Neural Mechanisms of Task Failure During Sustained Submaximal Contractions

A dissertation presented to
the faculty of
the College of Arts and Sciences of Ohio University

In partial fulfillment
of the requirements for the degree
Doctor of Philosophy

Petra S. Williams
August 2013

© 2013 Petra S. Williams. All Rights Reserved.
This dissertation titled

Neural Mechanisms of Task Failure During Sustained Submaximal Contractions

by

PETRA S. WILLIAMS

has been approved for

the Department of Biological Sciences

and the College of Arts and Sciences by

Brian C. Clark

Professor of Biomedical Sciences

Robert Frank

Dean, College of Arts and Sciences
ABSTRACT

WILLIAMS, PETRA S., Ph.D., August 2013, Biological Sciences

Neural Mechanisms of Task Failure During Sustained Submaximal Contractions

Director of Dissertation: Brian C. Clark

Fatigue is an expected and normal physiologic reaction to intense and to sustained activity. As fatigue develops during sustained isometric submaximal contractions, the amount of excitatory descending drive from supraspinal regions to the spinal motorneuron pool increases to compensate for the decline in spinal excitability by recruiting additional motor units in order to prolong task performance. However, despite the compensatory mechanisms from supraspinal inputs, task failure remains inevitable. Therefore, it remains largely unknown whether supraspinal mechanisms that could alter the amount of descending drive, including changes in motor cortex excitability and voluntary drive “upstream” to the motor cortex, also contribute to task failure. The focus of this dissertation research was to delineate the specific contributions that supraspinal circuits have in determining the time to task failure.

Experiment 1 compared adjustments in multiple neurophysiologic measures of supraspinal and spinal excitability taken throughout the performance of two different fatigue tasks (i.e. force-matching and position-matching) to determine the functional significance of the changes to task duration. Although no task-specific differences were found, task failure occurred for both tasks after a similar mean decline in motorneuron excitability developed coupled with a similar mean increase in corticospinal excitability. Additionally, the amount of intracortical inhibition dropped while the amount of intracortical facilitation and upstream excitation of the motor cortex remained
unchanged. Together the data for these two tasks indicate that, in general, the motor cortex is able to compensate for changes in spinal excitability until a critical amount of change in both regions develops. This suggests that unless more drive is provided to the motor cortex to sustain or strengthen the descending drive, failure occurs.

Experiment 2 examined whether delivering anodal transcranial direct current stimulation (tDCS), a non-invasive neurostimulation known to transiently increase cortical excitability, to the motor cortex during the performance of a sustained submaximal contraction would increase task duration compared to a sham tDCS condition. Anodal tDCS increased the time to task failure by more than 30% and also increased the amount of muscle fatigue by 6% in individuals whose time to task failure occurred prior to the termination of the anodal stimulation. Additionally, the stimulation increased the duration of time that the subjects were able to exert a high amount of effort. These findings suggest that the anodal tDCS provided the additional excitatory input to the motor cortex needed when task failure was eminent in order to overcome the increase in spinal resistance that could not otherwise be met by volitional drive.

Together the results from these two experiments provide complimentary evidence to support the conclusion that the capacity of supraspinal inputs to endlessly override the decline in spinal motoneuron excitability is eventually limited by the failure to increase intracortical facilitation as well as upstream drive delivered to the motor cortex and not the development of intracortical inhibition. The experience of fatigue in healthy populations is both physical and perceptual; however, the clinical symptom of perceived fatigue may not be associated with changes in motor performance. The application of these findings to clinical examination and treatment of physical performance fatigue and the symptom of perceived fatigue will benefit from both clinical
research as well as further research into the mechanisms of tDCS induced enhancements in task performance and also into the mechanisms behind the difference in time to task failure for the force-matching and position-matching tasks.
DEDICATION

For Eric (and Kit).

Thanks for waiting. We can go hiking now.
I am grateful that my Ph.D. journey led me to Dr. Brian Clark’s door. Your gifts for research and writing are matched by your willingness to keep things constantly moving forward. Thank you for taking me on—and all that went along with it these past seven years—and for providing the resources and support to make these experiments possible. It almost goes without saying, therefore it must be said that these experiments could not have been done without the help and skills of Rich Hoffman. The dedication and time you spent working with me to make the multiple components of these experiments work together so well, and so quickly, can never be repaid. Thank you.

I would also like to express my sincere gratitude to the members of my dissertation committee, Dr. Roger Gilders, Dr. Robert Staron, and Dr. Thad Wilson, for their guidance and thoughtful discussions during this process. Many, many thanks go to the DPT students from the classes of 2013 and 2014, as well as other members of the Ohio University community, for their willingness to participate in these experiments, I couldn’t have done this without you.

To my dear friend Meg, my clinical compatriot and best friend, thank you for spending countless hours talking through all of the scientific and clinical components of these studies, your excitement about each step were more than a godsend.

Finally, to Eric, the love of my life, thank you for all that you have done with me, now and in the future. I promise you do not have to be a subject next time.
# TABLE OF CONTENTS

Abstract ........................................................................................................................................... 3  
Dedication ......................................................................................................................................... 6 
Acknowledgments ............................................................................................................................. 7  
List of Figures .................................................................................................................................. 9  
List of Abbreviations ...................................................................................................................... 12  
Chapter 1: Introduction ................................................................................................................... 13  
  Background and Significance ......................................................................................................... 13  
  Innovation ..................................................................................................................................... 17  
  Assumptions and Limitations ......................................................................................................... 18  
Chapter 2: Review of the Literature .................................................................................................. 20  
  Fatigue .......................................................................................................................................... 20  
  Neurophysiologic methods to measure fatigue .......................................................................... 42  
Chapter 3: Cortical and Spinal Mechanisms of Task Failure of Sustained Submaximal Fatiguing Contractions with Different Load Compliances .................................................... 70  
  Abstract ......................................................................................................................................... 70  
  Introduction .................................................................................................................................... 72  
  Methods ......................................................................................................................................... 82  
  Results .......................................................................................................................................... 100  
  Discussion ...................................................................................................................................... 110  
  Conclusion ..................................................................................................................................... 127  
Chapter 4: Anodal Transcranial Direct Current Stimulation Enhances Time to Task Failure of a Sustained Submaximal Contraction ......................................................................................... 129  
  Abstract ......................................................................................................................................... 129  
  Introduction .................................................................................................................................... 131  
  Methods ......................................................................................................................................... 135  
  Results .......................................................................................................................................... 145  
  Discussion ...................................................................................................................................... 149  
  Conclusion ..................................................................................................................................... 162  
Chapter 5: Conclusions and Future Directions .................................................................................. 165  
  Conclusions .................................................................................................................................... 165  
  Future Directions ............................................................................................................................ 172  
  Summary ....................................................................................................................................... 177  
References ......................................................................................................................................... 179  
Figures ............................................................................................................................................. 208
**LIST OF FIGURES**

*Figure 1:* Possible sites of fatigue along the neuromuscular pathway. ...............................207

*Figure 2:* Decline in whole muscle force output (A) and motoneuron firing rates (B) associated with fatigue during a sustained maximum voluntary contraction. .............208

*Figure 3:* Sources of synaptic input to the alpha-motoneuron. ........................................209

*Figure 4:* Proposed mechanisms for declines in motoneuron firing rates mediated by changes in synaptic input from peripheral afferents (A and B) and descending drive (C) during fatigue. ..........................................................................................210

*Figure 5:* Experimental setup of the mechanical demands used for the force-matching (A) and position-matching (B) fatigue-tasks from prior studies. ........................211

*Figure 6:* Differences in limb stabilization for two different experiments with the knee extensors during the force-matching and position-matching tasks. ....................212

*Figure 7:* Etienne-Jules Marey around 1850 (A) and his myograph (B). .........................213

*Figure 8:* Two simulated motor unit action potentials discharging asynchronously, and the resultant EMG signal representing the sum of these respective motor units. ....214

*Figure 9:* Factors that influence the interpretation of neural drive to the muscle from the surface electromyogram (EMG). ..............................................................215

*Figure 10:* Schematic representation of a monopolar vs. bipolar electrode configuration. ..................................................................................................................216

*Figure 11:* Example of the interference EMG signal recorded with bipolar surface electrodes from the vastus lateralis muscle during a maximal voluntary knee extension task. ..................................................................................................................217

*Figure 12:* Compound surface EMG signal (A) from the soleus muscle in response to a single, supramaximal electrical stimulus to a peripheral nerve (tibial nerve) and intramuscular EMG recordings (B) obtained from the medial head of the biceps brachii. ..................................................................................................................218

*Figure 13:* Neuropathway of the Hoffmann (H) reflex response and that of cervicomedullary junction stimulation. ..............................................................................219
Figure 14: Transcranial magnetic stimulation delivered to the motor cortex (A), the motor evoked potential followed by the silent period in response to a single magnetic stimulus during a voluntary contraction (B), and the difference in amplitudes for paired-pulse protocols that assess intracortical inhibition and facilitation. .................................................................220

Figure 15: 3-D contour map of cortical representation of skeletal muscle plotting the motor evoked potential amplitude relative to the spatial location of the TMS coil. ..........221

Figure 16: Changes in surface EMG characteristics of the interference signal relative to the force output (A) and the power density spectrum (B) during a sustained, submaximal contraction. ........................................................................................................222

Figure 17: Plots of the current density magnitudes on the cortical surface for the TMS (left) and tDCS (right) (A) and current density vector plots on the gray matter surface for the TMS and tDCS brain stim models (C). .................................................................223

Figure 18: Overview of the experimental protocol. .................................................................224

Figure 19: Experimental setup of the force-matching (A) and position-matching tasks (B). ........................................................................................................................................225

Figure 20: Stimuli used to elicit cortical, cervicomedullary, and peripheral evoked potentials. ........................................................................................................................................226

Figure 21: Neurophysiologic outcome variables used as indices of corticospinal, intracortical, spinal and peripheral excitability quantified from electromyographic recordings of evoked potentials. ........................................................................................................229

Figure 22: Time to task failure (A) and percent decline in elbow flexor maximum voluntary contraction force (B) for the force-matching and position-matching fatigue-tasks. ........................................................................................................230

Figure 23: Individual times to task failure for men (filled circles) and women (open circles) during the force-matching and position-matching tasks (A) and for the difference in time to task failure relative to absolute target force (B) sustained during both fatigue-tasks. ........................................................................................................231

Figure 24: Ratings of perceived exertion during the force-matching and position matching tasks. .......................................................................................................................................232

Figure 25: The motor evoked potential amplitude (A) and silent period duration (B) during the force-matching and position-matching tasks. .................................................................233

Figure 26: Amplitudes of the cortically-evoked (A) and cervicomedullary-evoked (B) responses elicited during the silent period for the force-matching and position-matching tasks. ........................................................................................................234
Figure 27: Ratios for short-interval intracortical inhibition (A), intracortical facilitation (B), and long-interval inhibition (C) for the force-matching and position-matching tasks.

Figure 28: Comparisons between normalized values of corticospinal excitability with and without volitional drive (A) and between normalized values of corticospinal and spinal excitability without volitional drive (B) during the fatigue-tasks.

Figure 29: Comparisons between normalized values for short interval intracortical inhibition and intracortical facilitation (A) and between normalized values for long interval inhibition and silent period duration (B) during the fatigue-tasks.

Figure 30: Comparisons of the normalized value for the silent period duration with the normalized values for corticospinal and spinal excitability measured during the silent period.

Figure 31: Experimental Protocol.

Figure 32: Experiment setup and subject positioning.

Figure 33: Pilot study: After-stimulation effects of anodal tDCS on cortical excitability (n=4).

Figure 34: Time to Task Failure (n=18).

Figure 35: Individual time to task failure by stimulation condition (n=18) (A) and percent change in time to task failure (B) with anodal stimulation for subjects in the Full-Time group (n=8; filled circles) and Part-Time group (n=10; open circles).

Figure 36: Percent decline in MVC Force for the Full-Time group (n=8).

Figure 37: Rating of perceived exertion for the Full-Time group (A) and amount of contraction time spent at a rating of perceived exertion between 8-10 (B).

Figure 38: During-stimulation effects of tDCS and fatiguing contraction on cortical excitability for the Full-Time group (n=7).
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMT</td>
<td>Active motor threshold</td>
</tr>
<tr>
<td>COG</td>
<td>center of gravity</td>
</tr>
<tr>
<td>CMEP</td>
<td>cervicomedullary evoked potential</td>
</tr>
<tr>
<td>CS</td>
<td>conditioning stimulus</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>ICF</td>
<td>intracortical facilitation</td>
</tr>
<tr>
<td>LICI</td>
<td>long interval intracortical inhibition</td>
</tr>
<tr>
<td>LII</td>
<td>long interval inhibition</td>
</tr>
<tr>
<td>M_{MAX}</td>
<td>maximum compound muscle action potential</td>
</tr>
<tr>
<td>MEP</td>
<td>motor evoked potential</td>
</tr>
<tr>
<td>MT</td>
<td>motor threshold</td>
</tr>
<tr>
<td>MVC</td>
<td>maximum voluntary contraction</td>
</tr>
<tr>
<td>RPE</td>
<td>rating of perceived exertion</td>
</tr>
<tr>
<td>SICI</td>
<td>short interval intracortical inhibition</td>
</tr>
<tr>
<td>%SO</td>
<td>percent stimulator of stimulator output</td>
</tr>
<tr>
<td>SP</td>
<td>silent period</td>
</tr>
<tr>
<td>tDCS</td>
<td>transcranial direct current stimulation</td>
</tr>
<tr>
<td>TMS</td>
<td>transcranial magnetic stimulation</td>
</tr>
<tr>
<td>TS</td>
<td>test stimulus</td>
</tr>
</tbody>
</table>
In healthy individuals, fatigue is a normal and expected physiologic reaction to sustained activity that recovers with rest (123, 169). The experience of fatigue is both physical and perceptual (107, 169, 310). The physical experience is defined by a decline in force output, whereas the perceptual experience is the sense of effort needed to produce the force (28, 107, 123, 157, 310). Task failure is the inevitable consequence of fatigue; however, the physiologic adjustments within the different levels of the neuromuscular system (e.g., supraspinal, spinal, contractile, etc.) that cause the decline in force output that defines fatigue begin when the muscle contraction starts (7, 21, 23, 35, 123). It is well accepted that there is not one single cause of fatigue; instead, the mechanisms are specific to the mechanical task demands (i.e., intensity, duration, mode of contraction, muscle group, joint angle, and limb posture) that collectively stress different regions of the neuromuscular pathway in order to sustain the required force output (21, 35, 106, 123, 146, 148, 202). Therefore, the major question in fatigue studies for the past 30 years is “Which of these [physiologic] events determine performance and which are simply incidental by-products” because “finding those which are not responsible is as valuable as investigating those that are” (28, p. 693).

In general, it has been shown that the nervous system’s failure to maintain sufficient activation of the muscle is a significant contributor to the time to task failure for a sustained submaximal isometric contraction with the muscles in the extremities (13, 21-23, 123, 125, 129, 135, 196, 303). Studies over the past 10 years using novel
techniques to assess spinal motorneuron excitability (214, 218) and creative experimental strategies comparing physiologic adjustments between two tasks with identical mechanical demands that cause the same degree of physical and perceptual fatigue but differ in task duration (13, 104, 202) have together provided convincing evidence that early task failure is associated with a faster rate of recruitment of motor units by descending supraspinal inputs in order to compensate for a rapid decline in spinal excitability (17, 168, 202, 214, 218, 228, 279). Therefore, as fatigue develops during sustained submaximal contractions, the amount of excitatory descending drive from supraspinal regions increases to compensate for the reduced excitability of the spinal region (13, 21-23, 123, 125, 129, 135, 196, 279, 303). However, despite the compensatory mechanisms from supraspinal inputs, task failure remains inevitable. Thus, it remains largely unknown whether supraspinal mechanisms that could alter the amount of descending drive, including changes in motor cortex excitability and voluntary drive “upstream” from the motor cortex, also contribute to task failure.

**Global Research Question**

*What is the mechanistic role of supraspinal excitability in determining the duration of sustained submaximal elbow flexor contractions?*

**Specific Aims**

**Specific aim 1.** To delineate the task-specific adjustments in 1A) measures of motor cortical excitability, and 1B) measures of alpha-motorneuron excitability associated with the difference in the time to task failure for sustained submaximal force-matching and position-matching tasks with the elbow flexors. **Approach:** On two
different days, subjects performed two sustained submaximal isometric contractions with the elbow flexors under identical mechanical demands (i.e., identical joint torque, angle and stability) but different purpose (i.e., maintain force output vs. maintain joint position) to volitional failure. During the contractions a combination of transcranial magnetic stimulation (TMS) and cervicomedullary junction electrical stimulation was used to assess adjustments in indices of motor cortex and alpha-motorneuron excitability as they developed throughout task performance. **Hypothesis:** Premature task failure of the position-matching task will be associated with 1A) a greater rate of increase in cortical excitability and 1B) a greater rate of reduction in alpha-motorneuron excitability.

**Specific aim 2.** To determine the effect of manipulating cortical excitability on the time to task failure for a sustained submaximal force-matching contraction with the elbow flexors. **Approach:** Anodal transcranial direct current stimulation (tDCS) to the primary motor cortex increases motor cortical excitability. Accordingly, anodal tDCS was used to experimentally modulate cortical excitability while individuals performed a sustained submaximal force-matching task with the elbow flexors. The time to task failure was compared to that observed with sham tDCS. **Hypothesis:** Experimentally increasing cortical excitability will increase the time to task failure.

**Experiments**

Experiment 1 addressed Specific Aim 1 using a combination of single-pulse TMS, paired-pulse TMS, and paired cortico-cervicomedullary stimulation. The motor evoked potential amplitude elicited by TMS to the motor cortex is a composite index of excitability of the entire corticospinal system as the amplitude is known to depend upon the responsiveness of the cortex and the spinal cord (90, 91, 133, 170, 277, 282).
cervicomedullary-evoked potential amplitude evoked by electrical stimulation of the spinal cord tracts at the cervicomedullary junction provides an index of alpha-motorneuron excitability (308, 311, 327). Suprathreshold TMS delivered during a voluntary contraction causes a silent period or cessation of ongoing EMG by transiently interrupting volitional descending drive and interrupting motorneuron firing (62, 154). Therefore, motor evoked potentials and cervicomedullary evoked potentials elicited during the silent period provide an index of excitability of the corticospinal and spinal motor circuits, respectively, during fatigue that is independent from volitional descending drive (214, 216, 218). The ratio of the two different cortically evoked potentials provides an index of corticospinal inhibition (214, 217). The silent period duration traditionally indexes intracortical inhibition (123); however, paired-pulse TMS protocols that use a subthreshold conditioning pulse to preferentially activate intracortical neurons directly examines intracortical excitability and inhibition (92, 179, 231). Alone, these measures do not directly quantify the amount of neural activation; however, if interpreted relative to the others greater inference to the state of nervous system activity is possible (261, 270, 283).

Experiment 2 addressed Specific Aim 2 using an innovative tDCS paradigm to experimentally modulate cortical excitability. The transcranial application of weak direct currents (1.0-2.0mA) is known to induce an intracerebral current flow that is sufficient to reliably modulate human cerebral cortical function by inducing a focal and relatively prolonged (a few hours), but still reversible shifts of cortical excitability (235, 242, 331). This sham-controlled experimental approach provided an optimal strategy to examine the association/disassociation between cortical excitability and the time to task failure through the delivery of a targeted intervention.
Significance

Collectively, the findings from this dissertation add to the growing understanding of the neurologic mechanisms involved in the decline in force output that limits the duration of sustained submaximal contractions by delineating the contribution of supraspinal mechanisms relative to spinal adjustment. In the long-term this work will provide critical insight into the role of cortical processes that can be applied to clinical neurology and rehabilitation medicine as it has the potential to lead to improved diagnostic tests and treatment interventions in patient populations with fatigue.

Innovation

This work is innovative for two major reasons. First, a specific combination of advanced electrophysiological techniques were used to deliberately explore and delineate the cortical contributions to the inevitability of task failure in sustained submaximal contractions. While TMS has been used in humans to examine fatigue for close to 20 years (125, 312), the concurrent use of single pulse, paired-pulse TMS and paired cortico-cervicomedullary evoked potentials is innovative as it has allowed the unique opportunity to probe the segmental localization of the changes in excitability that occur during task performance that has remained both hypothetical and contradictory and therefore confusing and even misleading (104, 123). The extensive work done to determine the physiology of the observed intracortical facilitatory and inhibitory responses to paired pulse TMS has led to a detailed understanding of TMS that now allows the use of this technique to study the physiologic mechanisms of muscle fatigue.
Recent work combining the use of TMS with cervicomedullary stimulation provides a new and more direct measure of motoneuron excitability that can be measured throughout a fatiguing contraction (214, 218, 279). Accordingly, the use of these advanced techniques in combination with each other to examine the differences in time to task failure between the force and position task is an innovative strategy to probe the neural mechanisms of fatigue.

Second, this is the first study to use transcranial direct current stimulation to experimentally modulate cortical excitability during the performance of sustained submaximal contraction to modify task duration. tDCS has become one of the major tools used to induce temporary neuroplastic alterations in cortical excitability over the past few decades in both neurologically injured and non-injured populations due to its efficacy and ease of application (235). Nearly all studies to date using tDCS have measured the influence on motor skill acquisition and performance (15, 33, 145, 242, 269, 271). To my knowledge this work represents one of the first to use this technology to study the cortical mechanisms of muscle fatigue, and, as such, the proposed work represents a novel approach to studying the neural mechanisms of task failure.

