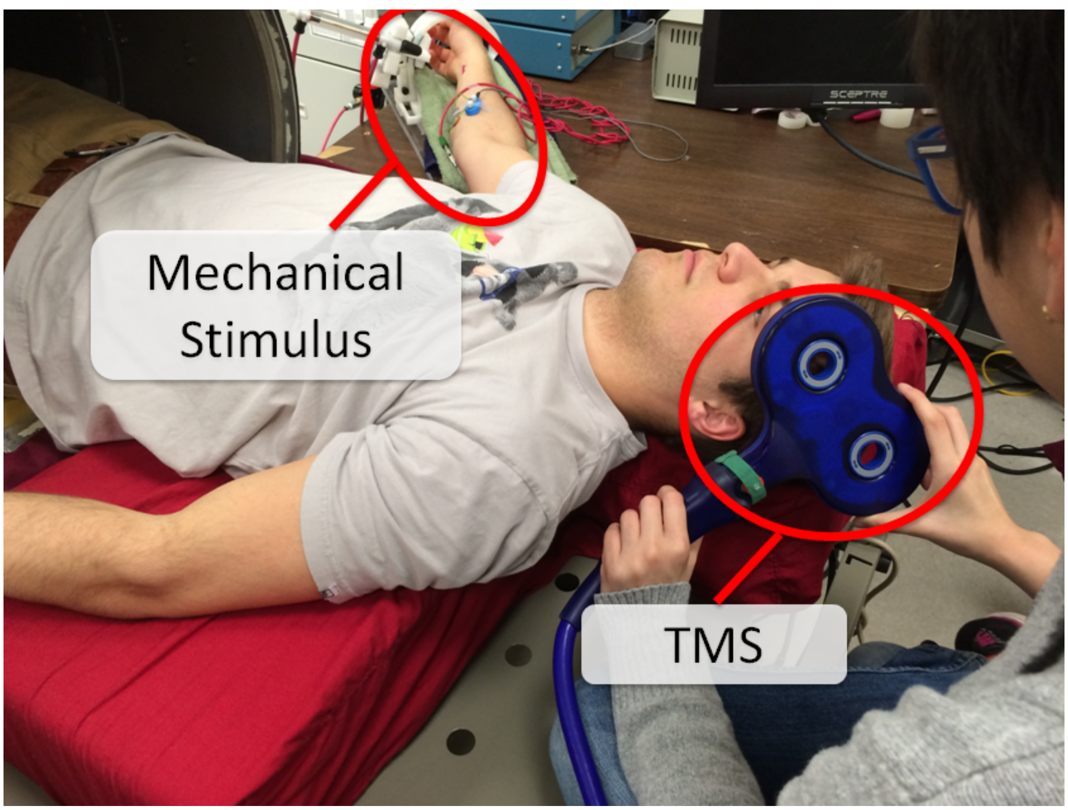


Figure 7.2: Subject with TMS and Mechanical Stimulus Device

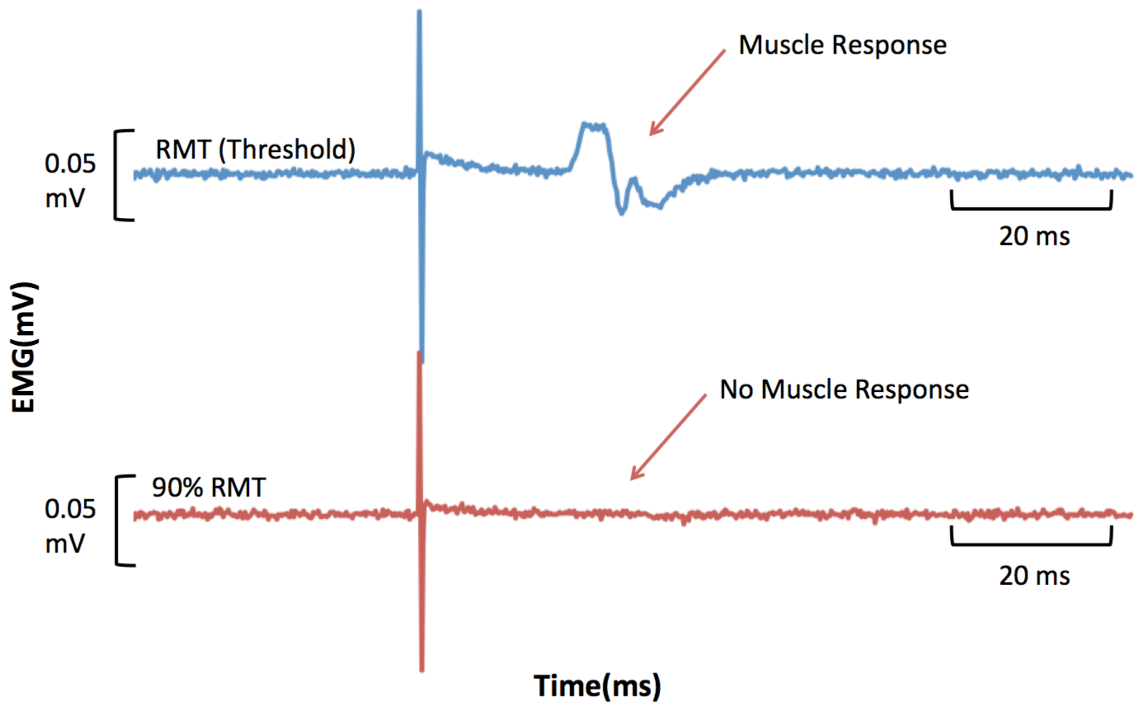


Figure 7.3: Threshold and 90% RMT TMS Responses

7.3 Procedure

Facilitation of subthreshold long latency response with afferent mechanical stimulation was investigated by conditioning subthreshold (90% RMT) TMS with mechanical stimulation (Figure 7.4). The individual mechanical and (90% RMT) TMS stimulus responses for one subject can be seen in Figure 7.5.

Subthreshold TMS stimulation was applied in 5ms intervals between 155ms and 215ms after the start signal of the mechanical stimulus. Figure 7.6 shows one interval EMG muscle response and the described time delay (Δt_d) between the mechanical input command and the TMS artifact (or start of magnetic stimulus). Pressure of the mechanical stimulation was set at 413.7kPa (60psi).