Assumptions and Limitations

Assumptions

1. Equipment employed will be in proper working condition, and all data collected from such equipment will be accurate.

2. Subjects will comply with all provided instructions (e.g., pre-testing instructions).
Limitation

1. There are several physiological variables that could be mechanistically associated with muscle fatigue. Thus, while this study has been designed to provide detailed insight into the neural mechanisms of muscle fatigue, it is still limited to a certain degree. The reasons that other variables have not been assessed are primarily due to either feasibility issues, financial constraints, or technical/equipment capability.

Delimitations

1. Subjects will volunteer for the study instead of being selected via random sampling, therefore conclusions can not be generalized for the entire population.

2. Subjects will be young, healthy, and free of diseases; therefore, conclusions can not be generalized for the entire population.
CHAPTER 2. REVIEW OF THE LITERATURE

The purpose of part A of the literature review is to provide a concise overview of the topic of fatigue in order to place the focus of this dissertation research, the contribution of supraspinal neural factors on the duration of sustained submaximal contractions, into context. Part B reviews the neurophysiologic techniques used to assess the neuromuscular system.

Fatigue

While the term fatigue is common, its definition varies across disciplines (i.e., basic science and clinical science). The first part of the fatigue section of the literature review will distinguish between fatigue in healthy individuals, the focus of this dissertation, and the clinical symptom of fatigue, as well as the different uses of the terms central and peripheral fatigue. The second part of this section will review the currently known physiologic mechanisms of fatigue in healthy individuals with particular emphasis on the contributions of the nervous system.

Defining Fatigue

The human experience of fatigue is both physical and perceptual (85, 107, 169, 310). While the physical and the perceptual dimensions of fatigue are usually experienced concurrently and share some common processes (i.e., motor command), the influence that physical fatigue and the perception of fatigue have on the other is neither direct nor universal (102, 107, 157). On one end of the spectrum, extreme
examples of this separation between the perception of fatigue from the physical decrement in performance are admired in cases of extreme survival experiences and ultra-endurance sports where an individual can push the body into and beyond its physiologic limits driven by a “will” to survive or win (50, 224). On a more routine basis, it is well known that the tolerance for and familiarity with the discomfort associated with acute fatigue as well as the level of subject motivation can influence physical performance on a day-to-day basis such that both are controlled for during experiments (28, 123). In these situations, the perception of effort can even be viewed as pleasurable, a sign of an effective workout or a job well done (131, 156). Conversely, the clinical symptom of fatigue is qualitatively different from fatigue in healthy individuals in that it does not resolve with rest, is present with or without physical activity, and can be so great that it effectively prevents participation in physical and cognitive activity (35, 59, 85, 94, 156, 169, 329, 343). Therefore, the complete experience of fatigue, as a combination of physical and perceptual aspects, as well as the definition of the term is specific to an individual person as well as to the disciplines that study it (35, 102).

In healthy individuals, fatigue is an expected and normal physiologic reaction to sustained and intense activity and it is assumed that both the physical and perceptual components of fatigue are transient, resolving after a period of rest (35, 59, 94, 106, 123, 131, 169). The physical experience of fatigue in healthy individuals involves observable decrements in performance such as a decline in force output or deterioration in the kinetic or kinematic accuracy of movements over time (28, 107, 123, 310). The associated perceptual experience of fatigue during performance is described by the increased sense of effort required to sustain the force or difficulty in meeting the goal of an activity (28, 107, 123, 157, 310). When a person becomes fatigued, task
performance will eventually cease because they physically cannot sustain the same level of physical performance needed for the task and/or because they perceive that the effort required to sustain the task is intolerable, having reached a subjective point of exhaustion.

Clinically, perceived fatigue is a symptom or a subjective patient complaint defined as an overwhelming and persistent sense of tiredness, a lack of physical and mental energy, and a feeling of exhaustion that interferes with usual activities of daily life both physical and cognitive (52, 58, 59, 85, 94, 343). Although this definition implies that the symptom of fatigue is associated with a concurrent activity-dependent decrement in physical performance, it is disconnected from it. Rather, the symptom perceived fatigue is described to “interfere(s) with usual activities” referring to the choices patients’ make in their daily lives about activity participation and are based upon their feelings of fatigue as opposed to direct objective measurement of physical performance. In clinical populations, the focus of the fatigue examination and treatment is on the patient-specific perceptual experience: “By definition, a patient who complains of fatigue is experiencing fatigue” (343, p. 3). The term performance fatigability, on the other hand, does refer to the objective declines in physical performance or activity dependent weakness that develop during sustained or intense activity; however, this physical change also is distinct from the symptom of perceived fatigue (94, 169). The symptom of perceived fatigue is typically quantified by patient responses to self-report questionnaires and instruments such as the Fatigue Impact Scale (113) or the Fatigue Severity Score (178) that do not include measures of performance fatigability (94, 102, 169, 343). Thus, it is important to recognize that the subjective clinical symptom of fatigue is a distinct diagnosis, characterized by its lack of dependence on physical activity to induce it and is
therefore not synonymous with the sense of effort associated with performance fatigue in healthy individuals.

Clarification also needs to be made between the discipline-specific uses for the terms “central” and “peripheral” in studies of performance fatigue in healthy individuals and clinical reports of the symptom of perceived fatigue. In the basic and physiologic sciences investigating the declines in physical performance associated with prolonged or intense activity, the distinction between central and peripheral is anatomical and addresses the two major systems involved in voluntary contractions (i.e., the nervous and muscular systems). In this context, “central mechanisms” refers to the composite neural drive delivered to the muscle from the motorneuron itself in the peripheral nervous system (PNS) as well as the neural structures in the central nervous systems (CNS) and periphery that synapse with the motorneuron (123, 310). The term “peripheral mechanisms” then refers to the neuromuscular junction and all the electrical and contractile elements of the muscle (28, 123, 169). In the clinical literature, however, this distinction is not as clear because “central” and “peripheral” can be used to refer to both an anatomical region where a pathological process is localized (e.g., the central nervous system (CNS), the peripheral nervous system (PNS), excitation-contraction coupling processes, etc.) as well as to phenomenological differences in fatigue (i.e. subjective symptoms or objective changes in performance). In neurologic and neuromuscular disorders “peripheral fatigue” is also known as fatigability or physiologic fatigue because it encompasses weakness that develops with physical exertion and is caused by diagnoses affecting the PNS and/or the muscle (52, 59, 85, 169, 343).

While the definition for peripheral or physiologic fatigue in the clinical disciplines does overlap with the definition used in the basic sciences, the difference comes from
the inclusion of the motorneuron as part of peripheral fatigue in clinical settings. The localization of the motorneuron to peripheral fatigue is consistent with the process of neurologic diagnosis, where the first step is to localize the lesion or problem as “central” or “peripheral” (276). The presentation of motor symptoms caused by pathology to the motorneuron, neuromuscular junction, and the muscle (e.g., Guillain-Barre-Syndrome (GBS), myasthenia gravis (MG), or Duchenne muscular dystrophy) fall into a “lower motor neuron” category that includes weakness, atrophy, hyporeflexia, and fatiguability (35, 52, 59, 85, 94, 343).

Conversely, the definitions for central fatigue do not share much overlap between the clinical and basic sciences. In the clinical disciplines “central fatigue” refers to the subjective symptom of fatigue defined above as a “constant feeling of exhaustion” that may or may not be accompanied by objective fatigability. In the clinical disciplines, central fatigue is largely a primary symptom reported by patients with neurologic diagnoses affecting the CNS including multiple sclerosis (MS), stroke, and Parkinson’s Disease (PD) (52, 59, 85). Unlike in peripheral fatigue where the symptomatology is relative to the pathology and severity of the disease process, central fatigue is largely independent of disease process and severity and is also influenced by other factors including mood, sleep, and stress (59, 94). However, it must be re-emphasized that clinically, individuals with known PNS pathology and presentation of physiologic fatigue can also present with this distinct primary symptom of CNS fatigue (59, 343). Therefore, the sense of effort experienced during fatigue in healthy individuals that is essentially partnered with changes in force output during sustained activity is not the same phenomenon as the clinical symptom of perceived fatigue reported by patients to their health care providers.
To ensure clarity in terminology, from this point forward the terms fatigue, muscle fatigue, or neuromuscular fatigue will refer to physical performance changes in force output. The perceptual component of fatigue defined as the effort reported during physical activity will be referred to as rating of perceived exertion or sense of effort. The phrases clinical symptom of fatigue, perceived fatigue or the symptom of fatigue will be used in reference to subjective reports of that are measured independent from objective physical performance. The terms central fatigue and peripheral fatigue will be avoided and instead, neural failure or mechanisms and muscular failure or mechanisms will be used.

Mechanisms of Fatigue During Single Joint Sustained Submaximal Contractions

Fatigue is an expected and normal physiologic reaction to sustained and intense activity (123, 169). In other words, it is accepted that activity cannot be endlessly sustained. Fatigue, like the generation of a voluntary contraction, is the product of a multi-factorial physiologic process involving the nervous system and the muscle both of which undergo functional adjustments as a contraction continues (Figure 1) (28). The major question in fatigue studies has been “which of these events determine performance and which are simply incidental by-products” because “finding those which are not responsible is as valuable as investigating those that are” (28, p. 693). The assumption being that if the limiting physiologic mechanisms can be found, then perhaps interventions can be used to effectively reduce fatigue and prolong performance. The physiologic mechanisms behind the declining force output that characterizes muscle fatigue and also prohibits indefinite task performance have been attributed to impairments in the contractile capacity of the muscle and also to inadequate
maintenance of neural activation of the muscle; however, the contributions of both systems is well known to be task specific (28, 106, 107, 123). In other words, there is no one single cause of fatigue nor factor that determines task duration (21, 22, 102, 107, 123, 148). The mechanical demands of the task including intensity (maximal or submaximal), duration (repetitions or sustained), and mode (dynamic or static) of contraction combined with the muscle group involved (extremity or trunk), joint angle, limb posture and proximal stabilization of the body during task performance together will stress differing regions of the neuromuscular pathway in order to sustain the required force output (106, 202).

Muscle fatigue is defined as the gradual decline in maximum muscle force capacity that occurs with the performance of sustained or repetitive contractions (13, 28, 107, 123). It can be viewed as the development of activity dependent weakness relative to pre-activity strength measures that recovers with rest (123). Task failure, on the other hand, is the point in time when the force output required for successful task performance, either maximal or submaximal, can no longer be sustained in the manner demanded by the activity (13, 107). Although stopping activity is the inevitable result of fatigue, fatigue is not the point in time when activity ceases (28, 106, 107, 123). Instead, the functional adjustments that occur in the neuromuscular system that cause fatigue begin when the contraction starts and then progress until task failure (Figure 1) (7, 21, 23, 123). Therefore, during sustained submaximal intensity contractions, muscle fatigue, as measured by the decline in maximal force output relative to pre-task values, will be present prior to task failure but task performance will continue for a period of time without appreciable disruption (28, 106). As the duration of the submaximal task increases, muscle fatigue will progress to a degree such that it will interfere with the
capacity to sustain the precise amount of submaximal force output required (e.g. force fluctuations around the target force disrupt accuracy of performance) and eventually prohibit effective task performance, thereby contributing to task failure (107, 153, 222).

The longer a motor unit stays active, the more its force output decreases. Both components of the motor unit undergo activity dependent changes that contribute to the loss of force. As fatigue develops, the contractile behavior of the muscle fibers in the motor unit slow and the discharge rate of the motorneuron innervating those fibers also slows (Figure 2) (23, 28, 123, 129, 196). The presence of slowed muscle contractile properties indicates that both the shortening velocity as well as relaxation time slow, the combined effect of both decreases the peak force of the motor unit (28, 130). The adjustments in contractile behavior have been found to stem from changes in the efficiency and effectiveness of the excitation-contraction coupling process mediated by the build up of various metabolites and the depletion of molecular substrates needed for energy supply (7, 114, 115). The accumulation of metabolites including the build up of H+ and inorganic phosphate ions together reduce the amount of force per actin/myosin crossbridge (7, 114). Additionally, both the release and reuptake of Ca²⁺ ions from the sarcoplasmic reticulum—and therefore, the amount of Ca²⁺ available within the myofiber—change the availability of Ca²⁺ for the contractile process (5, 6, 115). The excitation component of the coupling process can also be slowed due to changes in muscle fiber action potential conduction related to changes in ionic conductance shifts in K⁺ and Cl⁻ (7, 119).

In general, it has been shown that the nervous system’s failure to maintain sufficient activation of the muscle is a significant contributor to the decrease in force output and to the eventuality of task failure in sustained submaximal contractions as
compared to maximal contractions (Figure 2) (13, 27, 98, 123, 125, 135, 196, 303). Throughout a sustained submaximal voluntary contraction, the amplitude of the voluntary EMG signal progressively increases as the target force output is maintained to the point of task failure (23, 28, 148). This is consistent with increased activation of the muscle from enhanced excitatory drive to the motoneuron pool in an attempt to maintain a level of muscle activation sufficient to produce the required force output as fatigue develops (3, 23, 109, 119, 129, 196). As the intensity of the submaximal contraction decreases, the duration that the task can be sustained increases and so does the EMG amplitude as well as the amount of muscle fatigue measured at task failure (14, 28, 104). In other words low intensity, long duration contractions result in higher EMG amplitude and greater declines in muscle force at task failure as compared to higher intensity, shorter duration tasks (82, 98).

This observed relationship between increasing EMG amplitude and consistent force output in sustained submaximal contractions is transposed when subjects are required to maintain a constant level of EMG output. In this experimental condition used to keep the amount of neural drive to the muscle constant or “clamp motoneuronal output…hold motoneurone output steady” (214, p.3542), the force output progressively declines throughout the duration of task performance (23, 214, 264). The time to task failure is longer for the EMG controlled task, when compared to an equivalent magnitude torque controlled task, but the amount of muscle fatigue, measured as MVC decline, is the same (264). These characteristics suggest that the neural drive to the muscle is a significant variable that influences the duration that a submaximal contraction can be sustained (98, 195, 196).
Because the relationship between the absolute EMG amplitude and force output is not reliable or constant during fatiguing contractions as both have been demonstrated to vary independently of the other, EMG amplitude is not an accurate index of the amount of neural drive (22, 53, 104, 134). Composite EMG also does not indicate the causes for change in amplitude, namely changes in motor unit recruitment or discharge rates (110, 111, 163-165). Although in non-fatigued states the force output of a motor unit can be increased by increasing the firing rate the evidence suggests that is not the strategy used by the nervous system during prolonged tasks (17, 100, 196). Single motor unit studies reveal that the increased amplitude of the EMG signal during fatiguing contractions is associated with the recruitment of additional motor units during task performance as well as greater variability in, and slowing of, motor unit discharge rates (17, 129, 201, 226). This is also associated with increased burst rate within the EMG pattern, which is consistent with transient recruitment of motor units (134, 148, 193, 210). The recruitment thresholds of single motor units have been found to lower during submaximal fatiguing contractions thereby permitting more motor units to be recruited to sustain force output as the task persists (17, 109, 129, 274). This means that motor units with a recruitment threshold greater than the target force, when assessed during a ramped contraction, can be recruited at the lower force level needed to perform the task as fatigue develops.

During sustained *maximal* contractions the discharge rates of individual motor units are known to decrease consistent with a decline in voluntary EMG amplitude (26, 121); however, motor unit discharge rates during sustained submaximal contractions have been found to slow, maintain, or even increase depending upon when they were recruited during task performance (17, 129, 226). When the EMG output is sustained
(i.e., as opposed to a submaximal target force output) motor unit discharge rates decline in parallel with force (25). Overall, the discharge rate of most of the motor units slows during submaximal contractions, especially in those units recruited at the start of the contraction thereby necessitating the recruitment of new motor units to sustain adequate muscle activation (Figure 2) (17, 28). The muscle wisdom hypothesis states that the decline in motorneuron firing rate is done to match the contractile speed of the associated muscle fibers in the motor unit in order to minimize fatigue (123, 130, 204). While this co-decline may represent a functional adaptation, especially for maximal contractions, the mechanisms needed for such individualized motor unit self regulation requiring communication from muscle fiber to associated motorneuron are not found when contractile properties are manipulated independent from fatigue (30). Although the muscle wisdom hypothesis is somewhat controversial and may not be correct (107, 130), it does not mean that there is an absence of communication between the muscle and nervous system. Indeed several different synaptic inputs delivered to the motor pool during voluntary contractions mediated by afferent fibers from peripheral somatosensory receptors have been found to influence motorneuron firing rates (Figure 3) (123).

By holding a muscle ischemic at the end of a fatiguing contraction, the decline in motorneuron discharge rates do not recover until the ischemia is resolved (29). This has indicated that the Group III and IV peripheral afferents sensitive to intramuscular metabolites have a reflexive connection within the spinal cord—as well as other regions of the neuraxis—that modulate motorneuron firing rates through pre-synaptic inhibition of the Ia afferent fiber (Figure 4A and 4C) (207, 291, 337). Manipulation of Ia afferent input to the motor pool through short term vibration temporarily increases motor unit firing rates (123). Prolonged vibratory input has been found to decrease motor unit firing rates
and task duration (215, 229) or, alternatively, to increase the amplitude of the stretch reflex and motor unit discharge rates as well as fluctuations in force output (298). Complete withdrawal of Ia input to the motor pool has also been found to decrease motoneuron firing rates (Figure 4B) (123, 197). Therefore, sustained (a.k.a. lack of decline) motoneuron firing rates from a spinal cord level are most likely mediated by sustained Ia facilitation of the motoneuron during active contractions (123).

Evidence from in vitro microelectrode work on dissected preparations of motoneurons demonstrate that the motoneuron behavior can change in response to synaptic input (in this case injected current used to mimic synaptic input). In the presence of continued depolarization provided by intracellular current injection, motoneuron firing rates decline. This is suggested to be an intrinsic membrane property referred to as spike-frequency adaptation (166); however such adaptation may not occur in response to physiologic levels of stimulation (247). Physiologic levels of stimulation have been found to shift the motoneuron membrane conductance of ions, such that a persistent inward-depolarizing current develops, creating plateau potentials that can induce self-sustained motoneuron firing (140). Therefore, the presence of persistent inward currents may override, or otherwise negate, the effect of spike-frequency adaptations (247).

External stimulation of the nervous system at the peripheral nerve supplying the muscle of interest during voluntary contractions to superimposes a mechanical twitch was first used to investigate the contributions of the nervous system to fatigue (221, 225, 268). The technique, used primarily to study an individual subject’s capacity to maximally recruit the motoneuron pool of a muscle volitionally when performing a maximal voluntary contraction (MVC) (141), when applied during a sustained MVC,
reveals the presence of neural failure (i.e., central fatigue) when additional force is generated above voluntary levels at the instance of stimulation (123, 313). In other words, the muscle could produce more force if the nervous system could deliver it but, as fatigue develops, the nervous system becomes less and less able to sustain maximal activation of the muscle. Peripheral nerve stimulation directly activates the axons supplying the muscle and the added force indicates that the motor units are either not recruited or were not firing fast enough (141, 310). To investigate if supraspinal mechanisms were involved in neural failure, Gandevia and colleagues adapted this superimposed twitch strategy by using single pulse Transcranial Magnetic Stimulation (TMS) delivered to the motor cortex (125, 312, 322). The presence of an added force, in response to the cortical stimulation, to that generated by volitional effort is interpreted as evidence of supraspinal failure (310, 322, 323). Supraspinal failure, as a component of neural failure, indicates that the output from the motor cortex and/or the upstream input to the motor cortex are suboptimal (125, 313).

By definition the twitch superimposition technique, when applied during sustained submaximal intensity contractions, requires that subjects interrupt task performance to produce periodic MVCs at regular intervals during which the stimulation is delivered (23, 302, 303, 310). These studies using both peripheral nerve and motor cortex stimulation have found that the evoked force gets progressively greater suggesting declining neural activation that starts well before task failure (23, 125, 322). When compared to sustained MVC’s, up to 25-50% of the decline in force output, depending upon contraction intensity, that occurs by task failure during sustained submaximal contractions is due to inadequate neural drive of the muscle (123, 216, 314). While the magnitude of the twitch or added force indicates the presence of supraspinal failure, the
twitch itself does not provide insight to the origin of failure to any one segment of the neuraxis nor the mechanisms behind failure. Similar to the questions about the origin in changes in spinal excitability, it seems appropriate to ask: Is the source of supraspinal failure due to inhibition within the motor cortex or insufficient upstream activation to, or disfacilitation of, the motor cortex? Evidence from the evoked potentials recorded in response to the external stimulation can provide this insight.

Neurophysiologic studies investigating the neural mechanisms responsible for the observed changes in motor unit recruitment and discharge rates associated with task failure as well as the development of central fatigue have sought to delineate the segmental contributions from both supraspinal and spinal regions. The excitatory drive to the muscle by the motoneurons can be modulated by supraspinal synaptic inputs from descending pathways, spinal inputs from interneurons and peripheral afferents and also by intrinsic changes of the motoneuron itself during sustained fatiguing contractions (98, 123, 247). Evoked potentials elicited using transcranial magnetic stimulation (TMS) of the motor cortex, electrical stimulation of the spinal tracts or the peripheral nerve provide evidence about the state of excitability or responsivity of the nervous system to external stimulation during task performance and have been suggested to provide an indirect assessment of the amount of nervous system activation (8, 262, 270, 283). It is important to recognize that this experimental strategy does not directly assess the amount of activation provided to the motor pool from the motor cortex or spinal afferents rather it examines the state of excitability or responsiveness of the nervous system to external stimulation at the time of stimulation from which interpretations about the state of activity are made (283). However, when cortical, spinal and peripheral measures are evoked in real-time and also during different states of
activation (i.e., fatigued vs. non-fatigued, resting vs. active) inferences about the state of activation in a region are more plausible (214, 218, 270).