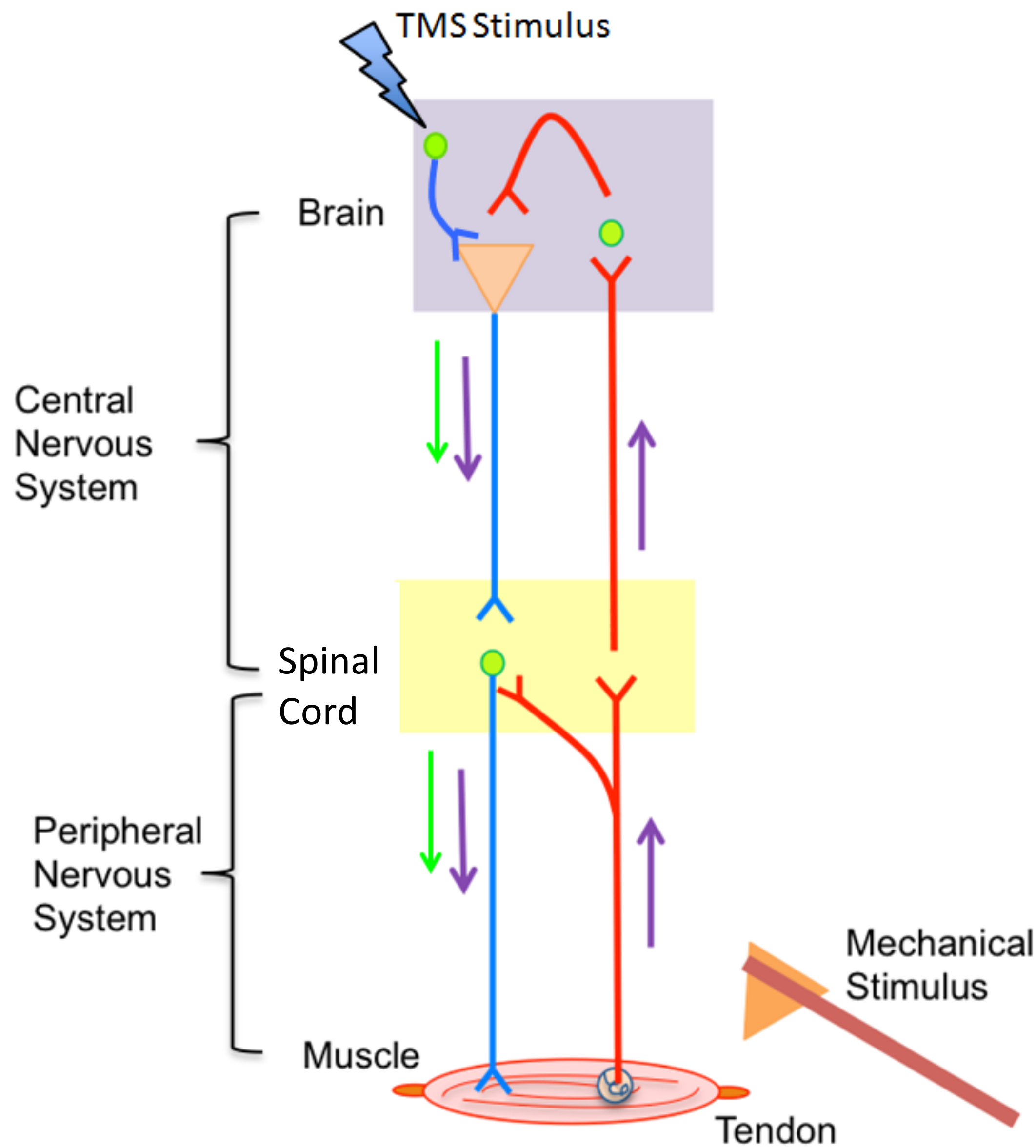


Figure 7.4: Nerve Response to Mechanical and TMS Stimuli

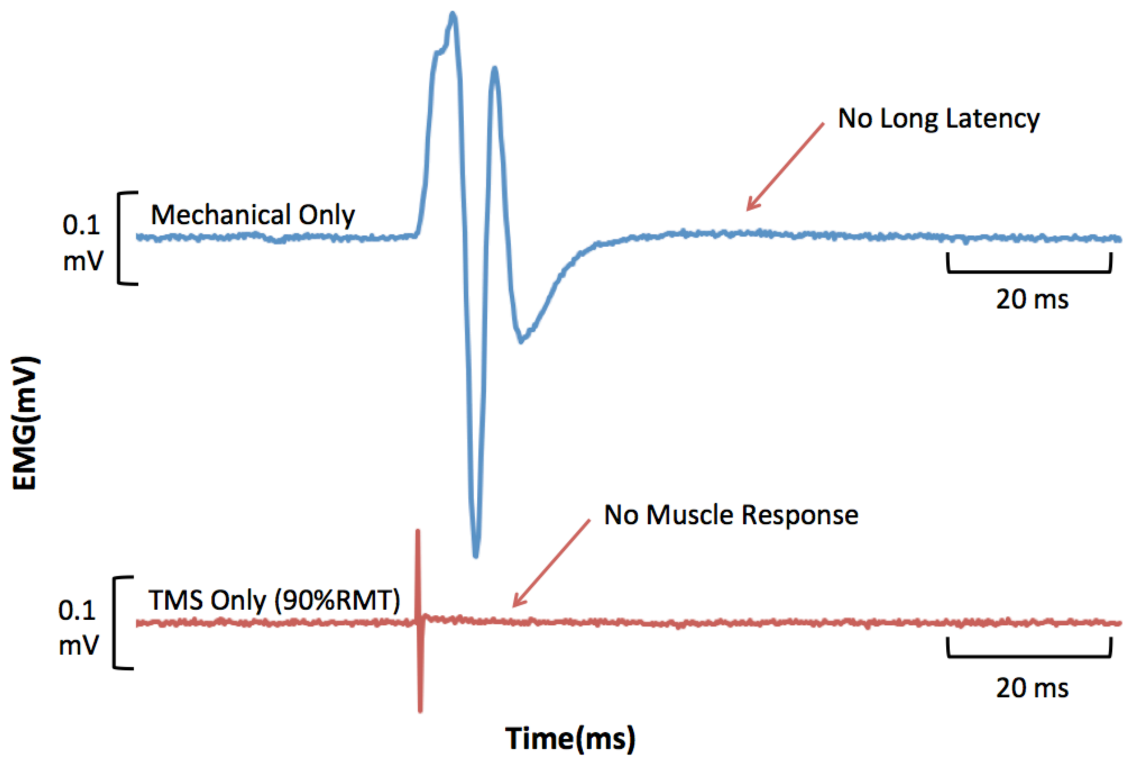


Figure 7.5: Mechanical Stimulus Only and TMS Only at 90% RMT

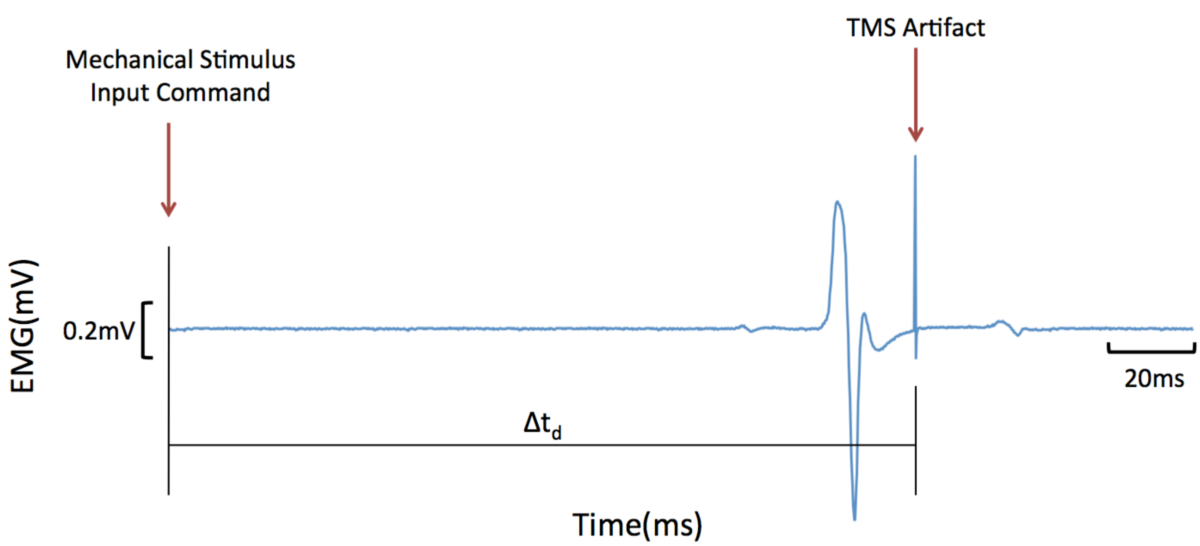


Figure 7.6: Mechanical Stimulus Input Command and TMS Artifact Time Delay

Twelve responses were collected at each interstimulus interval, subthreshold (90% RMT) TMS, and mechanical only stimulation. A ten-second rest followed each response and a two-minute rest followed each trial. The first two responses were discarded as potential startle responses. The remaining ten responses were trigger averaged, using the artifact of the TMS stimulus as the trigger. The peak-to-peak amplitude of the conditioned long latency response, defined as the peak-to-peak amplitude in the 45 to 70ms window following mechanical stimulation [30, 33], was then measured for each interstimulus.

7.4 Results

Conditioning the subthreshold TMS with the mechanical stimulus resulted in a pronounced increase in the overall evoked muscle activity following the mechanical stimulation, and this increase was evident across a wide temporal range for each subject.

Figures 7.7, 7.8 and 7.9 are the trigger averaged results for subjects 001, 002, and 003, respectively. An increase in overall evoked muscle activity can be observed at varying time windows for each subject. The increase in overall evoked muscle activity was evident across a 60 or 40ms time window depending on the subject (Table 7.1). The greatest peak-to-peak amplitude for the conditioned responses for subjects 001, 002, and 003 were 0.186, 0.0326, and 0.0498mV (Table 7.1 and Figure 7.10), respectively. The peak-to-peak amplitude at each interstimulus for each subject can be observed in Figure 7.10. The greatest peak-to-peak amplitudes for subjects 001, 002, and 003 occurred at time delay interstimuli of 175, 190, and 175ms, respectively (Figure 7.10).