The motor evoked potential (MEP) amplitude evoked by TMS to the motor cortex provides a composite index of excitability of the entire voluntary motor pathway, as the size of the response depends upon both cortical and spinal excitability (123, 133, 136, 170, 232). The amplitude of a cervicomedullary-evoked potential (CMEP) elicited by electrical stimulation at the cervicomedullary junction to the spinal cord tracts in order to trans-synaptically activate the motor neuron pool is regarded as a segmental index of spinal alpha-motorneuron excitability (308, 311, 326, 327). The CMEP response latency suggests that the evoked response reflects a monosynaptic relationship between the corticospinal tract and the motoneuron without influence from pre-synaptic inhibition of the corticospinal tract (206, 327). Conversely, the H-reflex, another common neurophysiologic outcome used to assess spinal excitability, is evoked by stimulation of the Ia afferent fibers in the peripheral nerve (1, 104, 232, 263). The amplitude of the H-reflex is influenced by not only alpha-motorneuron excitability but also by the excitability of the Ia fibers, which can be modified by presynaptic inhibition of the Ia terminals at the reflex synapse (65, 232, 263). Therefore, compared to the CMEP, the H-reflex is used as an index of global spinal excitability that represents the responsivity of both the motoneuron and the spinal reflex pathway (104, 263) peripheral nerve stimulation of the motor axons with a supramaximal intensity stimulus to evoke a compound muscle action potential ($M_{max}$), represents an index of muscle excitability (24, 82, 119, 158) and thus can be used to normalize the amplitudes of all evoked potential measures as fatigue develops during task performance.
During fatiguing submaximal contractions, much like the voluntary EMG signal, the amplitudes of both the MEP and the CMEP, when normed to the maximum compound muscle fiber action potential evoked by supramaximal stimulation of the peripheral nerve ($M_{max}$), have been shown to increase as task duration increases (123, 142, 192, 218, 299). This increase in responsiveness to the external stimulus has been attributed to enhanced voluntary drive both to and also from the motor cortex (in the case of the MEP) and to increased descending drive to recruit motor neurons (in the case of the CMEP) in order to sustain neural output and thus muscle activation (214, 218, 279, 283). These findings are consistent with the evidence of progressive recruitment of new, unfatigued motor units to sustain force output and increase the voluntary EMG amplitude as reported by single motor unit studies (3, 17, 53, 129, 196, 228). Conversely, the H-reflex amplitude, has been found to decrease throughout the duration of sustained submaximal fatigue tasks (98, 168) indicating that either the motor neuron itself has become less excitable or that there is a depression in the excitability of the sensory afferent synapsing on the motor neuron. Because of the synaptic relationship used to evoke the H-reflex, this progressive decline in H-reflex amplitude is currently thought to be more likely due to depression of the peripheral afferent axon’s excitability from modulations in pre-synaptic inhibition (13, 17, 98, 104, 106, 168, 202) as opposed to adjustments in motor neuron membrane properties that have been shown experimentally to occur during prolonged activation (166, 247). These findings, taken together, suggest that the source of enhanced excitatory drive to recruit more of the motor neuron pool during sustained submaximal contraction most likely comes from supraspinal descending inputs that must overcome a depression in spinal excitability that results from motor neuron resistance and/or disfacilitation from
peripheral afferents in order to provide sufficient muscle activation needed for task performance. However, these finding do not rule out the potential that supraspinal mechanisms influencing descending drive including motor cortex excitability and inputs upstream from the motor cortex can also contribute to task failure.

When a single supra-threshold TMS pulse is delivered during a voluntary contraction, the MEP is followed by an electrical silent period, which is observed as a transient cessation of ongoing EMG activity (62, 332). The duration of the silent period when measured during a non-fatiguing voluntary contraction has been attributed to an initial short period of spinal refractoriness, as seen after maximum stimulation to the peripheral nerve, that recovers (~50msec) combined with a longer period of cortical inhibition of volitional drive to the motor cortex and withdrawal of corticospinal input to the spinal motor pool (up to ~200 msec) (62, 120, 154, 252, 279). During fatiguing contractions the duration of the silent period has been demonstrated to increase in length, with those increases attributed to enhanced intracortical inhibition based upon the mechanisms proposed during non-fatiguing contractions (19, 104, 123, 310, 312). The interpretation of this finding during fatiguing contractions has posed somewhat of a conundrum in that despite an increase in excitability as measured by the MEP and CMEP amplitudes, there also appears to be a concurrent increase in intracortical inhibition as measured by a longer SP (19, 104, 123, 292, 293). This raises the question as to the segmental contribution of the motor cortex and also “upstream” inputs to the motor cortex to task failure (i.e. supraspinal failure) during sustained submaximal contractions (Figure 1) (21, 104, 123, 218, 310, 313). In other words, does active cortical inhibition develop during task performance and thus interfere with or limit the
capacity of supraspinal structures to sustain sufficient excitatory drive to the 
motorneuron pool and thus contribute to task failure?

To more directly address supraspinal contributions to neural mechanisms of 
fatigue, paired-pulse TMS protocols, including short interval intracortical inhibition (SICI) 
and intracortical facilitation (ICF), provide a strategy to more directly evaluate the 
excitability of intracortical interneuron networks within the motor cortex (90, 92, 93, 231, 
270, 282, 284, 285). The effect of a sub-threshold conditioning pulse that activates the 
cortical interneurons, on the MEP amplitude of a subsequent supra-threshold test pulse 
is compared relative to a single MEP. When separated by interstimulus intervals (ISI) of 
2-5msec, the evoked MEP amplitude decreases and the SICI ratio of the test MEP to the 
single MEP is less than 1.0 reflecting intracortical inhibition (see also Section B of this 
chapter) (179, 231). An ISI of 12-25 msec increases the test MEP amplitude and the 
ratio is greater than 1.0, interpreted as intracortical facilitation (92, 270). These two 
measures of intracortical excitability have been rarely used to monitor the ongoing 
adjustments in intracortical excitability related to fatigue (20, 209, 330) and, to date, have 
not been employed during the performance of submaximal contractions sustained to 
task failure

Recent work by McNeil et al. presents a technique to assess the excitability of 
the corticospinal system and the motoneurons independent of upstream voluntary drive 
to the cortex and descending drive to the spinal cord, by evoking MEPs and CMEPs 
during the silent period (i.e. evoking MEPs and CMEPs during the period of electrical 
silence attributed to a temporary suspension in volitional activation and spinal 
refractoriness after a single suprathreshold TMS pulse (214, 216, 218). In the non-
fatigued state, the amplitudes of a MEP or a CMEP evoked in the SP are less than those
evoked in the presence of voluntary activation such that a ratio of the SP evoked response to the single control pulse is typically <1.0 (216, 218). In addition, in the non-fatigued state the MEP ratio is also less than the CMEP ratio suggesting the added presence of intracortical inhibition during non-fatigued performance (214, 216, 218). The ratio of the MEP evoked in the SP (MEP in SP) to the single MEP is referred to as long-interval intracortical inhibition (LICI) and is thought to be influenced by mechanisms similar to those influencing the duration of the silent period (123, 137, 269, 325, 332). However, because the cortically evoked MEP amplitude depends upon composite cortical and spinal excitability whether or not it is evoked in the SP and recent work by McNeil et al. suggests that the term long-interval inhibition (LII) may be a more accurate label for this ratio (214-216, 218). During the performance of sustained submaximal contractions where subjects were asked to maintain a consistent level of voluntary EMG activity (as opposed to force output), the amplitudes of the CMEP evoked in the SP (CMEP in SP) and the MEP evoked in the SP (MEP in SP) declined in parallel to each other to values well-below pre-fatigue measures (214). Collision experiments have demonstrated that MEPs and CMEPs are transmitted in the same axons of the corticospinal tract, therefore it is practical to compare the two responses during the SP to differentiate cortical relative to spinal motoneuron adaptations as fatigue develops (46, 141, 206, 311, 327, 342) as opposed to the MEPs from the motor cortex having a greater decline, the motor cortex is not actively inhibited during sustained, submaximal contractions. Instead, they propose that the motoneurons become progressively resistant to stimulation as the task progresses suggesting that changes in LII as well as SP duration are more likely due to decreased motoneuron excitability rather than increased intracortical inhibition (214). Follow up studies investigating the influence of
vibration (to modulate ia afference (215)) and intramuscular saline (to modulate group III and IV afference (208)) on motorneuron firing rates during fatigue provide evidence to support that intrinsic motorneuron adaptations are most likely the dominant mechanism mediating the decline in spinal excitability, as opposed to changes in synaptic input from peripheral afference (e.g., Figure 4) (124, 208, 214-216, 218).

**Findings from the Force-Matching Position-Matching Paradigm**

Studying the differences in neurophysiologic adjustment between force-matching and position-matching tasks has provided valuable insight into the spinal mechanisms that limit the duration of sustained submaximal contractions. The difference in load compliance requires that individuals attend to distinct performance feedback variables during each task, either to the force output (*force-matching task*) or to the joint angle position (*position-matching task*) (Figure 5) (152, 202). Over the past 10 years, it has been well documented that the time to task failure for sustained contractions performed with the elbow flexors at a submaximal intensity up to 30% of maximum force, under otherwise identical task demands as listed above, is nearly twice as long for the force-matching task compared to the position-matching task, yet the amount of mechanical work performed by the muscle and the amount of muscle fatigue (i.e., the decline in maximum force output at task failure) are the same for the two tasks (16, 17, 152, 153, 168, 201, 265, 286, 288-290, 338).

The shorter duration position-matching task is typically associated with a faster rate of increase in voluntary EMG amplitude that, at task failure, is equivalent to the EMG amplitude attained at task failure for the longer duration force-matching task (106, 147, 201, 289). The difference in task duration between the two tasks has been
associated with lower motor unit recruitment thresholds and faster recruitment of the motor pool during the position-matching task in combination with greater slowing and greater variability in single motor unit discharge rates compared to their recruitment and discharge rates during the force-matching task (17, 104, 201, 226, 228). Therefore, when the elbow flexors perform the position-matching task, the same amount of muscle fatigue and the same amplitude of voluntary EMG develop as in the force-matching task, but they manifest in a shorter period of time and are associated with both more rapid recruitment of the motor pool and greater adjustments in motor unit firing rates (13, 17, 104, 226, 228).

However, while most common, the paradigm is far from ubiquitous and has several caveats. The magnitude of difference in task duration for the force-matching task over the position-matching task for extremity muscle groups has been found to depend upon: 1) the intensity of the submaximal contraction (104, 201, 288); 2) the posture of the limb and the body (286, 290); and 3) the amount of proximal stabilization and limb support provided during task performance (32, 265, 338) (Figure 6). The effect of each of these conditions is to reduce and even eliminate the difference in TTF between the two tasks because each condition has been found to influence the total amount of muscle activation required by not only the primary movers, but also synergists, accessory muscles and postural stabilizers. Recently, one study evaluating the trunk extensors reported that the position-matching task was significantly longer than the force-matching task (321).

Studies investigating the differences in neurophysiologic adjustments between the force-matching and the position-matching tasks have provided valuable insight into the spinal mechanisms that limit the duration of sustained submaximal contractions. The
key pieces of evidence discovered to date that demonstrate spinal mechanisms contribute to the shorter task duration of the position-matching task are 1) a greater reduction in the H-reflex amplitude (a global index of spinal excitability) during the position task (16, 168) combined with B) no decline in 1a pre-synaptic inhibition by descending inputs as measured in the conditioned H-reflex (an indirect index of pre-synaptic inhibition) when compared to the longer duration force-matching task (where 1a pre-synaptic inhibition was found to decrease) (17). To date, only one study has investigated the differences in supraspinal excitability between the force-matching and position-matching tasks using single pulse TMS (168). In this study, which also identified the changes to the H-reflex amplitude, non-significant differences were observed in the rate of increase in the single-pulse MEP amplitude with the longer duration force-matching task having a greater MEP amplitude at task failure compared to the shorter duration position-matching task. The SP duration increased significantly but only for the longer force-matching task (168). Contrary to previous work, there was no difference in the rate of increase in EMG amplitude between the two tasks as the EMG amplitude at task failure was greater for the longer force-matching task suggesting insufficient motor unit recruitment contributed to early task failure during the position-matching task (106). The results from this study, combined with those previously reported about the differences in recruitment threshold and discharge rates of single motor units during both tasks, have been interpreted to mean that the position-matching task is limited by decreased facilitation of the motoneuron pool from peripheral afferents due to sustained or even increased pre-synaptic inhibition of the 1a afferent by descending inputs in order to manage force fluctuations as opposed to intrinsic changes to the motoneuron itself (13, 104).
Taken together, the cited data from the previous experiments about the decreases in spinal motoneuron excitability that occur during sustained submaximal contractions as well as the differences in H-reflex excitability between the force-matching and position-matching tasks provide compelling evidence that spinal mechanisms are largely responsible for not only task failure in sustained submaximal contractions but also for the shorter duration of the position-matching task (17, 104, 168, 214). These changes could be due to both intrinsic adaptations of the motoneuron membrane (214) and/or to task-specific differences in the amount of facilitation available from peripheral afference as the tasks progress (17, 104, 168). The contribution of supraspinal mechanisms, and especially changes in the excitability of intracortical facilitatory and inhibitory circuits, remain largely unexplored in studies of task failure. More significantly, it remains unknown how supraspinal and intracortical excitability change relative to decreasing spinal excitability as the nervous system attempts to maintain sufficient voluntary drive to the motor pool to sustain muscle activation and force output during submaximal contractions.

**Neurophysiologic Methods to Measure and Manipulate Excitability**

Electromyography

Skeletal muscle fibers produce force and allow for motor acts via the excitation-contraction coupling processes (199). As such, skeletal muscle fibers are both electrical and mechanical in nature. The electrical activation of muscle fibers is under direct control of the nervous system, specifically the α-motoneurons which serve as the final common pathway to muscle fibers, and integrate inputs from descending pathways, spinal cord interneuron circuits, and peripheral sensory afferents. Electromyography (EMG) is the recording and analysis of the electrical activity from the muscle fiber membrane that initiates the mechanical activity of the muscle (14). Throughout its long and storied history EMG, as a technique, has been used for a wide-variety of purposes. For example, EMG has been used to study the degree and timing patterns of muscle activation associated with voluntary movement in exercise and ergonomics research, and has been used to assess the physiological function of both the nervous and muscular systems. The former approach commonly involves recording the EMG response to evoked contractions elicited at different spatial locations along the corticospinal pathway which has proven useful for clinical diagnostic applications as well as for developing a better basic understanding of the physiological properties of the neuromuscular system.

The historical underpinnings of EMG date back more than 300-years. During the 17th century, Italian physician Francesco Redi documented the connection between muscles and the generation of electricity when he discovered that specialized muscles of Torpediniformes fish (e.g., electric ray fish) were capable of producing electric discharges (14). At the end of the 18th century, Italian physicist and physician Luigi
Galvani demonstrated that electricity could directly initiate muscle contraction (122), and by the end of the 19th century French physiologist Etienne-Jules Marey had recorded the electrical activity associated with voluntary muscle contraction and introduced the term ‘electromyography’ (Figure 7) (203). During the first half of the 20th century, as technology advanced and more electrodes were developed, the ability to detect and the quality of EMG signals gradually improved. During the latter part of the 20th century the utilization and understanding of EMG dramatically improved in association with the development of computers and data recording equipment that allowed for improvements in signal-to-noise ratio, signal recording and processing and computer simulation studies. Today, in the 21st century, EMG continues to be used clinically and innovative approaches using EMG to studying physiology continue to be developed (e.g., using transcranial magnetic brain stimulation to evoke motor potentials at the level of the motor cortex).

Today, the myoelectric signal can be readily and easily detected from within the muscle by an indwelling electrode (intramuscular EMG), such as a needle or fine wire, or non-invasively through the skin overlying the muscle with surface electrodes (surface EMG). Depending upon the type of electrode and task being performed, electrical potentials can be recorded from single muscle fibers- that are commonly referred to as single motor unit recordings because individual muscle fibers are under the direct control of individual motor units- or from the summation of superimposed motor unit action potentials. Regardless of the recording electrodes, the detected EMG signals are generally amplified, filtered and converted from their analog form to a digital signal prior to their analysis which can be both qualitatively and quantitatively analyzed depending on the scientific or clinical reasoning behind the given recordings. However, for virtually
all EMG methods, it is essential to recognize that the quantitative and qualitative characteristics of the recorded signal do not faithfully represent the original myoelectric signal (14, 111, 163-165). Accordingly, in this section I will review the biophysical basis of the EMG signal, measurement issues of EMG and signal processing techniques, and discuss current applications of electromyography in the 21st century. A single section can not do complete justice to fully understanding the complexities of EMG; rather, in this section I aim to provide an overview of the basic fundamental principles of EMG and its many uses. To fully appreciate, utilize, employ and understand electromyography one must understand these basic principles and applications, because as Carlo J. DeLuca, Ph.D., a pioneer of modern EMG, eloquently stated: ‘Electromyography is a seductive muse because it provides easy access to physiological processes that cause the muscle to generate force, produce movement, and accomplish the countless functions that allow us to interact with the world around us… To its detriment, electromyography is too easy to use and consequently too easy to abuse’ (83).

**Biophysical basis, measurement issues and EMG signal processing.**

**Biophysical basis of EMG.** Excitable cells, such as those of nerve and muscle, have the ability to generate a propagating wave of depolarization (e.g., an action potential) (211). During muscle activity, both voluntary and evoked (a.k.a. electrically stimulated), there is an electrical potential change in the surface membrane of the skeletal muscle cell that is transmitted as an impulse across the sarcolemma to the interior of the muscle cell via a complex system of tubules (160, 211). In muscle tissue, the action potentials are generated at the neuromuscular junctions which are located in the middle of the fibers; thus, action potentials are propagated in both directions towards the end of the fibers (103, 211). In muscle cells, transmembrane potential remains
relatively stable over time based on the relative proportions of sodium, potassium, and chloride in the extracellular and intracellular mediums (211). When a neural impulse propagates down an α -motoneuron (motor unit action potential) and arrives at the motor endplate a depolarizing wave spreads across the muscle cell that, following an electromechanical delay of ~ 25-50 msec (57, 248), results in force production from muscle fibers. For both voluntary and evoked recordings, the origin of the EMG signal is the electrical activity going across the muscle fiber membrane. Specifically, the EMG signal comprises the extracellular waveform manifestation of the transmembrane voltage reversal process resultant from the potentials generated from the active motor units (99). In the case of numerous motor units being activated within the electrodes detection area, the EMG signal represents the sum of these respective motor units (Figure 8) (14, 111, 165).

**Recording and measurement of the EMG signal.** The basic equipment required for modern EMG recordings consists of electrodes that measure the change in voltage conducted through the tissues due to the flux of sodium and potassium ions across the muscle cell membrane associated with propagating action potentials connected with amplifiers, bandwidth filters (commonly 10-500 Hz for surface recordings and 10-1,000 Hz for intramuscular recordings) and analog-to-digital converters or oscilloscopes to display and measure the respective signals. There are a wide variety of electrode choices today with each providing advantages and disadvantages. The appropriate choice of electrodes eventually depends upon what the scientist or clinician is wishing to measure and assess. For example, surface electrodes range in size from very large (30 cm diameter) to small (< 4-mm diameter), while fine wire intramuscular electrodes are extremely small (0.05-mm diameter). The smaller the diameter of the
respective electrodes, the smaller the detection area. Thus, surface EMG recordings represent the activity of multiple motor units, whereas the intramuscular recordings can represent the activity of multiple motor units, but can also be used to detect single motor unit activity during low-force contractions where a limited number of motor units are activated. With surface EMG recordings the amplitude of the EMG signal is often considered a global measure of motor unit activity. However, because the characteristics of the surface EMG signal depend on many other factors such as the membrane properties of the muscle fibers and the timing of the motor unit action potentials, the EMG signal reflects both peripheral (muscle) and central (nervous) properties of the neuromuscular system (Figure 9) (111).

Regardless of the recording method (surface versus intramuscular) the measurement principles of EMG are similar. EMG activity can be recorded using either a monopolar or a bipolar recording arrangement (Figure 10). Monopolar recordings consist of a single electrode being placed on or in the muscle of interest while a second neutral (reference/ground) electrode being placed at an electrically quiescent site (e.g., bone). Bipolar recordings consist of two electrodes being placed on or in the muscle of interest along with a neutral electrode. The bipolar configuration allows for the determination of the electrical difference between the two recording electrodes which results in detected signals that are not common between the two electrodes to be dramatically attenuated. The bipolar configuration is utilized more as these signals are generally more stable, although monopolar recordings are certainly appropriate under certain conditions when measurement of the absolute magnitude of the voltage is desired. The bipolar configuration results in a dramatic reduction in the amplitude of the recorded signal, and the degree of effect varies depending on the interelectrode distance.
(distance between the two recording electrodes) and their relative location to the neuromuscular junction (219). Specifically, the amplitude will be lower with a smaller interelectrode difference as the signals detected between the two electrodes will be more similar due to the spatial proximity, and if the two electrodes span the neuromuscular junction (innervation zone) the amplitude will be reduced as the electrodes will record symmetrical potentials propagating in each direction.

**EMG signal processing.** In most applications, quantification of the EMG signal is desired. Throughout history there have been a wide number of approaches used, but in general the basic goal of all is to quantify a given component associated with the amplitude or frequency characteristics of the EMG signal. First, consideration will be given to quantifying the ‘interference EMG’ signal, that is, the EMG signal resultant of the detection of many motor units being asynchronously and concurrently active during a task (the voluntary EMG signal) (Figure 11). Because the interference EMG signal varies in both the positive and negative direction the mean of the signal is zero. Thus, to quantify the amplitude of the signal mathematical processing is required. The following are brief descriptions of common methods for quantifying the amplitude of the interference EMG signal:

- **Average rectified EMG:** This quantification process involves full-wave rectifying the EMG signal (converting negative values to positive values), and then taking the mean of the selected time of interest.

- **Root mean squared EMG:** This quantification process involves calculating the square root of the mean squared values of the EMG signal at any given time point. It is also sometimes called the quadratic mean, and in cases where the baseline is at zero (as is desirable) this also simply represents the standard
deviation. This quantification approach does not require full-wave rectification as the calculation incorporates the squared values of the original interference EMG signal.

- **Linear envelope EMG**: The linear envelope approach involves passing a low-pass filter through the full-wave rectified signal. As such, it is a type of moving average indicator of EMG amplitude. Low-pass filter frequencies tend to range between 3-50 Hz, with a 10-Hz frequency being relatively common.

Regardless of the quantification method employed, interpretation of the absolute value of EMG amplitudes between different individuals is, in general, not appropriate as there are numerous non-physiologic influences on the EMG signal (e.g., adipose tissue dramatically attenuates the EMG signal; Figure 9) (111). To circumvent this issue- it is necessary to normalize the EMG amplitude of a given task of interest to a reference value. The most common normalization procedures for interpreting EMG amplitudes between individuals or groups of individuals during exercise or ergonomic tasks is to express the amplitude during the task to that associated with either a maximal voluntary contraction of the given muscle, or better yet- to the EMG signal in response to supramaximal electrical stimulation (commonly referred to as $M_{\text{max}}$ or CMAP [for compound muscle fiber action potential]). Analyzing the interference EMG signal in the frequency domain can also yield useful information regarding the signals characteristics. Perhaps the most common approach to describe the frequency characteristics of the EMG signal is to quantify the mean or median frequency of the power density spectrum (PDS) (134).

In addition to the aforementioned quantification approaches, there are several other methods that are more specific to other signal patterns. For example, EMG
signals evoked by stimulating along the corticospinal pathway (e.g., cortical stimulation, peripheral nerve stimulation) results in the generation of a relatively synchronous motor unit response that yields a summated, compound EMG signal (Figure 12A). Similarly, single motor unit recordings yield one given action potential of interest (Figure 12B). As such, in these cases it is common to quantify the peak-to-peak amplitude of the EMG signal or the peak of the rectified signal. Additionally, the simple calculation of time or duration is commonly applied to these signals (e.g., to determine the time interval between a single motor unit discharge to then calculate its discharge rate or the variability in motor unit discharge rate).

The many faces of EMG: applications and interpretation.

Kinesiological EMG.

- Muscle activation patterns. EMG can be used to determine whether a muscle is simply active (on) or inactive (off). It has been utilized in this fashion by biomechanists for decades to characterize the timing of muscle activation patterns associated with various activities of daily living (e.g., walking), exercises (e.g., cycling), and ergonomic tasks (e.g., lifting). For applications of this nature surface EMG is most commonly used, with the EMG onset typically being defined as the point when the EMG amplitude exceeds a given threshold level that is based on a set amount above baseline levels (e.g., 2-3 x greater than baseline noise for a specified amount of time) (320). It is also relatively common for the onset latency of certain muscles to be calculated relative to those of other muscles using similar criteria. In addition to using EMG to determine whether a muscle is active or not, it can also be used in a variety of other more sophisticated ways to evaluate muscle activation patterns during certain tasks.
For example, the relative degree (magnitude) of activation of a given muscle relative to a maximum contraction or other agonistic and antagonistic muscles can be determined (64, 67, 68, 147, 150), as well as whether EMG bursting is present (transient changes in the interference EMG signal during a constant force voluntary task) (64, 175, 176).

- **Single motor unit behavior.** Using concentric needle and/or fine-wire EMG it is possible to observe and record activity of single motor units especially during lower force (< 20% of maximal strength) contractions (Figure 12B). Fine-wire EMG is most commonly performed by threading two sterilized, insulated fine-wires with hooked ends that have exposed bare wire (0.05 mm) through a needle (25-27 gauge) that is inserted into a muscle. Following insertion, the needle is removed and the wires are left embedded in the muscle tissue with the small exposed ends serving as the recording electrodes until they are removed. Accordingly, the detection area of the fine wires is small, and studying the behavior pattern of individual motor units under various environmental and pathological conditions is possible. The most commonly quantified outcomes of single motor unit activity involves calculating the average time interval between a single motor unit firing to determine its discharge rate (84, 111), calculating the discharge rate variability (174, 223, 324), and defining motor unit recruitment thresholds (111, 274). In recent years investigations on single motor unit behavior have provided valuable insight on motor unit adaptations associated with motor control and aging (105).

- **Muscle fiber membrane properties.** The compound muscle fiber action potential (CMAP) (Figure 12A), recorded with either surface or intramuscular electrodes, is
of interest in studying changes in muscle membrane properties. In general, CMAP’s are elicited by delivering a single, supramaximal electrical stimulation pulse (0.5-1 msec in duration) to a peripheral nerve and recording the EMG response (65, 66, 291). The CMAP represents the summated electrical activity (arising from motor unit action potentials) resultant of the synchronous depolarization of the muscle fiber innervated by the depolarized nerve. Thus, the CMAP waveform is determined by the effectiveness of temporal and spatial summation which is affected by various factors. Changes in the CMAP’s amplitude is influenced by various factors such as the muscle fiber conduction velocity, number of activated motor units, intracellular, while the CMAP duration is mostly notably affected by temporal summation or action potential characteristics (165).

- **Spinal reflexes and motorneuron excitability.** The EMG activity associated with electrical stimulation of peripheral nerves has also been utilized to investigate *in vivo* excitability of the spinal reflexes. The most common approach to investigating spinal reflex function has involved measuring the H-reflex (339). The H-reflex is evoked by electrically stimulating the peripheral nerve which elicits action potentials in the sensory Ia afferents that propagate to the spinal cord where they give rise to excitatory postsynaptic potentials and activate α-motorneuron axons (Figure 13). As such, the amplitude of the EMG reflex response provides a global measure of spinal excitability as it can be modified by a number of factors such as presynaptic inhibition, the amount of la neurotransmitter released, and the excitability of the α-motorneurons. The H-reflex (along with the stretch reflex which is similar to the H-reflex except for its
induction thru rapid stretch of the muscle spindle fibers) have been and will continue to be powerful investigative tools that are centrally dependent upon EMG (1, 66, 298). Additionally, recent methodological developments indicate that magnetic and electrical stimulation at the level of the cervicomedullary junction can evoke single descending volleys that can be detected with EMG recordings (308). These cervicomedullary evoked potentials activate α-motorneuron axons primarily through a monosynaptic connection, and have been suggested to more directly assess α-motorneuron excitability in vivo without the confounds inherent in the H-reflex (205, 207, 308, 311, 342).

• Motor cortical function and excitability. Transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) can be used to activate the human motor cortex and assess the integrity of the central motor pathways (170, 269, 272). While both methods are non-invasive, TMS is also relatively painless and as such it has rapidly increased in popularity and use. TMS is based on the principle of electromagnetic induction, where a pulse of current passing through a coil placed over a person's head creates a rapidly changing magnetic pulse that penetrates the skull and induces a secondary ionic current in the brain (Figure 14A). When the stimulus intensity is of sufficient strength to depolarize a sufficient number of descending neurons a motor action will occur in the stimulated muscles and an evoked EMG response can be detected (commonly referred to as motor evoked potentials [MEP's]). While TMS was introduced in humans more than 20-years ago (12), its use to study human cortical physiology has dramatically increased since the turn of the century.
From an EMG methodological perspective MEP’s are generally recorded in the same fashion as other EMG signals, and to the untrained eye appear similar to any evoked potential (i.e., a compound EMG potential). However, because the EMG signal is being elicited at the level of the brain the physiological underpinnings are more complicated than those of other responses. For example, the CMAP characteristics are primarily ascribed to those of the muscle cell membrane, whereas MEP characteristics are influenced by the muscle cell membrane properties along with cortical and spinal excitability. Because there are many applications and outcomes possible with brain stimulation, a complete discussion is beyond the scope of this chapter, and readers are referred to excellent reviews on this topic area for more detailed information (170, 269, 272). However, we will briefly provide an overview description of some of the more common applications of TMS that incorporates the evaluation of and quantification of MEP’s recorded using EMG.

Motor threshold refers to the lowest TMS intensity necessary to evoke MEP’s in the target muscle when single-pulse stimuli are applied to the motor cortex. Motor threshold is generally defined as the lowest intensity required to elicit MEP’s of a set threshold level (e.g., > 50 µV peak-to-peak amplitude in at least 50% of trials at rest). Changes in MT can reflect changes at a variety of levels (i.e., the neural membrane, axonal electronic properties, the structure and number of excitatory projections onto the primary motor cortex, or upregulation of receptors in this region) and hence represents a global assessment of the membrane excitability of pyramidal neurons (200, 340). The MEP amplitude is also a commonly quantified variable. When TMS is applied to the motor cortex at an intensity above MT high-frequency indirect waves (I waves) are elicited in the corticospinal tract (90). These waves are modifiable by many mechanisms
including neurotransmitters (i.e., glutamate, GABA), modulators of neurotransmission (i.e., acetylcholine, norepinephrine, and dopamine), and interneurones contacted by corticospinal tract cells which all function to influence the amplitude of the MEP (Figure 14B and 14C) (200, 340). The silent period is a duration of electrical quiescence following an MEP when TMS is performed during a voluntary muscle contraction (Figure 14B) (75). There are several mechanisms thought to contribute to the silent period, with spinal inhibitory mechanisms thought to be active in the early part and the latter part being specifically cortical in its origin and most likely mediated by GABAergic and dopaminergic cortical inhibitory mechanisms (37, 120, 154, 341).

In addition to the aforementioned parameters evoked with a single TMS pulse applied to the motor cortex, coupling two pulses (paired-pulse TMS) can also be used to modify evoked MEP’s. Here, a conditioning stimulus is delivered in combination with a test stimulus at different intervals. Specifically, the intensity of a conditioning pulse can be set below motor threshold, and the test pulse is set to a suprathreshold level to study intracortical inhibitory and facilitatory processes. Paired pulses with inter-stimulus intervals (ISI’s) between 1–5 milliseconds results in short-interval intracortical inhibition and it provides a means of studying the activity of GABAₐ inhibitory circuits within the primary motor cortex (decreases the MEP amplitude in comparison to a control pulse), whereas ISI’s between 10-25 milliseconds results in intracortical facilitation and it allows for the study of intracortical facilitation that is controlled by GABAₐ and NMDA receptors (Figure 14B) (170, 269). Further, longer interstimulus intervals (50-200 milliseconds) with suprathreshold conditioning and test stimuli also results in inhibition (long interval intracortical inhibition) (170, 269). While the underlying mechanisms of long interval intracortical inhibition are not fully understood, it is thought that it is mediated within the
primary motor cortex rather than subcortical structures (231). Pharmacological studies indicate that long interval intracortical inhibition is mediated by GABA$_B$ receptors (212, 334), and is likely to be mechanistically linked to the silent period.

• **Mapping cortical function and reorganization.** Since 1991, TMS evoked motor responses have also been used to map brain functions in a direct stimulus/evoked response manner previously only possible during invasive surgery when the surface of the brain was exposed (71, 259, 304). During cortical mapping, a grid is placed on the scalp (e.g., a swim cap with a grid pattern) and the MEP amplitudes evoked at numerous sites are determined and the values are plotted to create a 3-dimensional representation between spatial location (x and y axis') and MEP amplitude (z-axis) (Figure 15) (317). These cortical maps provide three pieces of information: the total area on the scalp from which MEP’s for the target muscle were recorded, the “hot spot” for a muscle (the location where the largest MEP is observed), and the amplitude weighted center of gravity (COG) (336). The COG corresponds to the center of the TMS map or the scalp location/topography where the most neurons can be activated for a muscle or a movement that may or may not be equivalent to the hot spot (45, 317). Shifts in the location of COG (medial lateral or anterior posterior directions) are commonly suggested to demonstrate cortical reorganization or plasticity in response to injury, spontaneous recovery, or due to rehabilitation intervention (45, 73).

These cortical maps, while insightful, need to be interpreted cautiously. Although the stimulation protocol is similar to the principles used by Penfield, it is important to recognize that the maps created using this technique do not
compare in precision to maps created using intracortical microstimulation (45, 317). Animal studies have demonstrated that individual corticospinal neurons innervate several motor neuron pools and thus different muscles and corticospinal neurons that innervate a particular muscle are distributed among other corticospinal neurons projecting to different muscle combinations (249, 278, 295). This mosaic somatotopy of the cortex and the overlapping spinal cord projections in combination with the lack of stimulus precision with TMS means that multiple muscles will respond to a single TMS pulse delivered at one point on the scalp matrix (89, 317). The maps usefulness can be further confounded by electrode placement that permits cross talk, or signals evoked at the same time from other muscles, to interfere with the specificity and quality of the recorded MEP (336).

• General safety issues of TMS. According to the National Institutes of Health (NINDS branch: http://intra.ninds.nih.gov/Research.asp?People_ID=196) “Transcranial magnetic stimulation is safe and noninvasive means of getting electrical energy across the insulating tissues of the head and into the brain. A powerful and rapidly changing electrical current is passed through a coil of wire applied near the head. The magnetic field, oriented perpendicular to the plane of the coil passes virtually unimpeded through the scalp and skull. In the brain, the magnetic field produces currents in the induced electrical field lying parallel to the plane of the coil. These currents are able to excite axons lying in the plane of the induced field in a manner roughly analogous to direct cortical stimulation with electrodes. TMS has been used as a probe of cortical function in clinical and basic neurophysiology and as a means of altering cortical function.”
technique was first described in 1831, was first applied to humans in 1896 and in 1985 the first report of magnetic stimulation of the human motor cortex (the portion of the brain responsible for movement) was published (12). At the present there are more than 3,000 TMS machines in use throughout the world. The potential side effects are discussed below. It should be noted that the present study will uses ‘single pulse TMS’ or ‘paired pulse TMS’ (where a 1 or 2 pulses are periodically applied) as opposed to repetitive TMS (where multiple pulses [up to 25 per second] are applied repetitively over time at set frequency). The reason this important distinction is to be made is because the risk and safety papers that exist in the literature are based on repetitive TMS which poses much higher risks. 

Because the electrical current induced into the neurons is through a rapidly changing magnetic field (versus the direct application of an electric current as in electrical stimulation) TMS is a relatively painless event. Subjects typically describe TMS as ‘weird’ but not painful. The rapid deformation of the stimulating coil when it is energized produces an intense, but deceptively mild-sounding click. After exposure to single pulse TMS humans have shown a transient increase in auditory threshold (257). The incidence of tinnitus ranges between 0-11% (198). The muscles and nerves near the stimulating coil are activated by TMS. Thus, in susceptible individuals TMS may cause persistent muscle tension-type headaches and neck pain. The incidence of headaches with repetitive TMS has been reported to be between 10-28% in healthy individuals with the wide variability in incidence thought to be related to the stimulation site (with a higher incidence in the pre-frontal area [we are not stimulating in this area]) {Machii, 2006 #487). The incidence of neck pain is reported in the range of 3-42%
Again, it should be noted that with single pulse TMS these incidence should be considerably less. These side effects have been reported to respond well to acetaminophen. It should also be noted that these side effects have been observed in sham-stimulation studies (nine studies have reported this), and it has been speculated that these side effects may be related to the subject having to sit still during this procedure. Developing after TMS— but it is difficult to know if this was due to TMS per se. Perhaps the most dangerous side effect of TMS is the potential for a seizure to be induced. It should be noted that, single and paired pulse TMS has never been reported to induce a seizure in a healthy person. There are a few clinical cases where single pulse TMS induced secondarily generalized or partial motor seizures in patients with stroke or other disorders involving the central nervous system. It is generally thought that TMS induced seizures are related to the rate of stimulation (i.e. seizure induction with repetitive TMS, while still very rare [1.6% according to data collected at the NIH and reported by Wasserman, 1998 #184], is thought to become more likely with a higher stimulation rate). Impairments in cognition and mood are uncommon (never reported in single pulse TMS studies, and a 0-5% incidence rate in repetitive TMS studies). These effects are thought to be related to stimulation of specific portions of the brain (i.e. stimulation of the left prefrontal cortex has been reported to induce crying and laughter).

**EMG and muscle fatigue.** Skeletal muscle fatigue has fascinated physiologists for more than a century (225). While muscle fatigue is associated with a variety of changes in physiological properties—many of these properties are electrophysiological in nature (or at a minimum manifest themselves with acute adjustments in electrophysiological properties) (82, 134, 219). For example, during a sustained,
submaximal fatigue task a gradual increase in the amplitude of the interference EMG signal is observed that is primarily due to an increase in the motor units recruited as fatigue progresses (Figure 16A) (14). Additionally, during a sustained contraction the depolarization and propagation of muscle fiber action potentials are modified. These modifications produce time-dependent changes in the surface EMG signal, which result in a shift of the power density spectrum to the lower frequencies (spectral compression) (Figure 16B) (134). Spectral compression during a fatiguing submaximal contraction has been attributed to a number of underlying physiological factors. One of the most popular hypotheses states that the decrease in muscle fiber conduction velocity seen with fatigue influences the power density spectrum, resulting in spectral compression (100, 193, 194, 220). This is most likely due to an accumulation of metabolites (i.e., hydrogen ion and extracellular potassium) (24, 158, 316), reducing intracellular pH (39) and, thus, decreasing sarcolemma excitability. However, this explanation appears to be incomplete, as a disassociation between median frequency and conduction velocity is observed during ischemia and different types of muscular contractions (210, 344). In addition to the changes in the interference EMG signal that are of interest for the study of muscle fatigue, many of the evoked EMG responses described previously are altered. For example, there is evidence that fatigue decreases the CMAP (119) and prolongs the silent period (126, 313). As such, EMG is a valuable tool to assess electrophysiological manifestations of fatigue.

**Clinical applications of EMG.** EMG began to be widely used for clinical applications in the 1950’s, and today it is still commonly utilized in many fields of medicine including neurology, neurosurgery, physical therapy, and physical medicine and rehabilitation. In the clinical context, patients with symptoms suggestive of
neuromuscular pathology are frequently referred to a neurologist or a clinical neurophysiologist/ electromyographer who conducts a variety of tests using EMG. The term “EMG” is commonly used by physicians and healthcare professions to refer to these specific tests; however, as stated earlier- the term EMG should be used to simply refer to the recording of electrical activity from the muscle fiber membrane. These tests frequently involve both surface and intramuscular recordings from resting muscles, during voluntary contraction as well as when electrically evoked and the information (EMG characteristics and responses) can provide insight into the pathologic mechanism, severity, and anatomical location of certain diseases (80). Additionally, for the patient with a known neurologic diagnosis, EMG is frequently used to monitor progression, to predict long term potential for functional recovery, to evaluate response to therapy and to elucidate underlying mechanisms of recovery (132, 162, 258, 319). Depending upon the techniques used and the understanding of normal neuromuscular physiology, the source of change in the EMG signal can be localized to the muscle, neuromuscular junction, peripheral nerve, spinal nerve root, spinal cord, or supraspinal structure based upon signature alterations to the EMG signal (80, 296). Accordingly, it is imperative that clinicians also be familiar with the technical and non-neuromuscular physiological influences on the EMG signal in order to be certain that the differences identified in the recorded EMG signal are truly due to an underlying pathological process and not due to an artifact of the recording and analysis procedures (80, 307). Below we will briefly describe some of the most common electrodiagnostic EMG tests as well as several other EMG applications that are clinically relevant.

- *Nerve conduction studies.* One of the most common clinical uses of EMG is to study the conduction properties of the peripheral neuromuscular system (162).
These are frequently conducted to diagnose conduction disorders such as radiculopathies and neuropathies. Conduction of sensory, mixed and motor nerves are all commonly assessed, and in general utilize surface EMG recordings and peripheral nerve stimulation where the latency of evoked EMG signals (e.g., M-waves or reflex waves) are evaluated or stimulation is applied at two peripheral nerve locations and the temporal separation of the two actions potentials relative to the distance between the two stimulation sites is determined. However, it should also be noted that from a clinical perspective measurements of interest associated with nerve conduction studies typically extend beyond simple velocities and latencies and EMG signal amplitudes and durations are also of interest (162).