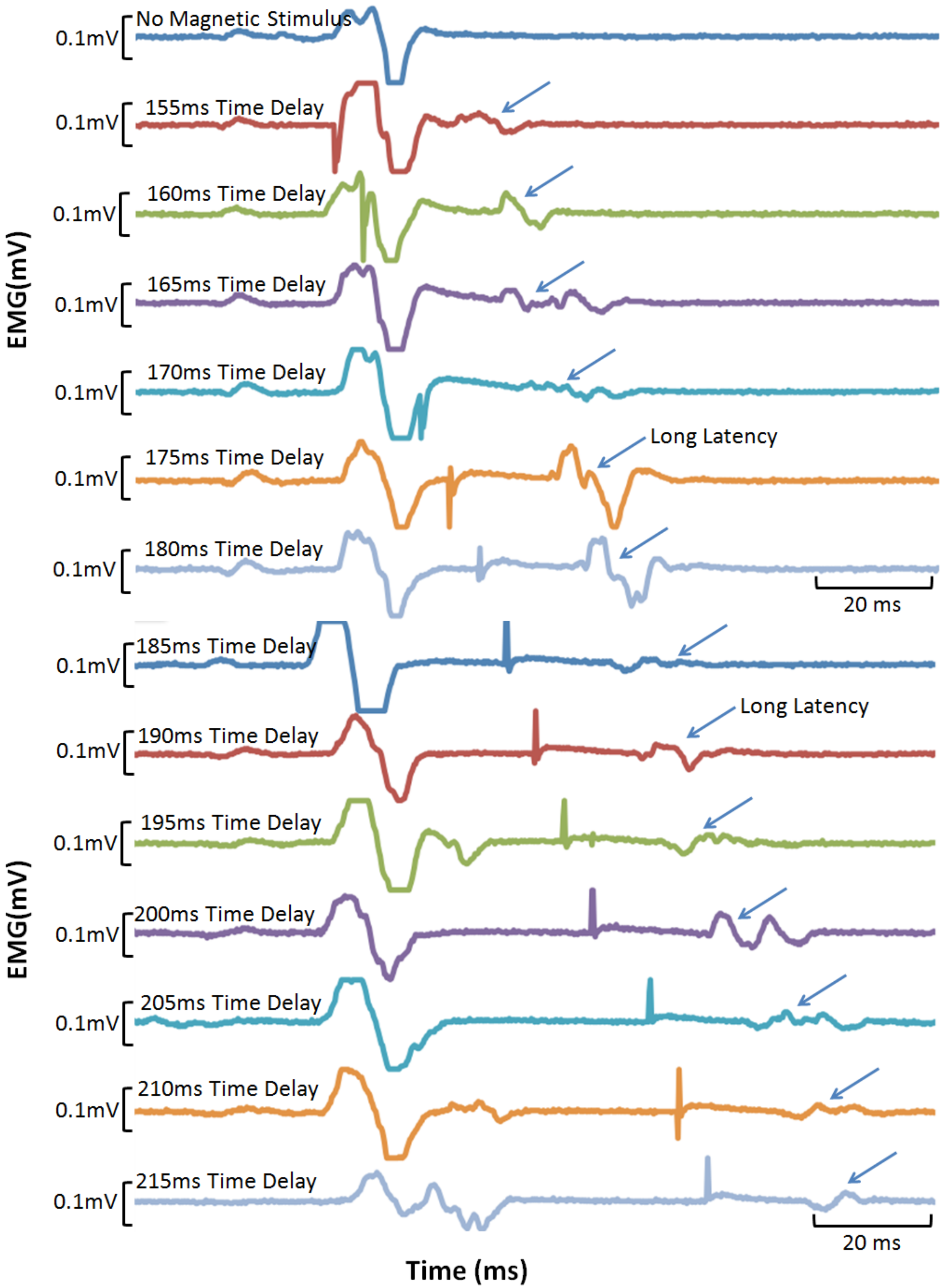


Figure 7.7: Conditioned Muscle Response for Subject 001
(Only displaying 0.2mV of data for each interstimulus to show long latency overlap)

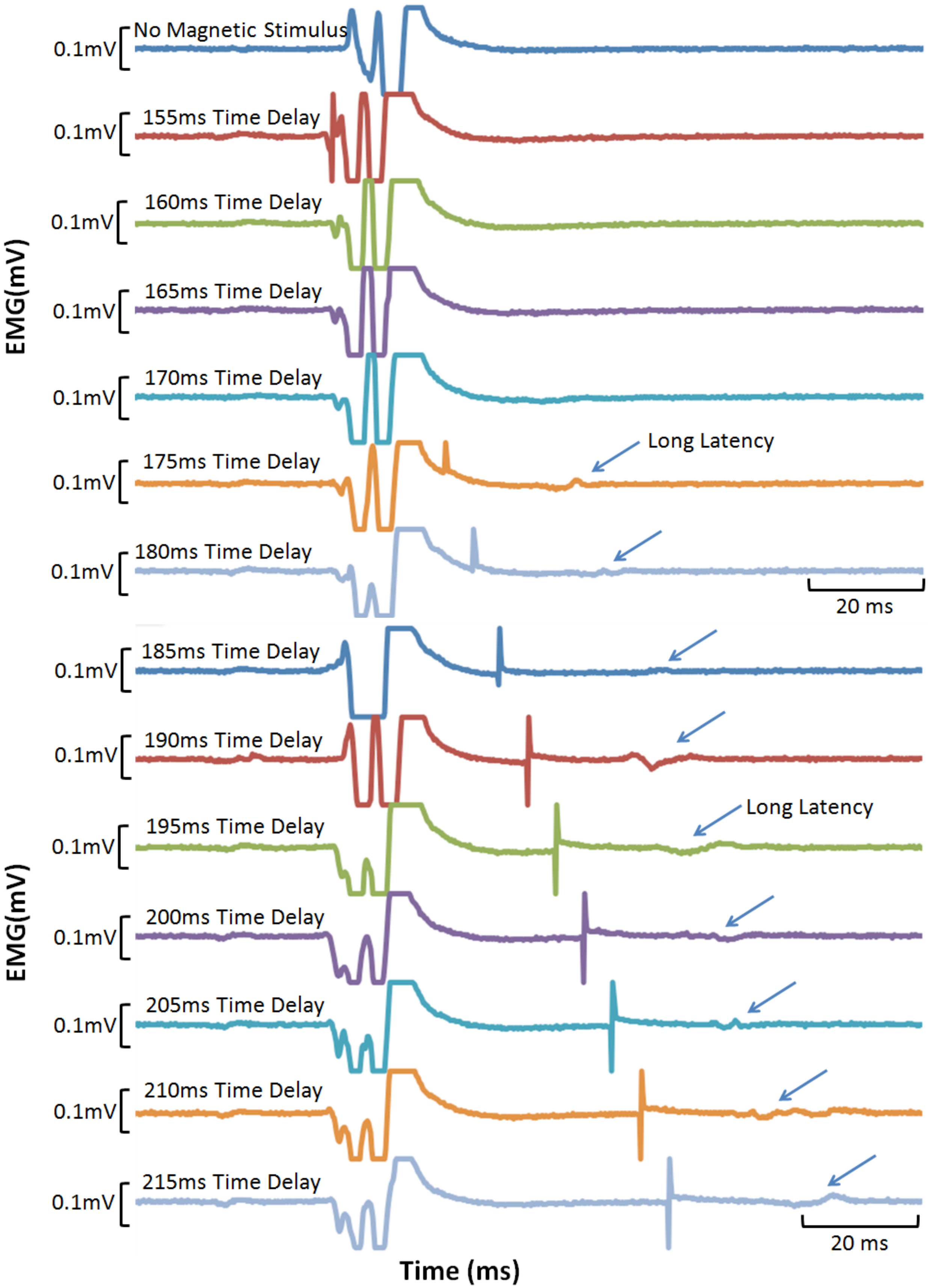


Figure 7.8: Conditioned Muscle Response for Subject 002
(Only displaying 0.2mV of data for each interstimulus to show long latency overlap)