• **Needle EMG.** While we feel the term ‘needle EMG’ is inappropriate and too non-descriptive to truly be associated with a particular diagnostic test- it is nonetheless commonly used to describe a relatively subjective examination where EMG is recorded and evaluated for spontaneous and insertional activity, as well as the general appearance and characteristics of single motor unit action potentials during low level voluntary contractions (162). In normal, healthy muscle there is little or no EMG activity under resting conditions; however, in certain disorders (e.g., ALS, polymyositis) spontaneous activity at rest and abnormal action potentials during contraction may be observed (80, 101, 162). Additionally, this clinical test can be suggestive of denervation which is commonly associated with increased EMG fibrillations, positive sharp waves, and giant motor unit action potentials (80). While the needle EMG recordings can provide valuable clinical insight, it should be noted that one of the limitations of
these examinations is its dependence of the skill of the examiner as many of the outcomes are qualitative in nature.

- **Motor unit number estimation.** Quantifying the number of motor axons innervating a muscle (or muscle group) is of clinical importance for diagnosing and monitoring the progression of a number of neurological diseases (e.g., amyotrophic lateral sclerosis, spinal muscle atrophy). However, counting individual motor units (as would be done in cadaveric studies) is not possible in vivo, but through the utilization of EMG recordings estimates can be attained. This EMG technique, referred to as motor unit number estimation (MUNE) is calculated based on a simple ratio of the CMAP divided by the average surface motor unit potential (40). The ‘surface motor unit potential’ is quantified by stimulating the peripheral nerve at different intensities and evaluating the response variability of different groups of axons. There are a number of technical issues and limitations associated with the methods of the MUNE technique, and for a further discussion of these the reader is referred to Bromberg (40).

- **Biofeedback.** Another clinical use of EMG is to provide biofeedback—generally based on the degree of surface signal amplitude—as an indicator muscle activity. The use of EMG biofeedback has been used for a wide variety of different applications mainly aimed at either ‘teaching’ people how to exert voluntary control of their muscles (both to increase and decrease the muscle activation depending on the rationale for the EMG biofeedback). For example, it has been used in urinary incontinence programs to provide feedback to patients regarding the activation of their pelvic floor muscles (77). Additionally, it has been used in
ergonomic applications to provide feedback to patients to reduce the overall EMG activity of their trapezius muscles during occupational computer work (143).

- **Changes in muscle activation patterns associated with movement dysfunction.**
  
  As described above in the section *Muscle activation patterns*, clinicians use both surface and needle electrodes to detect integrated EMG signals to detect changes in activation patterns of multiple muscles during functional activities such as gait and shoulder elevation (155, 335). The relative onset/offset timing, duration, and sequences of muscle EMG activity can be compared to data generated by biomechanists to identify the muscular sources for the observed kinematic changes during motion which could be caused by musculoskeletal injury or pain (72, 83, 320).

- **Other clinical applications.** There are numerous other clinically relevant applications using EMG that have yet to gain widespread use. For example, clinical applications of transcranial magnetic stimulation have begun to gain attention in recent years for a variety of possibilities, including its use to monitor injury to central motor pathways during surgery by examining changes in MEP’s (49), as well as diagnosing diseases such as ALS, myelopathies, and multiple sclerosis through the evaluation of the evoked EMG responses (e.g., silent period, central motor conduction time) (61). TMS methods are frequently used to predict the potential for functional recovery early after hemispheric stroke, especially in the upper extremity and hand (63, 73). Even when the patient presents with significant clinical deficits, the presence and amplitude of an MEP in the acute phase has a high positive predictive value for restoration of function whereas absence of or prolonged MEP latency and conduction times predict
poor return of hand motor ability (45). Additionally, EMG has been, and will continue to be evaluated as a potential marker for other diseases and disorders as illustrated by the recent work in evaluating EMG amplitude of the submentalis muscle in sleep behavior disorders (112). Thus, it seems that the continual growth and expansion of clinical applications of EMG will continue to be developed in the 21st century.

**Perils of EMG.** EMG has been used to expand our knowledge base regarding human movement and neuromuscular disorders for many years. This chapter provides an overview of the fundamentals for a basic understanding and appreciation of electromyography and its many applications. However, we must caution that there are many pitfalls and perils associated with these applications that must be understood for appropriate research design and data interpretation (14, 108, 111). For example, as stated earlier, the absolute amplitude of EMG signals is of trivial consequence when comparisons are being made between individuals, muscles and even over time (189). Even normalizing the EMG to a maximal voluntary contraction has limitations due to the assumption of this normalization technique assuming that the maximal voluntary contraction is not associated with any failure in central activation. One approach to circumventing this issue would be to normalize the EMG data to an electrically stimulated maximal contraction, but this requires that a peripheral nerve be accessible (as direct muscle stimulation will result in too much artifact to allow for recording stable CMAP’s) which is not feasible in many muscles. Other perils of using EMG to evaluate muscle activation patterns are the difficulty in dealing with movement/wire artifact, issues related to cross-talk (signals detected from nearby muscles), as well as issues surrounding interpreting EMG during dynamic tasks where the detection area of
underlying muscles changes in relation to surface electrodes located on the skin as the muscle shorten and lengthens during movement (108). Further, day-to-day variation in electrode placement, temperature and state (state-dependency) can confound longitudinal studies. However, despite its limitations, when used appropriately EMG can provide a window into the state of the human neuromuscular system.

**Transcranial Direct Current Stimulation**

Transcranial Direct Current Stimulation (tDCS) involves the application of weak (1.0-2.0 mA) direct electrical currents to the brain through two sponge electrodes on the surface of the skull (260). tDCS differs from other brain stimulation techniques such as transcranial magnetic stimulation (TMS) because it does not stimulate axons and cause them to discharge like TMS does (33). Instead the current delivered to the exposed tissue temporarily modifies the resting membrane potential by either depolarizing or hyperpolarizing it, which then alters spontaneous neuron activity. Hence, tDCS can be considered a neuromodulatory intervention that is polarity, duration and intensity dependent (235).

tDCS has become one of the major tools to induce neuroplastic alterations in cortical excitability in over the past few decades in neurologically injured and non-injured populations (145, 241). Transcranial application of weak direct currents is known to induce intracerebral current flow which is large enough to reliably modulate human cerebral cortical function inducing focal and prolonged but still reversible shifts of cortical excitability (235). tDCS differs from other brain stimulation techniques such as TMS because it tDCS does not stimulate axons and cause them to discharge like TMS does (Figure 17) (33, 331). Instead the current delivered to the exposed tissue temporarily
modifies the resting membrane potential by either depolarizing or hyperpolarizing it, which then alters spontaneous neuron activity. Hence, tDCS can be considered a neuromodulatory intervention (235).

The actual amount of current that reaches the brain tissue as well as the spatial focality is influenced by the tissue properties of the scalp, the skull, the folds/gyri on the brain surface, and the cerebrospinal fluid (79, 127, 331). Therefore, individual variability in these factors will affect both the magnitude and spatial distribution of the cortical electric field (79). Using a spherical model of the head, Miranda et al. 2006 determined that up to 50% of the current is diverted through the scalp. The remainder flows between the two electrodes with the current density distributed homogeneously under the electrodes, with the highest under the anodal electrode (assuming current flows from the anode to the cathode using 25 cm² electrodes and a current of 2.0 mA).

The effects and safety of brain stimulation depends on the type of device used, the strength of current, the size of the electrodes and the duration of the stimulation (127, 266). It is not possible to directly measure or quantify the amount of excitation or inhibition induced by the delivered dosage of tDCS. The safety cutoffs for stimulus delivery (current density mA/cm² and total charge mA/cm² x duration) were originally determined from animal studies with the intent of protecting the brain tissue from damage and in practice are several fold lower than the limits required (238). As reported by Nitsche et al 2008, these parameters have been found to not (1) cause heating effects under the electrode, (2) elevate serum neurone-specific enolase level which is a sensitive biomarker of neuronal damage, and (3) result in changes of diffusion weighted or contrast-enhanced magnetic resonance imaging (MRI), EEG activity, or cognitive distortion. Additionally, as of 2008 these protocols had been tested in more than 2000-
3000 subjects in laboratories worldwide and no serious side effects were reported except for a slight amount of itching under the electrodes, and rarely occurring headaches, fatigue, and nausea (Nitsche, 2008 #144).

Safety and efficacy studies have been reported for the tDCS protocol and delivery device characteristics that were used in this study (15, 266). The effects of tDCS are ascertained in two ways in humans: 1) through changes in the amplitude of motor evoked potentials (MEPs) evoked by TMS both during and after the stimulation (241) and 2) through changes in behavioral performance (15). Because tDCS dosage is influenced by the amount of current delivered per surface area (current density) and the electrode/skin impedance, it is recommended that the stimulation device be a “current controlled” device rather than a voltage controlled device (260). Because the current strength determines the intensity of the electrical field in tissue, a constant voltage device could result in unwanted increases in current strength, if resistance decreases or impedance increases (235).

Nitsche & Paulus (2001) conducted a feasibility study to determine if tDCS can be applied to induce changes in cortical excitability that outlast the period of stimulation. They report that 5- and 7-minute tDCS resulted in after-effects lasting for no longer than 5 minutes, tDCS from 9 to 13 minutes resulted in elevations of MEP amplitudes [i.e. measures of corticospinal excitability] from 30 (9-minute tDCS) to 90 (13-minute tDCS) minutes. These elevations are in the range of about 150% above baseline values. (241). Since this landmark 2001 study, several protocols have been applied both before and during motor training (15, 33, 145). The maximum amount of time reported as safe to use—and also that is typically used in motor training studies with both healthy and neurologic patients—is 20 minutes (15).
In a 2007 study by Poreisz et al., they analyzed data from studies conducted in their laboratories that included 567 tDCS sessions involving 102 participants. They reported that: “None of the subjects requested the stimulation be terminated, or needed any medical intervention during or after the end of tDCS.” (266, p. 210). The most common adverse event was “a mild tingling sensation” reported by 70.6% of the subjects during and 7.8% after the stimulation. Moderate fatigue was the second most frequent effect (35.3% during tDCS and 22.6% after tDCS). A light itching sensation directly under the electrodes was reported by 30.4% during and by 14.9% after the stimulation. 21.6% said they felt a slight burning and 15.7% reported a mild pain sensation under the electrodes during the stimulation. Visual sensations when the tDCS current was switched on and off occurred in 10.8%. 17.7% of the volunteers found the stimulation mildly unpleasant.

It is important to note that while side effects may occur, they are unlikely. A double-blind, sham-controlled study conducted by Gandiga et al. in 2006 found that 20 minutes of tDCS and 30 minutes of Sham stimulation (stimulator is briefly turned on and then the current is turned off after 30s) caused a similar level of discomfort such that the two conditions could not be distinguished by study participants and investigators. tDCS has been found to be easy to use to conduct placebo stimulation-controlled studies because, with the exception of a slight itching sensation and visual flashes, subjects rarely experience sensations related to the treatment (235) and has become a preferred strategy for non-invasive brain stimulation studies (33).
CHAPTER 3: CORTICAL AND SPINAL MECHANISMS OF TASK FAILURE OF SUSTAINED SUBMAXIMAL FATIGUING CONTRACTIONS WITH DIFFERENT LOAD COMPLIANCES

Abstract

Evidence indicates that task failure for sustained submaximal contractions is associated with a faster rate of motor unit recruitment by descending supraspinal drive to compensate for the decline in spinal excitability. However, these findings do not rule out that supraspinal mechanisms influencing descending drive (i.e., intrinsic motor cortex excitability and voluntary drive “upstream” to the motor cortex) can also contribute to task failure. Therefore, the purpose of this study was to compare the adjustments in cortical and spinal excitability during the performance of two fatigue tasks with identical mechanical demands but different task durations (i.e. the force-matching and position-matching tasks) in order to further delineate the contribution of supraspinal mechanisms to task failure. Ten healthy volunteers (5 men and women; 24.5±3.10yrs) performed the force-matching and position-matching tasks at an intensity of 15% of maximum voluntary contraction (MVC) with the elbow flexors on two separate days (6.5±1.1 days). Single-pulse transcranial magnetic stimulation (TMS), paired-pulse TMS, paired cortico-cervicomedullary stimulation, and electrical stimulation of the brachial plexus were delivered in a sequence of 6 different stimuli at baseline and then every 2-3 minutes throughout the duration of each fatigue-task. Performance variables included time to task failure (TTF), amount of muscle fatigue (%MVC decline) and ratings of perceived exertion (RPE). Neurophysiologic variables quantified from electromyographic
recordings of the evoked potentials included the peak-to-peak amplitude, rates of change, and normalized ratios (as % of pre-fatigue baseline) for the 1) motor evoked potential (MEP) amplitude, 2) silent period duration (SP), 3) MEP elicited during the corticospinal silent period, 4) paired pulse MEP ratio of long interval inhibition (LII), 5) paired pulse MEP ratio of short intracortical inhibition (SICI), 6) paired pulse MEP ratio of intracortical facilitation (ICF), 7) cervicomedullary potentials (CMEP) elicited during the corticospinal silent period, and 8) maximum compound muscle action potential (M_max).

Contrary to expectations, the TTF for the force-matching task was 42% shorter (17.5±7.9 min) than the position-matching task (26.9±15.11 min; p<0.01, ES=0.60); however, as expected, both tasks caused the same amount of muscle fatigue (MVC % decline; p=0.59) and changes in RPE. There were no differences found between the force-matching and position-matching tasks for the amount or rate of change for the eight neurophysiologic outcome variables (p>0.05). Therefore, during both fatigue-tasks, a similar amount of increase in corticospinal excitability occurred (MEP: force-matching 26±25%M_max, position-matching 25±19% M_max, p<0.01, ES=0.54; and MEP elicited in the silent period: force-matching 19±32%M_max, position-matching 12±19%M_max, p=0.04, ES=0.29) coupled with a similar decline in spinal excitability (CMEP elicited in the silent period: force-matching -24±20M_max, position-matching 19±27%M_max, p=0.01, ES=0.44).

This suggests that the motor cortex compensates for changes in spinal excitability until a critical amount of change develops and, without drive to the motor cortex, the task fails. Intracortical inhibition in the motor cortex decreased (SICI ratio: force-matching 0.81±0.24, position-matching 0.70±0.22, p<0.01, ES=0.31); however, both intracortical facilitation (ICF ratio: force-matching 1.17±0.21, position-matching 1.04±0.09, p=0.36, ES=0.11) and upstream excitation of the motor cortex (MEP vs. MEP elicited in the silent
period in the LII ratio: force-matching 0.75±0.41, position-matching 0.57±0.34 \( p=0.15 \), ES=0.22) remained constant. These results indicate that the decrease in intracortical inhibition exceeded the amount of change in both intracortical facilitation and excitation delivered to the motor cortex from upstream drive. Although there were no task specific differences in changes of corticospinal and spinal excitability due to fatigue, together, these results suggest that as fatigue develops prior to task failure, the increase in corticospinal excitability observed in relationship to the decrease in spinal excitability results from a combination of decreasing intracortical inhibition and constant levels of intracortical facilitation and upstream excitability that together eventually fail to provide the excitatory input to the motor cortex necessary for descending drive to overcome the spinal cord resistance, thereby contributing to task failure.

**Introduction**

Fatigue is an expected and normal physiologic reaction to sustained and to intense activity (123, 169). Muscle fatigue is defined as the gradual decline in maximum muscle force capacity that occurs with the performance of sustained or repetitive contractions (25, 28, 107, 123). It can be viewed as the development of activity dependent weakness relative to pre-activity strength measures that resolves with rest (94, 123). Task failure, on the other hand, is the point in time when the force output required for successful task performance, either maximal or submaximal, can no longer be sustained in the manner demanded by the activity (13, 148). Therefore, during sustained submaximal intensity contractions, muscle fatigue, as measured by the decline in maximal force output relative to pre-task values, will be present prior to task
failure but task performance will continue for a period of time without appreciable
disruption (13, 23, 28, 106, 123). As the duration of the submaximal task increases,
muscle fatigue will progress to a degree such that it will interfere with the capacity to
sustain the precise amount of submaximal force output required (e.g. force fluctuations
around the target force disrupting accuracy of performance) and eventually prohibit
effective task performance, thereby contributing to task failure.

The physiologic mechanisms behind the declining force output that characterize
muscle fatigue and prohibits indefinite task performance have been attributed to
impairments in the contractile capacity of the muscle and also to inadequate
maintenance of neural activation of the muscle; however, the relative contributions of
both systems are known to be task specific (28, 102, 107, 123). The combination of the
mechanical demands of the task including intensity (maximal or submaximal), duration
(repetitions or sustained), and mode (dynamic or static) of contraction as well as the
muscle group involved, joint angle, limb posture and proximal stabilization of the body
during task performance together will stress differing regions of the neuromuscular
pathway in order to sustain the required force output (21, 106, 123, 147, 202, 338). In
general, it has been shown that the nervous system’s failure to maintain sufficient
activation of the muscle is a significant contributor to the decrease in force output and to
the eventuality of task failure in sustained submaximal contractions as compared to
maximal contractions (13, 21-23, 123, 125, 129, 135, 196, 303). Additionally, neural
mechanisms that limit the duration of sustained submaximal contractions have also been
shown to vary based upon the compliance of the load used during task performance
(e.g., exert a constant force against a rigid restraint or to hold an equivalent inertial
weight) (13, 104, 106, 202, 288). The difference in load compliance requires that
individuals attend to distinct performance feedback variables during each task, either to the force output (force-matching task) or to the joint angle position (position-matching task) (202). Over the past 10 years, it has been well documented that the time to task failure for sustained contractions performed with the elbow flexors at a submaximal intensity up to 30% of maximum force, under otherwise identical task demands as listed above, is nearly twice as long for the force-matching task compared to the position-matching task, yet the amount of mechanical work (i.e., force x distance) performed by the muscle and the amount of muscle fatigue (i.e., the decline in maximum force output at task failure) are the same for the two tasks (104, 202, 288).

Neurophysiologic studies investigating the neural mechanisms responsible for the observed changes in motor unit behavior associated with task failure have sought to delineate the segmental contributions from both supraspinal and spinal regions. The excitatory drive to the muscle by the motoneurons can be modulated by supraspinal synaptic inputs from descending pathways, spinal inputs from interneurons and peripheral afferents and also by intrinsic changes of the motorneuron itself during sustained fatiguing contractions (17, 98, 106, 123, 196, 247). Evoked potentials elicited using transcranial magnetic stimulation (TMS) of the motor cortex, electrical stimulation of the spinal tracts or the peripheral nerve provide evidence about the state of excitability or responsivity of the nervous system to external stimulation during task performance and have been suggested to provide an indirect assessment of the amount of nervous system activation (8, 262, 270, 283). It is important to recognize that this experimental strategy does not directly assess the amount of activation provided to the motor pool from the motor cortex or spinal afferents rather it examines the state of excitability or responsiveness of the nervous system to external stimulation at the time of stimulation...
from which interpretations about the state of activity are made (283). However, when cortical, spinal and peripheral measures are evoked concurrently in real-time and also during different states of activation (i.e., fatigued vs. non-fatigued, resting vs. active) inferences about the state of activation in a region are more plausible (214, 218, 269).

The motor evoked potential (MEP) amplitude evoked by TMS to the motor cortex provides a composite index of excitability of the entire voluntary motor pathway, as the size of the response depends upon both cortical and spinal excitability (123, 133, 136, 170, 232). The amplitude of a cervicomedullary-evoked potential (CMEP) elicited by electrical stimulation at the cervicomedullary junction to the spinal cord tracts in order to transynaptically activate the motor neuron pool is regarded as a segmental index of spinal alpha-motorneuron excitability (308, 311, 326, 327). The CMEP response latency suggests that the evoked response reflects a monosynaptic relationship between the corticospinal tract and the motorneuron without influence from pre-synaptic inhibition of the corticospinal tract (206, 327). Conversely, the H-reflex, another common neurophysiologic outcome used to assess spinal excitability, is evoked by stimulation of the la afferent fibers in the peripheral nerve (104, 232, 263). The amplitude of the H-reflex is influenced by not only alpha-motorneuron excitability but also by the excitability of the la fibers, which can be modified by presynaptic inhibition of the la terminals at the reflex synapse. Therefore, compared to the CMEP, the H-reflex is used as an index of global spinal excitability that represents the responsivity of both the motorneuron and the spinal reflex pathway (104, 263).

During fatiguing submaximal contractions, much like the voluntary EMG signal, the amplitudes of both the MEP and the CMEP, when normed to the maximum compound muscle fiber action potential evoked by supramaximal stimulation of the
peripheral nerve ($M_{\text{max}}$), have been shown to increase as task duration increases (123, 142, 168, 218, 299). This increase in responsiveness to the external stimulus has been attributed to enhanced voluntary drive both to and also from the motor cortex (in the case of the MEP) and to increased descending drive to recruit motorneurons (in the case of the CMEP) in order to sustain neural output and thus muscle activation (214, 218, 279, 283, 299). These findings are consistent with the evidence of progressive recruitment of new, unfatigued motor units to sustain force output and increase the voluntary EMG amplitude as reported by single motor unit studies (3, 17, 129, 196, 228).