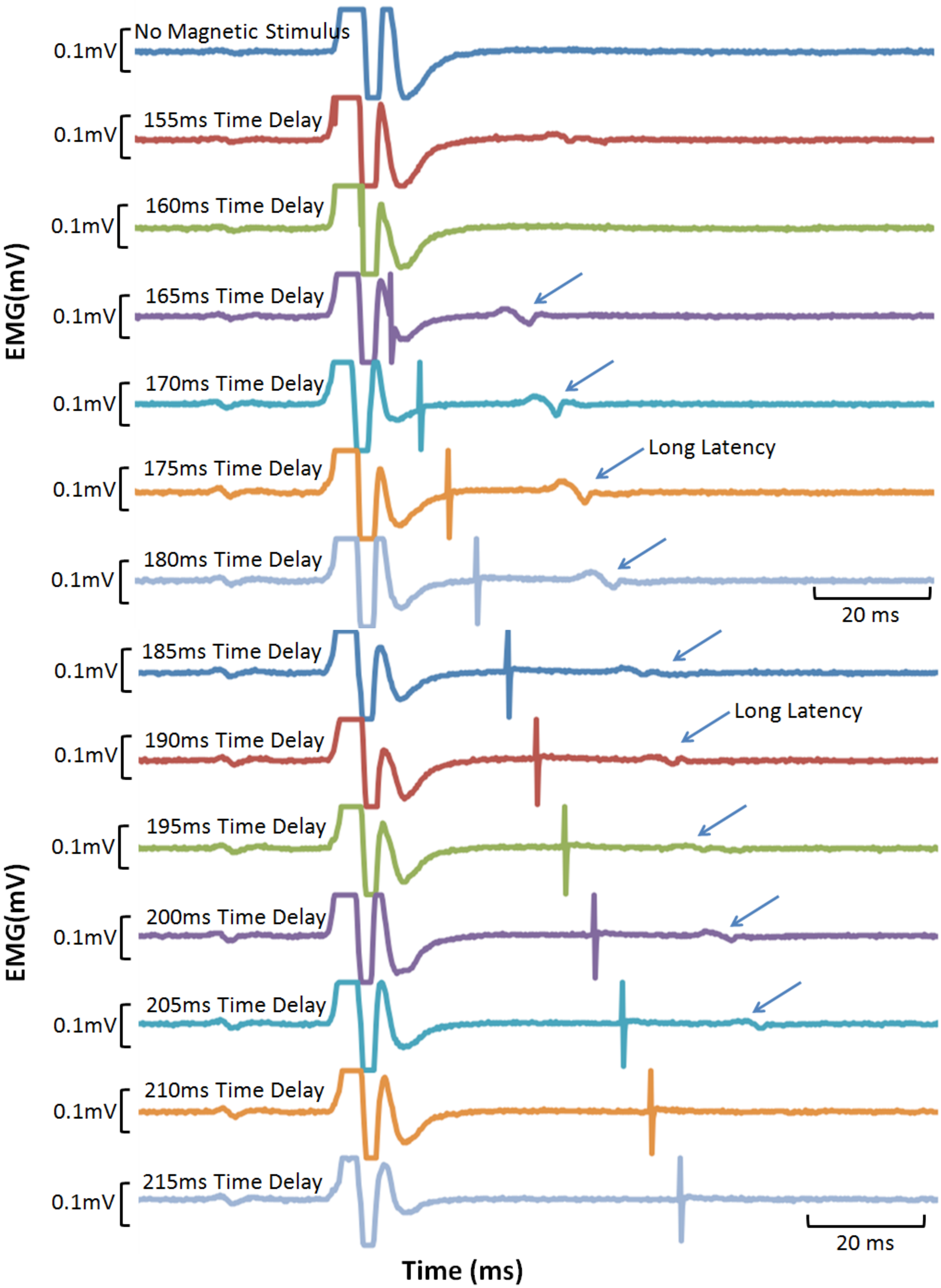


Figure 7.9: Conditioned Muscle Response for Subject 003
(Only displaying 0.2mV of data for each interstimulus to show long latency overlap)

Table 7.1: Time Window of Muscle Response and Maximum
Peak-to-Peak Amplitude of Muscle Response for Each Subject

Subject	Time Window of Muscle Response Increase (ms)	Start of Time Window (ms)	End of Time Window (ms)	Max Peak-to-Peak Amplitude (mV)	Delay Time (ms) of Max Peak-to-Peak
001	60	155	215	0.186	175
002	40	175	215	0.0326	190
003	40	165	205	0.0498	175