Conversely, the H-reflex amplitude, has been found to decrease throughout the duration of sustained submaximal fatigue tasks (98, 168) indicating that either the motorneuron itself as become less excitable or that there is a depression in the excitability of the sensory afferent synapsing on the motorneuron. Because of the synaptic relationship used to evoke the H-reflex, this progressive decline in H-reflex amplitude is currently thought to be more likely due to depression of the peripheral afferent axon’s excitability from modulations in pre-synaptic inhibition (17, 104, 168) as opposed to adjustments in motorneuron membrane properties that have been shown to occur during prolonged activation (166, 247). These findings, taken together, suggest that the source of enhanced excitatory drive to recruit more of the motorneuron pool during sustained submaximal contractions most likely comes from supraspinal descending inputs that must overcome a depression in spinal excitability that results from motorneuron resistance and/or disfacilitation from peripheral afferents in order to provide sufficient muscle activation needed for task performance. Nevertheless, these finding do not rule out the potential that supraspinal mechanisms influencing descending drive, including
motor cortex excitability and voluntary drive “upstream” from the motor cortex, can also contribute to task failure.

When a single suprathreshold TMS pulse is delivered to the primary motor cortex during a voluntary contraction, the MEP is followed by an electrical silent period, which is observed as a transient cessation of ongoing EMG activity (62, 332). The duration of the silent period when measured during a non-fatiguing voluntary contraction has been attributed to an initial short period of spinal refractoriness, as seen after maximum stimulation to the peripheral nerve, that recovers (~50msec) combined with a longer period of cortical inhibition of volitional drive to the motor cortex and withdrawal of corticospinal input to the spinal motorpool (up to ~200 msec) (62, 120, 154, 252, 279). During fatiguing contractions the duration of the silent period has been demonstrated to increase, with those increases attributed to enhanced intracortical inhibition based upon the mechanisms proposed during non-fatiguing contractions (19, 104, 123, 310, 312). The interpretation of this finding during fatiguing contractions has posed somewhat of a conundrum in that despite an increase in excitability as measured by the MEP and CMEP amplitudes, there also appears to be a concurrent increase in intracortical inhibition as measured by a longer SP (19, 104, 123, 292, 293). This raises the question as to the segmental contribution of the motor cortex and also “upstream” inputs to the motor cortex to task failure (i.e. supraspinal failure) during sustained submaximal contractions (104, 123, 218, 310, 313). In other words, does active cortical inhibition develop during task performance and thus interfere with or limit the capacity of supraspinal structures to sustain sufficient excitatory drive to the motorneuron pool and thus contribute to task failure?
To more directly address supraspinal contributions to neural mechanisms of fatigue, paired-pulse TMS protocols, including short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), provide a strategy to more directly evaluate the excitability of intracortical interneuron networks within the motor cortex (90, 92, 93, 231, 270, 282, 284, 285). The effect of a subthreshold conditioning pulse that activates the cortical interneurons, on the MEP amplitude of a subsequent suprathreshold test pulse is compared relative to a single MEP. When separated by interstimulus intervals (ISI) of 2-5 msec, the evoked MEP amplitude decreases and the SICI ratio of the test MEP to the single MEP is less than 1.0 reflecting intracortical inhibition (179, 231). An ISI of 12-25 msec increases the test MEP amplitude and generally, the ratio is greater than 1.0, which is interpreted as representing intracortical facilitation (92, 270). These two measures of intracortical excitability have rarely been used to monitor the ongoing adjustments in intracortical excitability related to fatigue (20, 209, 330) and, to date, have not been employed during the performance of submaximal contractions sustained to task failure.

Recent work by McNeil et al. presents a technique to assess the excitability of the corticospinal system and the motorneurons independent of upstream voluntary drive to the cortex and descending drive to the spinal cord by evoking MEPs and CMEPs during the silent period (i.e. evoking MEPs and CMEPs during the period of electrical silence attributed to a temporary suspension in volitional activation and spinal refractoriness after a single suprathreshold TMS pulse) (214, 216, 218). In the non-fatigued state, the amplitudes of a MEP or a CMEP evoked in the SP are less than those evoked in the presence of voluntary activation such that a ratio of the SP evoked response to the single control pulse is typically <1.0 (216, 218). In addition, in the non-
fatigued state the MEP ratio is also less than the CMEP ratio suggesting the added presence of intracortical inhibition during non-fatigued performance (216, 218). The ratio of the MEP evoked in the SP (MEP in SP) to the single MEP is referred to as long-interval intracortical inhibition (LICI) and is thought to be influenced by mechanisms similar to those influencing the duration of the silent period (123, 137, 269, 325, 332). The cortically evoked MEP amplitude depends upon composite cortical and spinal excitability—whether or not it is evoked in the SP—and recent work by McNeil et al. suggests that the term long-interval inhibition (LII) may be a more accurate label for this ratio (214-216, 218). During the performance of sustained submaximal contractions where subjects were asked to maintain a consistent level of voluntary EMG activity (as opposed to force output), the amplitudes of the CMEP evoked in the SP (CMEP in SP) and the MEP evoked in the SP (MEP in SP) declined in parallel to each other to values well-below pre-fatigue measures (214). Collision experiments have demonstrated that MEPs and CMEPs are transmitted in the same axons of the corticospinal tract, therefore it is practical to compare the two responses during the SP to differentiate cortical relative to spinal motorneuron adaptations as fatigue develops (46, 141, 206, 311, 327, 342). McNeil and colleagues concluded that because the values for the cortical and spinal measures declined in parallel, as opposed to the MEPs from the motor cortex having a greater decline, the motor cortex is not actively inhibited during sustained, submaximal contractions. Instead, they propose that the motorneurons become progressively resistant to stimulation as the task progresses suggesting that changes in LII as well as SP duration are more likely due to decreased motorneuron excitability rather than increased intracortical inhibition (124, 214-216, 218).
Studies examining the differences in neurophysiologic adjustments between the force-matching and the position-matching tasks has provided valuable insight into the spinal mechanisms that limit the duration of sustained submaximal contractions. The key pieces of evidence discovered to date that demonstrate spinal mechanisms contribute to the shorter task duration of the position-matching task are 1) a greater reduction in the H-reflex amplitude (a global index of spinal excitability) during the position task (16, 168) combined with 2) no decline in 1a pre-synaptic inhibition by descending inputs as measured the conditioned H-reflex (an indirect index of pre-synaptic inhibition) compared to the longer duration force-matching task (where 1a pre-synaptic inhibition did decrease) (17). To date, only one study has investigated the differences in supraspinal excitability between the force-matching and position-matching tasks using single pulse TMS (168). In this study, which also identified the changes to the H-reflex amplitude, non-significant differences were observed in the rate of increase in the single-pulse MEP amplitude with the longer duration force-matching task having a greater MEP amplitude at task failure compared to the shorter duration position-matching task. The SP duration increased significantly but only for the longer force-matching task (168). Contrary to previous work, there was no difference in the rate of increase in EMG amplitude between the two tasks as the EMG amplitude at task failure was greater for the longer force-matching task suggesting insufficient motor unit recruitment contributed to early task failure during the position-matching task (104, 106, 168). The results from this study, combined with those previously reported about the differences in recruitment threshold and discharge rates of single motor units during both tasks, have been interpreted to mean that the position-matching task is limited by decreased facilitation of the motoneuron pool from peripheral afferents due to sustained
or even increased pre-synaptic inhibition of the Ia afferent by descending inputs in order to manage force fluctuations as opposed to intrinsic changes to the motorneuron itself (13, 104)

Taken together, the cited data from the previous experiments about the decreases in spinal motorneuron excitability that occur during sustained submaximal contractions as well as the differences in H-reflex excitability between the force-matching and position-matching tasks provide compelling evidence that spinal mechanisms are largely responsible for not only task failure in sustained submaximal contractions but also for the shorter duration of the position-matching task (17, 104, 168, 214). These changes could be due to both intrinsic adaptations of the motorneuron membrane (214) and/or to task-specific differences in the amount of facilitation available from peripheral afference as the tasks progress (17, 104, 168). The contribution of supraspinal mechanisms, and especially changes in the excitability of intracortical facilitatory and inhibitory circuits, remain largely unexplored in studies of task failure. More significantly, it remains unknown how supraspinal and intracortical excitability change relative to decreasing spinal excitability as the nervous system attempts to maintain sufficient voluntary drive to the motor pool to sustain muscle activation and force output during submaximal contractions. Therefore, the purpose of this study was to delineate the supraspinal and intracortical adjustments in excitability relative to the spinal adjustments in excitability during the force-matching and position-matching tasks. I hypothesized that the shorter time to task failure for the position-matching task would be associated with a greater rate of increase in the measures of cortical excitability, without a concurrent increase in intra-cortical inhibition, and a greater rate of reduction in alpha-motorneuron excitability.
Methods

Subjects

Ten healthy, right-handed individuals volunteered to participate in this study (5 men, 5 women; 24.5±3.10 yrs, 174.5±12.5 cm, 75.73±20.92 kg). Prior to participation, each subject attended an orientation session where they completed a series of questionnaires to confirm they were free from any known contraindications to either stimulation (magnetic or electrical) or exercise due to a neurologic disorder, cardiovascular disease, or musculoskeletal injury in the upper extremities. Subjects identified themselves as highly active (n=2, 1 male, 1 female,) moderately active (n=5, 3 male, 2 female), or low active (n=3, 1 male, 2 female) based on the Lipid Research Clinics Physical Activity Questionnaire (4), but denied participating in resistance training in the prior 3-months. Handedness was evaluated using the Edinburgh Handedness Inventory (mean score: 74±19%) with scores greater than 40% indicating right hand dominance (250). During the orientation, subjects were familiarized to the neurophysiologic testing methods and the experimental procedures, but they remained naïve to the prior research on differences in time to task failure for the two tasks. The Institutional Review Board at Ohio University approved the study protocol, and all study participants provided written informed consent.

General Overview of the Experiment and Testing Sessions

Subjects participated in two experimental sessions separated by 5-8 days (mean days separating sessions: 6.5±1.1 days) conducted at the same time of day for each
subject. During each testing session, subjects performed one of two sustained, submaximal fatiguing contraction tasks with the elbow flexors of the non-dominant arm at an intensity equal to 15% of maximal voluntary contraction (MVC) until volitional task failure. The two fatigue tasks followed an identical protocol and had identical mechanical demands, including identical net muscle force, joint angle, limb posture and stabilization, but differed in load compliance (i.e., force-matching vs. position-matching task). The difference in load compliance required the subjects to attend to distinct performance feedback variables during each task; either the force output from the elbow flexors (force-matching task) or the joint angle position of the elbow joint (position-matching task). During the force-matching task, subjects were asked to sustain a consistent 15% MVC force output for as long and as accurately as possible as they pulled against a force transducer tethered to the chair whose length, when taut, prevented the elbow from flexing more than 90°. For the position-matching task, subjects supported a free-hanging, untethered weight equivalent to 15% MVC force and focused on maintaining the elbow joint position at 90° as long and as precisely as possible until task failure. Subjects received task-specific visual feedback about either the force output or joint position throughout task performance. The order of the force-matching and position-matching tasks was counterbalanced across subjects and genders (i.e., half the individuals performed the position-matching task first and half the individuals performed the force-matching task first). Adjustments in cortical, spinal, and muscle excitability during task performance were assessed prior to and during the fatigue tasks. Here, a sequence of 6 electrical and magnetic stimuli were delivered to the motor cortex (TMS), the cervicomedullary junction, and the brachial plexus at regular intervals. The performance outcomes were time to task failure (TTF), and muscle
fatigue quantified as the reduction in MVC force immediately following the fatigue task. Eight neurophysiologic outcome measures were quantified from evoked responses: 1) MEP amplitude, 2) SP duration, 3) MEP elicited during the corticospinal silent period (MEP in SP), 4) paired pulse MEP ratio of long interval inhibition (LII), 5) paired pulse MEP ratio of short intracortical inhibition (SICI), 6) paired pulse MEP ratio of intracortical facilitation (ICF), 7) CMEP’s elicited during the corticospinal SP (CMEP in SP) as an index of motorneuron excitability independent from descending drive, and 8) M_{max}, which was used as an index of muscle excitability and to permit normalization of all of the neurophysiologic amplitude evoked potential measures. Additionally, to enable comparisons of changes in the neurophysiologic outcome variables relative to each other during the fatigue-tasks, seven normalized response outcome variables for the TMS and cervicomedullary stimulii were calculated by normalizing the fatigue value to the baseline pre-fatigue value (e.g. MEP fatigue task/MEP baseline x100).

The experimental protocol for both testing sessions was identical and consisted of four phases (Figure 18). During Phase 1, subjects were positioned in a custom-made chair, fit with a wrist orthosis, and prepped for electromyographic recordings. Phase 2 started by testing the elbow flexor MVC to measure pre-fatigue strength and determine the 15%MVC target force to be sustained during the fatigue tasks. Subjects then performed several 15% MVC short-duration (3-5 sec) force-matching contractions during which the stimulation intensities for TMS, cervicomedullary, and peripheral nerve stimulation were determined. The values for the target force and the stimulus intensities identified in test session 1 were confirmed during test session 2, and used for both test sessions. During phase 3, a total of 3 pre-fatigue baseline values for each neurophysiologic outcome variable were obtained. At the conclusion of the baseline
testing, subjects were given a break before starting the fatigue task. For phase 4, subjects performed either the force-matching or the position-matching fatigue task to task failure. One-minute into the fatigue task, subjects were asked their rating of perceived exertion (RPE) using the Modified Borg 0-10 scale (34), which was immediately followed by a 60-sec sequence of 6 total magnetic and electrical stimulation pulses (1 every 10-secs). The RPE/stimulation measures were repeated every 2-min up to 7 minutes (e.g. 1, 3, 5, and 7-min), after which they were taken every 3-min (e.g. 10, 13, 16-min, etc.) until task failure. Subjects were not informed of the timing of stimulation or their contraction times. A final RPE was taken at task failure. Five seconds after task failure, subjects performed one last MVC. Subjects were only told their time to task failure after completing both test sessions.

**Experimental Setup and Mechanical Recordings (Figure 19)**

To provide consistent mechanical demands between the two tasks, the upper limb position, proximal segment stabilization, and joint torque (force x moment arm) were identical. Subjects were seated in an upright adjustable chair with the left arm positioned next to the body in 10-15° of humeral abduction which placed the olecranon process of the elbow joint on the small padded rest used to support the weight of the upper arm. This shoulder joint alignment has been shown to minimize stress on the rotator cuff muscles during fatigue-task performance (287). The elbow rest did not restrict motions of the humerus or the forearm. With the torso resting against the back of the chair and the shoulder joint aligned with 0° flexion/extension, the humerus was vertical and the forearm parallel to the ground to position the elbow joint at 90°. The forearm was in neutral rotation with the thumb pointed towards the ceiling. The shoulder
joint was oriented in neutral rotation so that when the elbow flexed, the thumb aimed towards the acromion process of the shoulder, not the subject’s chin. To obviate the use of the hand and wrist muscles during testing as well as to provide a secure attachment for the loads, the forearm and hand were immobilized in a pre-fabricated Wrist-Hand-Thumb-Orthosis (Model 100, Orthomerica, Newport Beach, CA). This composite arm posture has been found to provide a consistently significant difference in TTF between the force-matching and position-matching tasks with the elbow flexors for loads below 45% MVC for both men and women between ages 18 and 45 years (17, 151, 286, 288).

A 14-inch computer monitor that provided visual feedback about task performance was placed 1-meter in front of the subject and the height aligned at eye level to ensure that subjects would not alter their sitting posture (and therefore their arm position) in order to view the screen (138). It is important to note that external supports (i.e. straps) were not used to restrict motions at the shoulder or the torso in order to equalize the demand placed on synergists, proximal joints, and postural stabilizers between the two fatigue-tasks.

The loads were attached on the ulnar side of the wrist to the bend of a “U” shaped bolt that was secured around the orthosis just proximal to the wrist joint. This permitted the load to slide unrestricted in the frontal plane thus uncoupling forearm pronation and supination motions from elbow joint flexion angle. For the MVC tests and the 15% MVC force-matching task, the orthosis was tethered to an anchor point on the chair base. The length of the tether was set so that when it was pulled taut by the vertically directed force of the contracting elbow flexors, the elbow joint was flexed to 90° with the forearm parallel to the ground. Unlike in other studies where the orthosis was clamped into place, restricting forearm motion in all planes (17, 149, 152, 228, 286, 288),
the tether only prevented further elbow flexion beyond 90°; no other motions in the arm were restricted. During the position-matching task, the total weight suspended from the orthosis was equivalent to 15%MVC. To ensure consistent torque demands between tasks, the moment arm length for the force was the measured distance between the “U” bolt and the posterior elbow on the padded rest and the forearm parallel to the ground with the humerus vertical creating a 90° angle at the elbow joint. Elbow flexor force (N) was measured with an isometric force transducer (TSD121C, 0-100kg range, Biopac Systems Inc., Goleta, CA) placed in series between the orthosis and either the anchor point of the tether or the suspended weight. The force transducer signal was differentially scaled (i.e. calibrated) to measure the MVC (Range 125.7-491.5N) and the 15%MVC target force (Range 13.3-76.2N) to enhance signal resolution at the submaximal force level. The force signal was sampled at 2.5 kHz and smoothed at 200 samples/sec (MP 150, BioPac Systems, Inc. Goletta, CA) then displayed on the computer screen to provide visual feedback to the subject. Elbow joint position (degrees) in the sagittal plane (flexion/extension) was measured with an electrogoniometer (TSD130B Twin-Axis Goniometer 150, (-)90°- (+)90° range, BioPac Systems, Goleta, CA) secured to the skin over the lateral side of the humerus and forearm using double-sided surgical tape. The position signal was sampled at 2.5kHz and displayed as visual feedback.

**Strength Testing of the Elbow Flexors**

Elbow flexor strength was defined as the maximal MVC value for the elbow flexors and was assessed at the start of each session and again just after task failure. To establish baseline MVC, subjects performed a minimum of three maximum isometric
contractions by pulling against the tethered force transducer. With the tether pulled taut and the elbow in 90° flexion, subjects were instructed to gradually increase their elbow flexion force to maximum over 3-secs and then to hold that maximum force for 3-sec before relaxing. Standard verbal encouragement was provided (123) throughout the contraction and subjects were given visual feedback of their force output on the computer monitor. There was a 1-2 minute rest between each contraction. Subjects performed additional contractions if the MVC trials were not within 5% of each other or if subjects produced more force with each successive trial. One final MVC was performed ~5-secs after fatigue task failure (5-secs was required to reconnect the tether to the force transducer after the position-matching task). Baseline MVC for each session was defined as the greatest force output from that session and was used to compare to the final MVC performed after task failure. The highest force output during test session 1 was used as the reference level for the 15% MVC target force that was used in both test sessions. Baseline MVC did not differ between test sessions (Test session 1 MVC: 276.39±101.67 N, Test session 2 MVC: 272.0±102.85 N; p = 0.40).

Force-Matching and Position-Matching Fatigue Tasks

During the fatigue-tasks, subjects were asked to sustain a submaximal fatiguing contraction with the elbow flexors equivalent to 15% of their MVC when the elbow joint was in 90°-flexion until task failure under two different conditions. Subjects focused their attention on either maintaining a consistent 15% MVC force output during the force-matching task or preventing their elbow joint angle from moving away from 90°-flexion during the position-matching task. Task-specific visual feedback of force output or joint position was displayed as a horizontal line that spanned the width of the computer
screen. To optimize real-time performance feedback, a 100-ms time window was used
to display the signal permitting the horizontal line to fluctuate above and below the target
line with increases and decreases in force output or joint angle. For both fatigue-tasks,
subjects were instructed, and reminded throughout task performance, to keep the signal
line representing their force output or the elbow joint position as close to the target line
for as long as possible by only flexing at the elbow joint while keeping the thumb aimed
towards the ceiling. Limb position, including elbow contact on the padded rest, and
postural alignment were monitored by close visual inspection and corrective verbal
feedback regarding compensations was provided by the same investigator (PSW) for all
test sessions. Task failure during the force-matching fatigue-task occurred when
subjects could no longer sustain their force output within ±5% of the target force (i.e.
15% MVC ± 1.50% MVC) or when subjects could not perform the task without
compensations for ≥ 5 seconds. For the position-matching task, task failure occurred
when subjects could not keep the elbow joint flexed within ±10° of the 90° target position
(i.e. between 80° and 100°) or if, as with the force-matching task, the subjects could not
correct their compensations for ≥ 5 seconds. Typical compensations included forearm
supination, shoulder extension, shoulder adduction with external rotation or shoulder
abduction with internal rotation. For both tasks, the visual feedback failure criteria
spanned a 10-cm bandwidth around the target line on the computer screen, such that
the resolution for the visual gain during the force-matching task was 0.3% MVC/cm and
2°/cm during the position-matching task (152, 226, 228).
Electrical Recordings

Voluntary and evoked electromyographic (EMG) signals were recorded from the biceps brachii and the brachioradialis muscles using bipolar surface electrodes (Ag-AgCl, 8-mm diameter, interelectrode distance 25-mm, Trace 1, Nikomed, Huntingdon Valley, PA) located longitudinally over the muscle bellies on shaved, abraded and cleaned skin. The reference electrode was placed on the medial epicondyle. EMG signals were amplified (1,000x), band-pass filtered (10-500 Hz), and sampled at 2,500 Hz (MP150, BioPac Systems Inc., Goleta, CA).