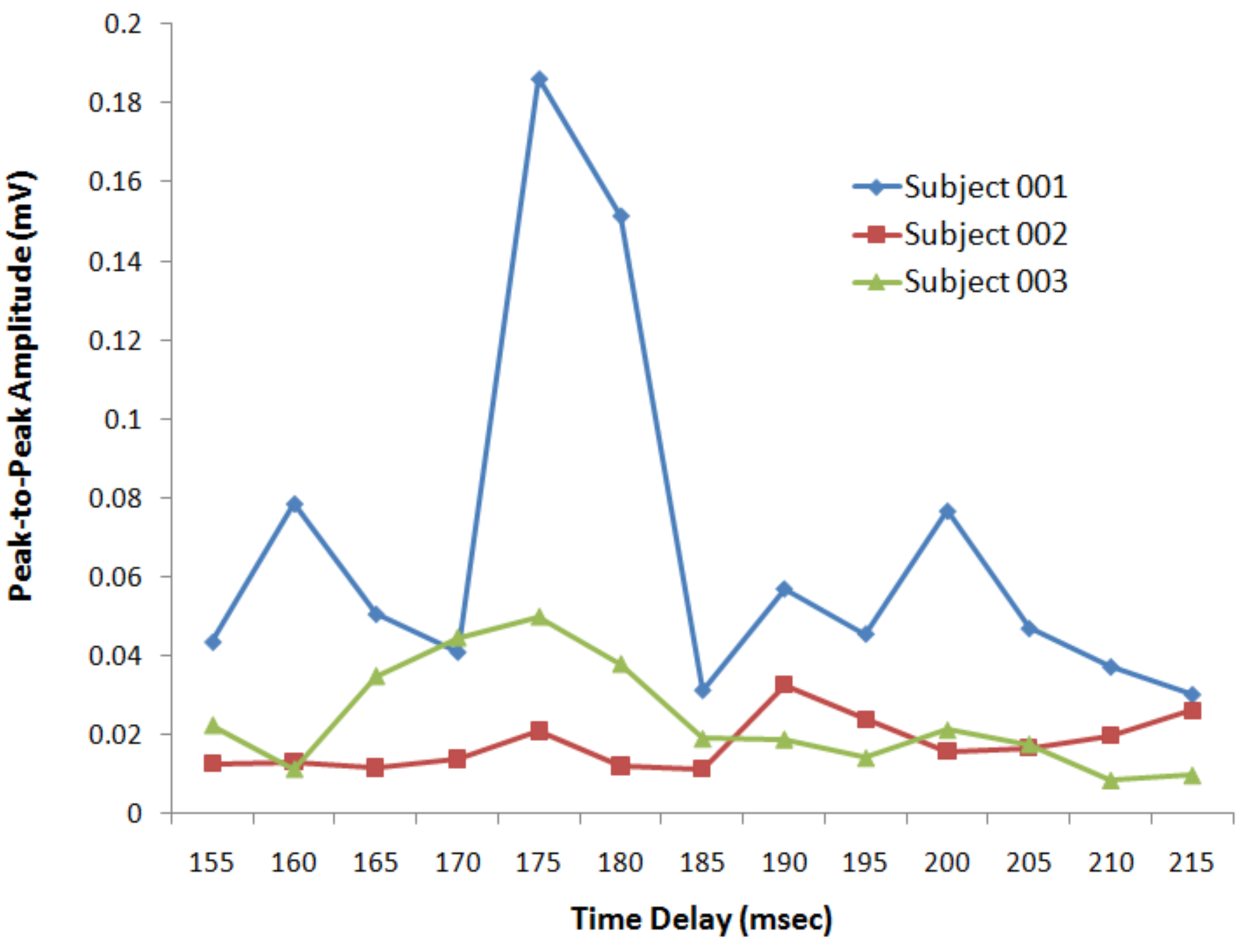


Figure 7.10: Subjects' Peak-to-Peak Amplitude of Muscle Response at Each Interstimulus

7.5 Discussion

The muscle response following mechanical stimulation was significantly increased across a wide temporal range for each subject and suggests that the mechanical stimulus is creating a subthreshold long latency response. The increase in motor response due to the conditioning of the subthreshold TMS with the mechanical stimulus suggests an interaction of the two stimulations specifically in the long latency response time window of 45 to 70ms following the stimulus as suggested in [30] and [33]. By themselves, the subthreshold TMS and mechanical stimulus excite only some intracortical interneurons and brings the descending corticospinal track neurons closer to threshold, but not enough to cause descending volley [29]. However, when the subthreshold TMS encounters depolarized corticospinal tract neurons from the mechanical stimulus long latency response. It increases the descending neurons' activity and results in a greater motor response at the muscle. Therefore, the results suggest that the mechanical stimulus is capable of creating a long latency reflex, however the reflex is not great enough to cause descending volley or subthreshold.

The peak-to-peak amplitude of the conditioned muscle response for each subject was significantly increased when compared to the muscle response to the mechanical stimulation without the subthreshold TMS stimulation. The maximum peak-to-peak amplitudes ranged from 0.186 to 0.0326mV depending on the subject. This wide range in maximum peak-to-peak amplitudes was probably caused by the variability of an individual's response to a stretch. The population's reflexive response ranges from hyper-, normo-, and hyporeflexic. The median peak tap force for eliciting a reflexive response is 12.8N, 38.0N, and 85.2N, respectively for hyper-, normo-, and hyporeflexic individuals

[38]. The pneumatic actuator pressure was held constant at 413.7kPa (60psi) throughout each subject test. Therefore the resultant constant actuator force may have created a subthreshold long latency response closer to threshold in some subjects than in others. In order to better understand subjects' mechanical long latency response threshold, a different actuator should be implemented in the experiment to find the mechanical long latency response threshold for each subject.