Brachial Plexus Stimulation (Figure 20A)

Electrical stimulation (single pulses, 100-µsec pulse width) to the brachial plexus at Erb’s point in the supraclavicular fossa were delivered using a constant current stimulator (Digitimer D7SAH, Digitimer Ltd., Hertfordshire, UK) to evoke a maximal compound muscle action potential ($M_{max}$) in the biceps and brachioradialis muscles both before and during the fatiguing contractions. The anodal electrode (Ag-AgCl, 8 mm) was placed on the acromion and the cathodal electrode (Ag-AgCl, 8mm) at the optimal stimulating point in the supraclavicular fossa. The intensity of the electrical stimulus was gradually increased until the evoked M-wave amplitude in the biceps plateaued. A supramaximal stimulus intensity (100-400 mA) equivalent to 120% of the plateau value was used to evoke the $M_{max}$ response during the 15% MVC baseline and fatiguing contractions. The amplitude of the biceps $M_{max}$ under resting conditions was used as the reference value for the target size of an unconditioned MEP and unconditioned CMEP.
(i.e.~50%$M_{\text{max}}$, see below) and the mean value did not change significantly between visits (Test session 1: 9.57±2.78mV, Test session 2: 9.13±3.97mV; $p=0.72$).

**Transcranial Magnetic Stimulation (Figure 20B-20D)**

Single and paired monophasic magnetic pulses were delivered over the right motor cortex region for the left upper extremity using a hand-held 70-mm figure-of-8 focal coil connected to a BiStim$^2$ stimulator (Jali Medical Inc. Woburn, MA) attached to two Magstim 200$^2$ stimulators (The Magstim Co Ltd, Whitland, UK). For cortical paired-pulse protocols one stimulator delivered the conditioning stimulus (CS) and the other the test stimulus (TS). The response to TMS pulses over the motor cortex, the motor evoked potential (MEP), was quantified by the peak-to-peak amplitude of the evoked response in the muscle (277). To induce a current field that flowed perpendicular to the central sulcus, from posterior-lateral to anterior-medial direction in the brain, the coil was positioned tangential to the lateral surface of the head and angled 45° from the sagittal plane so that the stimulator handle was pointed in a posterior-lateral direction (37, 342). With the coil in this location and current flow in this direction, studies evaluating MEP latency, single motor unit behavior, and epidural recordings within the spinal cord have shown that the TMS pulse primarily activates the axons of both excitatory and inhibitory interneurons that then synapse on the corticospinal tract neurons, rather than activating the corticospinal system directly (91-93, 301, 333). Therefore, unlike peripheral nerve or cervicomedullary electrical stimulation which elicits a single synchronous activation of motorneurons, the TMS pulse evokes a descending volley of action potentials in the corticospinal neurons that are temporally summated by the motorneuron pool (261, 280).
The optimal spatial location on the head where the TMS pulse consistently evoked the largest MEP peak-to-peak amplitude in the contralateral biceps muscle at rest (i.e. the motor hotspot) was found by moving the coil in 1-cm steps over the anatomical location of the upper extremity region of the motor cortex while delivering slightly suprathreshold stimuli. Once found, this position was marked with a sticker on the hair or a dot on the scalp to ensure consistent coil placement during all TMS protocols for that day (86, 133). Active motor threshold (AMT) was defined as the minimum stimulator intensity (reported as % of Stimulator Output: % SO) that evoked an MEP with a peak-to-peak amplitude ≥ twice the amplitude of the averaged EMG baseline during a 15% MVC in at least 50% of the trials (75, 213). To determine AMT, subjects performed short-duration 15% MVC force-matching contractions (3 to 5-secs) during which a single pulse was delivered. The subject maintained the force output to the target force line after the TMS pulse until instructed to relax. The maximum EMG baseline peak-to-peak amplitude was quantified across the 500 milliseconds prior to the stimulus artifact and averaged across 4 trials. To confirm AMT, the stimulator intensity was varied by 3% and 4 more trials conducted with the process repeating until AMT was determined. AMT values were consistent between test sessions (Test session 1 AMT: 50±9% SO; Test session 2 AMT: 46±8% SO, p=0.17; ICC3,1=0.67 p<0.05).

The conditioning stimulus (CS) intensity used for the first stimulus pulse in the paired-pulse protocols for SICI and ICF was set as 70% of AMT for each session (Test session 1 CS: 35±6% SO, Test session 2 CS: 33±6% SO, p=0.17; ICC3,1=0.67 p<0.05) (253, 284). The stimulator intensity was then increased to establish the suprathreshold test stimulus (TS) intensity, which was used for single pulse MEP (i.e. unconditioned MEP), the TS (i.e. second stimulus pulse) in SICI and ICF, and for both the CS and TS
in the LII paired-pulse protocol. The TS was defined as the stimulus intensity that, when delivered alone during a 15%MVC contraction, was sufficient to evoke an unconditioned MEP amplitude ~50% of the resting $M_{\text{max}}$ amplitude and with a SP duration greater than 75-msec in the biceps. The value for the TS was consistent between sessions (Test session 1 TS: 75±14% SO, Test session 2 TS: 72±11% SO, $p=0.21$; ICC$_{3,1}=0.88$, $p<0.01$) and was equivalent to 150±24% of AMT during test session 1 and 157±30% of AMT during test session 2 ($p=0.22$; ICC$_{3,1}=0.82$, $p<0.01$). The TS evoked MEP amplitude did not differ between visits (Test session 1 MEP: 4.18±2.19 mV, Test session 2 MEP: 4.86±3.75 mV; $p<0.05$) and was equivalent to 45.8±22.1% of resting $M_{\text{max}}$ for test session 1 and 57.2±43.9% of resting $M_{\text{max}}$ for test session 2 ($p=0.36$). The interstimulus intervals (ISI) between the CS and TS were 3-msec to assess SICI and 15-msec for ICF. Both LII and paired cortico-cervicomedullary stimulation had a 75-msec ISI. The SP duration was consistent between sessions at baseline (Visit 1: 133±20 msec, Visit 2: 129±20 msec, $p=0.46$; ICC$_{3,1}=0.67$, $p<.01$) and therefore, sufficiently long enough for the 75-msec ISI used for the LII and paired cortico-cervicomedullary stimulation paired pulse protocols (see below).

**Paired Cortico-Cervicomedullary Stimulation (Figure 20E)**

Direct stimulation of the descending spinal tracts is considered to be the best available method to assess motorneuron excitability because the corticospinal/motorneuron synapse is not modified by Ia presynaptic inhibition, unlike both the H-reflex and the F-wave (206, 233). Stimulation at the cervicomedullary junction is preferable because there is less of a chance of activating the spinal nerve roots and the bend in the corticospinal tract, as it crosses to the contralateral side of the
body in the medullary pyramids, facilitates current activation of the spinal cord tract axons (326, 327). Recent work comparing the change in MEP and CMEP amplitudes, during sustained submaximal fatiguing contractions have found that both the MEP and CMEP amplitudes continue to increase relative to their baseline values and follow a similar pattern of response, but the CMEP amplitude compared to the MEP amplitude (normalized to $M_{\text{max}}$) is lower (142, 192). McNeil et al., using a paired pulse cortico-cervicomedually electrical stimulation protocol where a conditioned CMEP is evoked during the silent period after a suprathreshold TMS pulse during an active contraction, found that the conditioned CMEP amplitude progressively declined to below pre-fatigue values during fatiguing maximal contractions and sustained, submaximal contractions (214, 216, 218). They concluded that the motor cortex is not actively inhibited during sustained submaximal contractions but instead that the motorneurons become progressively resistant to stimulation. When evoked during the fatiguing contraction, the CMEP represents the excitability of the spinal motor circuits in the presence of supraspinal drive (214, 216, 218). If, however, the CMEP is evoked during the cortically induced silent period (analogous to a conditioned MEP in LII), the conditioned CMEP offers a more direct view of the motorneuron responsiveness during fatigue independent of descending inputs (215, 216, 218, 279).

For this experiment, electrical stimulation (single pulse, 100-µsec pulse duration) of the descending spinal tracts at the cervicomedullary junction was delivered using the same constant current stimulator previously described. The electrical current was passed between two self-adhesive surface electrodes (Ag-AgCl, 8mm) that were affixed to the skin just medial to the mastoid processes on the soft-tissue adjacent to the inferior occiput with the anode on the left side of the spinal column (327). The stimulus intensity
(200-500mA) was set to evoke, during brief 15% MVC force-matching contractions, an unconditioned CMEP (i.e. CMEP delivered alone) with a peak-to-peak amplitude ~ 50% $M_{\text{max}}$ (Test session 1: 41.5±19.9% of resting $M_{\text{max}}$, Test session 2: 56.6±42.4% of resting $M_{\text{max}}$; $p=0.34$), and equivalent to the MEP amplitude evoked in response to the TS. The mean amplitude for the unconditioned CMEP did not differ between sessions (Test session 1 CMEP: 3.73±1.72 mV; Test session 2 CMEP: 4.57±3.34 mV; $p=0.41$) and was similar to the MEP amplitude for both visits (Test session 1 CMEP amplitude vs. MEP amplitude: ICC$^{3,1}=0.90$, $p<0.01$; Test session 2: CMEP amplitude vs. MEP amplitude: ICC$^{3,1}=0.94$, $p<0.01$). As the stimulus intensity increased, the CMEP latency was monitored to be sure it did not “jump” (i.e. sudden 1-2 msec decrease in the latency) indicating that the cervical spinal nerve roots were activated by the stimulus masking the spinal cord tract activation (308). The paired cortico-cervicomedullary electrical stimulation protocol is analogous to LII, except that the spinal cord stimulation replaces the second TMS pulse (214, 218). One of the TMS stimulators delivered the first pulse (suprathreshold TS intensity) to the motor cortex to evoke an unconditioned MEP followed by a SP and simultaneously triggered the electrical stimulator to stimulate the cervicomedullary junction after a 75-msec ISI to evoke the CMEP during the SP.

**Stimulation Protocol**

During the fatigue task the stimulation sequence started by eliciting an $M_{\text{max}}$, followed by paired-pulse TMS to evoke three different conditioned MEP’s (i.e. for SICI, ICF and LII), plus one single TMS pulse to evoke an unconditioned MEP (Figure 18). The sequence ended with paired cortico-cervicomedullary stimulation in order to evoke a conditioned CMEP during the silent period. Each of the magnetic and electrical stimuli
briefly disrupts volitional force output with an involuntary spike in force output immediately followed by an electrical silent period (i.e. interruption in the interference EMG signal) that transiently (50-150ms) ceases motor output (51, 120, 154). Subjects were instructed to restore their force output or joint angle to the target line and the investigator monitored limb position during the stimulation protocol to ensure the subjects returned to the correct alignment if the stimulation disturbed their position. RPE measures were taken just prior to the stimulus protocol to ensure that the subjects were reporting their level of fatigue/effort associated with task performance and not the effort associated with the transient disruption caused by the stimuli. The subjects were familiarized to the effect of the stimuli on task performance and the associated visual feedback during the pre-fatigue baseline measures. To obtain pre-fatigue measures for the neurophysiologic outcome variables, subjects performed 3 sets of 6 short-duration, non-fatiguing, task-specific contractions (i.e. either force-matching or position-matching per fatigue-task used that test session) during which one stimulus was delivered per contraction. The stimuli were delivered in the same sequence used during the fatiguing contractions. As with the fatigue task, subjects were instructed to restore their force output, or their joint position, to the target line after each stimulus prior to relaxing so that the pre-fatigue measures replicated the motor behavior required during the fatigue task.

**Data analysis**

For each fatigue-task, the TTF was measured from the recorded torque output signal starting from when the torque signal reached the target force and ending when the failure criteria were met. The outcome measures for all of the evoked signals were analyzed off-line using the AcqKnowledge software package version 4.2.0 (Biopac
Peak-to-peak amplitude, rather than response area, was used to be consistent with recommendations for analyzing TMS protocols (277). Before further analysis, to control for non-experimental influences on the interpretation of the evoked responses as well as for changes in the muscle fiber excitability associated with fatigue, all absolute values evoked responses were normalized to the corresponding $M_{\text{max}}$ amplitude recorded at each time point (86, 111, 164).

Ratios representing SICI, ICF, and LII were calculated by dividing the corresponding conditioned MEP amplitude by the single-pulse unconditioned MEP amplitude evoked during the same fatigue-stimulus protocol time point. The pre-fatigue values for each dependent variable represent the average of the three baseline measures normalized to the average pre-fatigue $M_{\text{max}}$; therefore, the pre-fatigue ratio values for SICI, ICF, and LII were calculated from these averages. The overall rate of change for each evoked response was calculated as the slope of a regression line fit to all of the data points during each TTF per individual. An initial rate of change using a regression line fit to the shared time points of 0, 1-min, 3-min and 5-min was also calculated. All values recorded from the biceps and brachioradialis muscles were respectively averaged to represent composite elbow flexor dependent variables (it should be noted that exploratory analyses were performed to examine muscle-specific differences, but no differences were observed for the outcomes, and thus a composite average chosen).

In order to compare changes in alpha-motorneuron, corticospinal and intracortical excitability relative to each other, seven normalized outcome variables were calculated as the ratio of the fatigue value divided by the pre-fatigue value, expressed as a percentage (214, 218). To examine the effect of volitional drive on corticospinal
excitability as measured by MEP amplitude during the fatigue-tasks, the 1) normalized MEP evoked in the silent period (MEP in SP%pre-fatigue) when volitional drive has been temporarily suspended and the 2) normalized unconditioned MEP (MEP%pre-fatigue) evoked during ongoing volitional output were calculated. To examine changes in corticospinal and motorneuron excitability during the silent period without volitional drive 3) normalized CMEP evoked in the silent period (CMEP in SP%pre-fatigue) was calculated and compared with the MEP in SP%pre-fatigue. To compare changes in intracortical inhibition and facilitation the normalized ratios for 4) SICI (SICI%pre-fatigue) and 5) ICF (ICF%pre-fatigue), were calculated. To assess changes in the composite measures of corticospinal inhibiton, normalized ratios for 6) LII (LII%pre-fatigue) and 7) SP duration (SP%pre-fatigue) were also calculated. Figure 21 summarizes the neurophysiologic outcome measures.

To explore the time-course of changes in the neurophysiologic measures during the fatigue-tasks, the data were compared over time in 20% intervals of the TTF calculated for each individual’s TTF (Pre-fatigue, 20%, 40%, 60%, 80% and 100% of TTF). The absolute times relative to the TTF were found for each individual and the responses measures for the stimuli delivered closest to that time, or the average of two stimuli delivered within an equal time frame on either side of the time point, were used. The last stimulus protocol was delivered within 0.73±0.48 minutes of the TTF and represents the final measure and is thus considered to represent 100% of TTF even if the subject continued to contract for a short period of time after the stimulation protocol was finished.
Statistical analysis

SPSS version 20 for Mac (SPSS Inc, Chicago, IL) was used for the statistical analyses. Data are reported as mean±SD in the text with effect size (ES=partial $\eta^2$) and means±SE in the figures. An $\alpha$ of 0.05 was required for statistical significance. A paired $t$-test was used to compare the TTF between the two respective tasks, task-specific baseline values, and the rate of change (i.e. slope) for each neurophysiologic measure between the two respective tasks. Two-way repeated measures ANOVA (RM ANOVA) was used to compare changes in MVC with TASK (2: Force, Position) and TIME (2: pre-fatigue, task failure) as repeated factors. A mixed model ANOVA with TASK (2: POSITION, FORCE) as a repeated factor and GENDER (2: women, men) was used to compare the TTF between women and men. The effect of target force was analyzed by an ANCOVA (TASK, GENDER WITH TARGET FORCE COVARED FOR). Simple linear regression was then used to examine relationships between TTF and target force. Analysis of serial measures of RPE and the eight neurophysiologic variables during the fatigue-task protocols was conducted with a two-way RM ANOVA with TASK and TIME (6: Pre-Fatigue, 20, 40, 60, 80, Task-Failure) as factors. A three-way RM ANOVA with TASK, TIME, and STIMULUS was used to compare the seven normalized outcome variables were compared in pairs (e.g. STIMULUS 2 levels: MEP in SP%pre-fatigue and CMEP in SP%prefatigue). When a significant main effect and/or interaction terms were observed a follow-up post-hoc Sidak test was used to control for alpha inflation.
Results

Performance Outcomes (Figures 22 - 24)

Time to task failure and decline in MVC (Figures 22 and 23). The mean TTF for the position-matching task was 1.5 times longer than the mean TTF for the force-matching task (26.9±15.11 min vs. 17.5±7.9 min, p<0.01, ES=0.60) (Figure 22A). The decline in MVC following the fatigue tasks did not differ between the two task conditions (Position-matching MVC %-Decline: 30.09±18%, Force-Matching MVC %-Decline: 30.07±15%; MVC TASK X TIME INTERACTION: p=0.59) (Figure 22B). Individual values for TTF for the respective tasks are illustrated in Figure 23A. Interestingly, women exhibited a greater magnitude of difference in TTF (TTFDiffP-F) between the two fatigue-tasks (TASK X GENDER interaction p<0.01); however, when the absolute 15% MVC target-force was statistically covaried, the effect of GENDER on TTFDiffP-F was no longer significant (TASK X GENDER INTERACTION: p=0.81; it should be noted that TASK MAIN EFFECT persisted in the covariat analysis, p<0.01). There was an inverse relationship between the absolute value for the 15% MVC Target force and the TTFDiffP-F ($r^2=0.85$, $t_{(1,8)}=21.52$, p<0.01) (Figure 23B). The absolute value for the target force predicted a significant amount of the between-subject variability in TFF for the position-matching task ($r^2=0.81$, p<0.01) and the force-matching task ($r^2=0.72$, p<0.01), as well as for the TTFDiffP-F ($r^2=0.73$, p<0.01). Thus, stronger subjects with a higher absolute target force were more likely to have similar TTF between the two tasks, whereas weaker subjects with a lower absolute target force had a greater difference in TTF between tasks with a significantly longer TTF for the position-matching task.
Rating of perceived exertion (Figure 24). Rating of perceived exertion (RPE) increased throughout both fatigue tasks from 0 to equivalent mean values of 9.5±0.26 during the force-matching task and 9.7±0.21 for the position-matching task (TASK X TIME INTERACTION: p=0.81, ES=0.02; TASK MAIN EFFECT: p=1.00, ES=0.00; TIME MAIN EFFECT: p<0.01, ES=0.96). The RPE values between pre-fatigue and 80% of TTF were significantly greater than the previous interval (pairwise comparison p<0.01) and then plateaued between 80% and 100% TTF (p=0.72).

Neurophysiologic Outcomes (Figures 25-30)

$M_{\text{max}}$ The absolute $M_{\text{max}}$ amplitude did not differ by TASK at baseline (force-matching $M_{\text{max}}$ 7.10±2.87mV, position-matching $M_{\text{max}}$ 8.97±3.45; p=0.15). During the fatigue-tasks, a TASK by TIME interaction was not observed for $M_{\text{max}}$ (p=0.33, ES=0.11) and the $M_{\text{max}}$ amplitude did not change significantly throughout either fatigue-task (TIME MAIN EFFECT: p=0.80, ES=0.03) nor differ significantly between fatigue-tasks (TASK MAIN EFFECT: p=0.33, ES=0.11).

MEP amplitude (Figure 25A). The unconditioned MEP amplitude evoked from single-pulse TMS was greater for the force-matching task at baseline (Force-matching Unconditioned MEP: 59.43±18.4% $M_{\text{max}}$ vs. Position-Matching Unconditioned MEP: 48.48±16.26%$M_{\text{max}}$; p=0.03, ES=0.43). During the fatiguing contractions there was no interaction between TASK and TIME (p=0.46, ES=0.09); however there were main effects for both. Specifically, the amplitude of the unconditioned MEP was greater during the force-matching task (TASK MAIN EFFECT: p=0.00, ES 0.66), and gradually increased during the fatigue-tasks by 26.45±25.01% $M_{\text{max}}$ in the force-matching task and 24.76±19.02%$M_{\text{max}}$ in the position-matching task (TIME MAIN EFFECT: p<0.01, ES 0.54).
Post-hoc pair-wise comparisons for TIME revealed statistically significant increases in MEP amplitude relative to pre-fatigue baseline values starting at 60% of TTF (p<0.05), with the 60% TTF measurement also being significantly greater than the values at both 20% and 40% TTF. The rate of change in MEP amplitude across the entire task duration did not differ between the two tasks (force-matching slope MEP: 1.85±1.47%M$_{\text{max}}$/min vs. position-matching slope MEP: 1.49±1.54%M$_{\text{max}}$/min; p=0.35), nor did the rate of change during the initial part of the fatigue task (i.e., the first 5-mins) (initial force-matching slope MEP: 3.83±3.02%M$_{\text{max}}$/min vs. initial position-matching slope MEP: 3.14±3.22%M$_{\text{max}}$/min; p=0.68).

Silent period duration (Figure 25B). The SP duration was longer for the position-matching task at baseline (Force-matching SP: 127.97±22.39 msec vs. Position-Matching SP: 148.33±24.74 msec; p<0.01, ES=0.72). During the fatiguing contractions there was no interaction between TASK and TIME (p=0.23, ES 0.15); however there was a main effect for TIME (p=0.02, ES 0.37) but not for TASK (p=0.20, ES 0.18). The SP duration gradually increased to 146.30±40.15 msec at task failure for the force-matching task and to 159.70±21.55 msec at task failure during the position-matching task. There were no significant pair-wise comparisons for TIME (p>0.05) (It should be noted that pair-wise comparisons using an LSD post-hoc tests were significant between baseline and all time intervals and for 20% and 40% and task failure, p<0.05). The rate of change in SP duration across the entire task duration did not differ between the two tasks (force-matching slope SP duration: 0.74±5.21 msec/min vs. position-matching slope SP duration: 1.19±1.54 msec/min; p=0.77, ES=0.01) nor did the rate of change during the initial part of the fatigue task (initial force-matching slope SP duration: 0.74±5.21 msec/min vs. position-matching slope SP duration: 1.19±1.54 msec/min; p=0.77, ES=0.01).
2.20±6.29 msec/min vs. initial position-matching slope SP duration: 1.00±2.35 msec/min; p=0.64, ES=0.03).