Motor response following the mechanical stimulus was substantially facilitated by the subthreshold TMS across a wide range for each subject: 60 to 40ms. This can be due to the temporal dynamics of the afferent mechanical stimulation interacting with the TMS stimulation. The variance of the duration of the cortical facilitation due to the mechanical stimulation between subjects can be due to the varying temporal dynamics of each subject. The long latency response from stimulation can be affected by a variety of different factors [47-49], which may explain the variance of the peak-to-peak amplitude of facilitation, the start time of facilitation, and the temporal range between subjects.

The wide 60 to 40ms ranges may also be due to the large variance in the pneumatic system. The large variance in the pneumatic system may cause the observed 60 to 40ms facilitation ranges to be larger than the actual cortical facilitation range. According to Chapter 6, the pneumatic system at 413.7kPa (60psi) has a delay range of 34ms. This large range may cause the facilitation range to be wider than the actual cortical facilitation range. However, the system was capable of exciting facilitation across a wide range of 60 to 40ms. The actual cortical facilitation range should be further studied.

The temporal range of increased facilitation for each subject was substantially wider with the mechanical stimulus (60 to 40ms) than with the electrical stimulus (15ms) as studied in Chapter 3. This is may be due to the differences in the application of the stimuli to the subject. The electrical stimulation was applied to the subject along the median nerve and quickly discharged. The afferent electrical stimulus therefore only excites the intracortical interneurons for a narrow temporal range. The mechanical stimulation, however, was applied to the subjects' FCR tendon, which causes a stretch in the muscle. The stretch is sensed by muscle spindles inside the FCR, which send ascending nerve responses to the spinal cord. The muscle spindles are excited at varying times as the muscle is stretched, therefore exciting the median nerve for a longer period of time than the electrical stimulus. The afferent mechanical stimulus therefore excites the intracortical interneurons for a wider temporal range than the electrical stimulus.

7.6 Conclusion

The muscle response following mechanical stimulation was significantly increased and suggests that the mechanical stimulus from the rehabilitation device is creating a subthreshold long latency response. The conditioned response was substantially increased across a wide temporal range of 60 to 40ms for each subject. The mechanical stimulus achieved an increase in facilitation across a wider temporal range than the electrical stimulation. The device therefore achieves a subthreshold long latency response with a wide temporal range of at least 40ms.

CHAPTER 8

CONCLUSIONS & FUTURE WORK

The neuromuscular mechanism associated with the repetitive facilitation exercise is most likely the long latency response of a stretch reflex. Studying the overlap of the long latency reflex from electrical stimulation with TMS stimulation resulted in cortical facilitation across a wide temporal range of 15ms. In order to study the temporal dynamics of the neuromuscular mechanism an fMRI study was proposed. A robotic rehabilitation device was then designed to meet a timing precision requirement of at least 15ms and to be fMRI-compatible. To confirm fMRI-compatibility, fMRI images were collected and distortion was analyzed with and without the device. After a preliminary study with the device, a wide range of reservoir pressures achieved the 15ms requirement for cortical facilitation, however the device was unable to evoke a suprathreshold long latency response with the fMRI-compatible pneumatic actuator. A TMS study was then completed with the device. The muscle response following mechanical stimulation was significantly increased across a wide temporal range of 60 to 40ms for each subject when overlapped with subthreshold TMS. This result suggests that the mechanical stimulus is creating a subthreshold long latency response.

The designed rehabilitation device is capable of creating a long latency response from a quick stretch of the FCR tendon, however the long latency response was subthreshold for each subject. During the study, the percentage below threshold was unknown. Therefore the mechanical stimulus may have been creating a long latency response closer to threshold in some subjects than in others. In order to better characterize the subjects, a study should be conducted with an actuator that can produce a resultant force output great enough to cause a long latency response in subjects. Understanding the force necessary to cause a long latency response and knowing the constant pressure of the actuator on the device, the percentage below threshold can easily be calculated for each subject.

The subthreshold long latency response, created by the mechanical actuating device, was substantially increased across a wide temporal range of 60 to 40ms, depending on the subject. The start time delay of the overlap also varied from subject to subject. In order to find statistical results, such as the mean and standard deviation of temporal range, start time delay of overlap, and percent change in muscle response, more subjects should be studied. Although it is clear to see overlap of the mechanical stimulus and TMS stimulus in each subject, the temporal dynamics should be studied more in the future to gain statistically findings.

In order strengthen the findings, a force sensor should be added to the tip of the hammer to help gain an understanding of the actual force subject's are experiencing from the pneumatic actuator. The addition of the sensor would also provide details about the start time of the tendon tap and the time delay between initial tendon tap and muscle response. Understanding the timing of the muscle response and how it varies among subjects would strengthen the time range of overlap findings and possibly explain some of the differences in start time delay of overlap between subjects.

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