**MEP elicited during the silent period (Figure 26A).** The amplitude of the conditioned MEP evoked in the silent period (MEP in SP) did not differ between tasks at baseline (Force-matching MEP in SP: 38.20±17.94% M_max; Position-Matching MEP in SP: 27.52±18.06% M_max; p=0.09, ES=0.28). During the fatiguing contractions, there was no interaction between Task and Time (p=0.79, ES 0.04); however there were main effects for both. The amplitude of the MEP in SP was greater during the force-matching task (Task Main Effect: p=0.03, ES 0.45), and gradually increased during the fatigue-tasks by 19.90±32.17%M_max in the force-matching task and 12.83±19.57%M_max in the position-matching task (Time Main Effect: p=0.04, ES 0.29). There were no significant pair-wise comparisons for Time (p>0.05) (it should be noted that pair-wise comparisons using LSD post-hoc tests were significant between baseline and 80% and task failure, and for 40% with 60%, 80% and task failure p<0.05). The rate of change in MEP in SP amplitude across the entire task duration did not differ between the two tasks (force-matching slope MEP in SP: 2.33±2.76 %M_max/min vs. position-matching slope MEP in SP: 0.94±1.87 %M_max/min; p=0.10, ES=0.27), nor did the rate of change during the initial part of the fatigue task (initial force-matching slope MEP in SP: 3.05±3.94 %M_max/min vs. initial position-matching slope MEP in SP: 1.49±2.13 %M_max/min; p=0.26, ES=0.14).

**CMEP elicited in the silent period (Figure 26B).** The amplitude of the conditioned CMEP evoked during the silent period (CMEP in SP) did not differ between tasks at baseline (Force-matching CMEP in SP: 41.64±20.13% M_max vs. Position-Matching CMEP in SP: 30.11±24.27%M_max; p=0.09, ES=0.29). A 2-way RM ANOVA investigating the pre-fatigue baseline differences between the two silent period
responses (i.e., MEP elicited in the SP vs. CMEP elicited in the SP) did not have a significant interaction for STIMULUS X TASK \((p=0.09, \ ES 0.00)\) and revealed only a significant main effect for TASK \((p<0.05, \ ES 0.38)\) and not for STIMULUS \((p=0.63, \ ES 0.03)\) meaning that the amplitudes of the two responses evoked in the silent period did not differ from each other prior to the fatigue task and that both were greater for the force-matching task at baseline. During the fatiguing contractions, there was no interaction between TASK and TIME \((p=0.52, \ ES 0.07)\); however there was a main effect for TIME \((p=0.01, \ ES 0.44)\) but not for TASK \((p=0.30, \ ES 0.12)\). The CMEP in SP gradually decreased to 24.18±20.29%\(M_{\text{max}}\) at task failure for the force-matching task and to 19.44±26.74%\(M_{\text{max}}\) at task failure during the position-matching task. There were no significant pair-wise comparisons for TIME \((p>0.05)\) (It should be noted that pair-wise comparisons using LSD post-hoc tests were different from baseline starting with 40% to task failure, and for 20% and 40% with 80% and task failure \(p<0.05\)). The rate of change in CMEP in SP amplitude across the entire task duration did not differ between the two tasks (force-matching slope CMEP in SP: -1.64±1.72 %\(M_{\text{max}}\)/ min vs. position-matching slope CMEP in SP: 0.98±1.46 %\(M_{\text{max}}\)/ min \(p=0.24, \ ES=0.14)\), nor did the rate of change during the initial part of the fatigue task (initial force-matching slope CMEP in SP: -1.82±2.81 %\(M_{\text{max}}\)/ min vs. initial position-matching slope CMEP in SP: -1.65±2.57 %\(M_{\text{max}}\)/ min; \(p=0.90, \ ES=0.00\)).

**Short-Interval Intracortical Inhibition ratio (Figure 27A).** The SICI ratio did not differ between tasks at baseline (Force-matching SICI ratio: 0.81±0.24; Position-matching SICI ratio: 0.70±0.22; \(p=0.25, \ ES=0.14)\). During the fatiguing contractions, there was no interaction between TASK and TIME \((p=0.77, \ ES 0.04)\); however there was a main effect for TIME \((p<0.01, \ ES 0.31)\) but not for TASK \((p=0.09, \ ES 0.29)\). The value
for the SICI ratio increased during fatigue-task performance to approach values of ~ 1.0 at task failure (force-matching SICI ratio: 0.94±0.22; position-matching SICI ratio: 0.88±0.32) indicating decreasing intracortical inhibition. There was a statistically significant difference for the SICI ratio between the 20% of TTF interval and task failure (p<0.05). The rate of change in SICI ratio across the entire task duration did not differ between the two tasks (force-matching slope SICI ratio: 0.02±0.02 min⁻¹ vs. position-matching slope SICI ratio: 0.004±0.02 min⁻¹ p=0.22, ES=0.16), nor did the rate of change during the initial part of the fatigue task (initial force-matching slope SICI ratio: 0.003±0.04 min⁻¹ vs. initial position-matching slope SICI ratio -0.005±0.02 min⁻¹; p=0.59, ES=0.03).

**Intracortical facilitation ratio (Figure 27B).** The ICF ratio did not differ between tasks at baseline (Force-matching ICF ratio: 1.17±0.21; Position-matching ICF ratio: 1.04±0.09; p=0.15). During the fatiguing contractions, there was no interaction between TASK and TIME (p=0.32, ES 0.12), and there were no main effects for TIME (p=0.36, ES 0.11) or for TASK (p=0.50, ES 0.05). The mean amplitude of the ICF ratio was above 1.0 for both tasks (force-matching ICF ratio 1.07±0.15, position-matching ICF ratio at task failure 1.03±0.12) indicating sustained intracortical facilitation. The rate of change in ICF ratio across the entire task duration was significantly greater during the position-matching task (force-matching slope ICF ratio: -0.01±0.03 min⁻¹ vs. position-matching slope ICF ratio: 0.001±0.03 min⁻¹ p<0.01, ES=0.67), but the rate of change during the initial part of the fatigue task did not significantly differ (initial force-matching slope ICF ratio: -0.012±0.05 min⁻¹ vs. initial position-matching slope ICF ratio: -0.02±0.05 min⁻¹; p=0.72, ES=0.02).
Long interval inhibition ratio (Figure 27C). The LII ratio did not differ between tasks at baseline (Force-matching LII ratio: 0.75±0.41 vs. Position-matching LII ratio: 0.57±0.34; p=0.15, ES=0.22). During the fatiguing contractions, there was no interaction between TASK and TIME (p=0.84, ES 0.03), nor a main effect for TIME (p=0.54, ES 0.07). The mean LII ratio remained below 1.0 during both fatigue-tasks. A main effect for task was not observed (p-0.057), although a modest effect size existed (ES=0.35) suggesting a trend towards a greater LII ratio in the force-matching task which suggests less corticospinal inhibition during the shorter-duration task (force-matching LII ratio: 0.66±0.28, position-matching LII ratio : 0.53±0.26). The rate of change in LII ratio across the entire task duration did not differ between the two tasks (force-matching slope LII ratio: 0.007±0.036 min⁻¹ vs. position-matching slope LII ratio: -0.00±0.023 min⁻¹ p=0.48, ES=0.06), nor did the rate of change during the initial part of the fatigue task (initial force-matching slope LII ratio: -0.002±0.047 min⁻¹ vs. initial position-matching slope LII ratio: -0.003±0.035 min⁻¹; p=0.95, ES=0.00).

Normalized MEP vs. normalized MEP elicited in the silent period (Figure 28A). A 3-way RM-ANOVA comparing the normalized unconditioned MEP (MEP%pre-fatigue baseline) and the normalized MEP evoked in the silent period (MEP in the SP%pre-fatigue baseline) revealed only a main effect for TIME (p=0.00, ES 0.58). No interactions nor other main effects were found (TASK X TIME X STIMULUS INTERACTION: p=0.58, ES=0.06; TASK X TIME INTERACTION: p=0.61, ES=0.06; TASK X STIMULUS INTERACTION: p=0.49, ES=0.06; TIME X STIMULUS INTERACTION: p=0.51, ES=0.08, TASK MAIN EFFECT: p=0.88, ES=0.00; STIMULUS MAIN EFFECT: p=0.86, ES=0.00). These results suggest that the amount of corticospinal excitability both with and without volitional drive during the fatiguing contractions did not significantly differ. Overall,
corticospinal excitability progressively increased throughout the fatigue tasks by 200.4±76.8% above pre-fatigue baseline. Significant pair-wise comparisons for TIME were found between pre-fatigue and the 60%TTT, 80%TTF, and 100%TTF; for 20% with 60%TTF and 80%TTF; and 40% with 100%TTF (p<0.05).

**Normalized MEP elicited in the silent period vs. normalized CMEP elicited in the silent period (Figure 28B).** A 3-way RM-ANOVA comparing the normalized MEP elicited in the silent period (MEP in the SP%pre-fatigue baseline) and the normalized CMEP evoked in the silent period (CMEP in the SP%pre-fatigue baseline) revealed a significant interaction between STIMULUS and TIME (p=0.00, ES 0.55), but all other interactions were not significant (STIMULUS X TASK X TIME INTERACTION: p=0.51, ES 0.07; TASK X TIME INTERACTION: p=0.68, ES 0.04; STIMULUS X TASK INTERACTION: p=0.71, ES=0.01). The normalized MEP elicited in SP was greater than the normalized CMEP elicited in SP throughout the fatigue tasks. There was not a TASK X TIME interaction nor main effect for TASK in either stimulation condition (p>0.05, ES<0.01). The normalized MEP elicited in SP gradually increased throughout the fatigue-tasks to 212.0±125.2% of pre-fatigue baseline levels (TIME MAIN EFFECT: p=0.01, ES=0.40) while the normalized CMEP elicited in the SP progressively decreased to 56.4±27.5% of pre-fatigue levels (TIME MAIN EFFECT: p=0.00, ES=0.52). Specifically, the normalized CMEP elicited in SP was significantly reduced at the 80%TTF and 100%TTF time points relative to baseline (p<0.05).

**Normalized SICI ratio vs. Normalized ICF ratio Figure 29A).** A 3-way RM-ANOVA comparing the normalized SICI ratio (SICI%pre-fatigue baseline) and the normalized ICF ratio (ICF%pre-fatigue baseline) revealed a significant main effect for STIMULUS (p=0.02, ES=0.46). An interaction for STIMULUS X TIME was not significant but
demonstrated a moderate effect size (p=0.057, ES=0.21); however, all other interactions and main effects were not significant (STIMULUS X TASK X TIME INTERACTION: p=0.31, ES=0.12; TASK X TIME INTERACTION: p=0.68, ES=0.03, TASK MAIN EFFECT: p=0.42, ES=0.07; TIME MAIN EFFECT: p=0.29, ES=0.13). The normalized SICI mean value was significantly greater throughout fatigue-task performance compared to the mean normalized ICF value (97.4±3.0%). The mean value for the normalized SICI was > 100% (115.5±5.0%) during the fatigue-tasks, indicating a reduction in short interval intracortical inhibition during the fatigue tasks.

**Normalized LII ratio vs. Normalized silent period duration (Figure 29B).** A 3-way RM-ANOVA comparing the normalized LII ratio (LII%pre-fatigue baseline) and the normalized SP duration (SP%pre-fatigue baseline) did not reveal any significant interactions or main effects; therefore, each normalized ratio was further analyzed individually. During the fatiguing contraction, there was no interaction for TASK by TIME for the normalized LII ratio (p=0.62, ES=0.05) and did not significantly differ between TASKS (p=0.97, ES 0.00) or change over TIME (p=0.0.26, ES 0.13). The mean value for the normalized LII ratio was 106.2±13.8% during the force-matching task and 105.5±13.4% during the position-matching task which suggests no increase in corticospinal inhibition during the fatigue tasks.

Because there was no interaction between the normalized SP duration and the normalized LII ratio, to explore the relationship between SP duration and measures of corticospinal and motorneuron excitability in the silent period, a final 3-way RM-ANOVA (TASK (2), TIME (6), STIMULUS (3)) comparing the normalized values for SP duration, CMEP evoked during the silent period, and MEP evoked during the silent period was done (Figure 30). This analysis revealed a significant interaction between STIMULUS and
TIME ($p=0.00$, ES 0.52). There were no other significant interactions or a main effect for TASK ($p=0.59$, ES 0.03). Therefore, during the fatiguing contractions, as the SP duration increased to $111.3\pm10.7\%$ pre-fatigue and the MEP in SP increased to $82.78\pm72.38\%$ pre-fatigue, the CMEP in SP amplitude decreased to $56.4\pm27.3\%$ of pre-fatigue values.

Follow-up pairwise comparisons of TIME per STIMULUS collapsed over TASK for the normalized CMEP elicited in the SP found significant decline between baseline and 80% and 100% of TTF ($p<0.05$). For the normalized SP duration, significant pairwise comparisons were found between pre-fatigue and the 20%TTF interval ($p<0.05$). With the Sidak correction, no TIME based pair-wise comparisons were found for the normalized MEP elicited in the SP; however, using LSD post-hoc tests significant pairwise comparisons for TIME were found between baseline and all intervals $\geq 40\%$ TTF and also between 20% TTF and all intervals $\geq 60\%$ TTF. Follow-up pairwise comparisons of TIME interval by STIMULUS collapsed over TASK for the normalized CMEP elicited in the SP found significant decline between baseline and 80% and 100% of TTF ($p<0.05$) and for the normalized SP duration between pre-fatigue and 20%TTF ($p<0.05$). Pairwise comparisons of STIMULUS by TIME collapsed over TASK revealed significant differences starting at 40%TTF with normalized CMEP elicited in the SP being less than the normalized MEP elicited in the SP as well as the normalized SP duration ($p<0.05$). Starting at 80% TTF significant pairwise differences were seen with the normalized SP duration less than the normalized MEP elicited in the SP ($p<0.05$).
Discussion

The purpose of this study was to compare the task specific differences in the adjustments in cortical and spinal excitability that developed during the performance of the force-matching and position-matching tasks with the elbow flexors in order to further delineate the contribution of supraspinal mechanisms to task failure during sustained submaximal contractions. There were five main findings from this experiment. First, contrary to expectations, the duration of the position-matching task with the elbow flexors was 45% longer than the force-matching task when performed under identical mechanical demands without proximal stabilization or restraint of the forearm (Figure 22A). Second, there was a significantly greater absolute magnitude of corticospinal excitability during the force-matching task (Figures 25A and 26A); however, there were no task-specific differences found for the magnitude and rate of change for the eight neurophysiologic outcome variables (Figures 25-27). Third, the amount of corticospinal excitability (i.e., MEP and MEP elicited in the silent period) increased throughout fatigue task performance while the amount of spinal excitability (i.e., CMEP elicited in the silent period) decreased to task failure (Figure 28A and 28B). Fourth, the amount of intracortical inhibition within the motor cortex decreased (i.e., SICI ratio) during fatigue task performance (Figure 29A). Both intracortical facilitation within the motor cortex (i.e., ICF ratio) and upstream excitation of the motor cortex (i.e. MEP vs. MEP elicited in the SP, LII ratio) remained constant (Figure 28A, 29A, 29B). Lastly, the increase in the duration of the silent period followed the progressive decrease in spinal excitability throughout fatigue-task performance but deviated from the progressive increase in corticospinal excitability (Figure 30). Below, these key results will be discussed further.
Task-Specific Differences in Performance

Consistent with the paradigm identified in prior studies with the elbow flexors comparing the task duration of two sustained submaximal contractions that differ by load compliance, both tasks resulted in the same amount of muscle fatigue and change in RPE despite significant differences in contraction times (104, 152). Surprisingly, the duration of the position-matching task was found to be nearly 42% longer than the duration of the force-matching task. Therefore, the shorter TTF for the force-matching task observed here is in disagreement with the majority of the current literature comparing the task duration between the force-matching and position-matching tasks (16, 17, 152, 153, 168, 201, 265, 286, 288-290, 338).

Prior studies examining sustained submaximal contractions (i.e. ≤30%MVC) of the elbow flexors with the upper extremity positioned next to the body, the elbow flexed to 90° and the forearm in neutral as positioned in this study (Compare Figure 5 with Figure 19) have consistently found that the TTF for the position-matching task was on average 40% shorter than the TTF for the force-matching task (17, 152, 168, 286, 288). Additionally, the most common results reported for studies comparing the duration of the force-matching and position-matching tasks when performed by extremity muscles other than the elbow flexors (i.e. ankle dorsiflexors, knee extensors, wrist extensors, first dorsal interossei) (16, 153, 201, 265, 289, 338) and also for the elbow flexors in a different arm posture (286, 290, 321) are for the force-matching task to have a significantly longer TTF than the position-matching task varying between 21-53% depending upon contraction intensity and muscle tested.
However, while most common, the paradigm is far from ubiquitous and has several caveats. The magnitude of difference in task duration for the force-matching task over the position-matching task for extremity muscle groups has been found to depend upon: 1) the intensity of the submaximal contraction (104, 201, 288); 2) the posture of the limb and the body (286, 290); and 3) the amount of proximal stabilization and limb support provided during task performance (32, 265, 338). The effect of each of these conditions is to reduce and even eliminate the difference in TTF between the two tasks because each condition has been found to influence the total amount of muscle activation required by not only the primary movers but also synergists, accessory muscles and postural stabilizers. Thus, while this is not the first study to find results about task duration that differ from the most common result, this is the first extremity muscle study to report the direct opposite result: the TTF for the position-matching task with the elbow flexors was 42% longer than the force-matching task. Recently, one study evaluating the trunk extensors has also reported similar results (321). Two aspects of the experimental setup used in this study may have contributed to the reversal in task duration result: 1) subject stabilization and 2) sensitivity of the visual feedback (Note: Both of these factors will be discussed below as both are plausible explanations for the task specific differences found for the absolute magnitude of corticospinal excitability as well).

Prior to discussing the factors that could explain the unexpected TTF result as well as the associated neurophysiologic outcomes, to ensure the validity of the experimental strategy and therefore its usefulness for addressing the stated hypotheses about neural mechanisms of task failure in sustained submaximal contractions, it is worth highlighting the performance results that were consistent with prior force-
matching/position-matching studies. First, despite the differences in TTF, the amount of muscle fatigue that developed throughout the duration of the contractions, as measured by the decline in MVC force at task failure, was similar for the two tasks (i.e. 30±15% and 30±18%). This result is comparable to the results reported from prior studies of the elbow flexors using a 15%MVC (17, 152). Second, at task failure, the amount of perceived effort reported by subjects, using the RPE scale, increased to the same value for both tasks. Therefore, consistent with the paradigm, at task failure both the force-matching and position-matching tasks ended with the same amount of physical and perceptual fatigue despite having a 42% difference in task duration (104, 152, 202, 288). Third, consistent with the intensity/duration characteristics of sustained submaximal contractions (i.e. lower intensity contractions have a longer duration), the absolute target force the individual subjects exerted with the elbow flexors was a significant contributor to the TTF for both the force-matching and the position-matching tasks (98, 287) and eliminated the gender differences found for TTF (150). As one of the caveats stated above, prior studies examining the difference in TTF for these two tasks performed with the elbow flexors, as well as other extremity muscle groups, have found that for greater contraction intensities (i.e. ≥45%MVC), the difference in TTF between the two tasks is no longer significant (104, 201, 288). This suggests that for stronger contractions, less motor units are available to be recruited as the task progresses because more motor units will be recruited at the start of the sustained submaximal fatigue task. Additionally, the magnitude of the absolute target force explained 73% of the variability in the difference in TTF between the two tasks. The stronger subjects who sustained a higher absolute target force were more likely to have similar TTF for both tasks, whereas weaker subjects with a lower absolute target force had a greater difference in TTF.
between tasks with a significantly longer TTF for the position-matching task. In prior studies, the difference in TTF has been attributed to faster and/or greater recruitment of the motor pool during the shorter task (17, 228). Therefore, in this study, for the stronger subjects with a higher magnitude absolute target force, most likely a greater proportion of the motor pool was recruited at the start of both fatigue tasks in order to produce the force output needed for task performance. This then would have left fewer unrecruited motor units available to be recruited as the contraction duration progressed thus eliminating the different in TTF.

**Task-Specific Differences in Measures of Supraspinal and Spinal Excitability**

The absolute magnitude of corticospinal excitability, both with (MEP) and without volitional drive (MEP elicited in the SP), was greater throughout performance of the force-matching task relative to the position-matching task (MEP: Figure 25A; MEP elicited in the SP: Figure 26A). However, the two tasks had similar absolute magnitudes of spinal excitability (CMEP elicited in the SP: Figure 26B) and did not differ in values for intracortical excitability (ICF, SICI: Figure 27A and 27B) and corticospinal inhibition (SP, LII: Figure 25B and 27C). In other words, a greater amount of corticospinal activity was needed in order to meet the mechanical demands of the force-matching task compared to the position-matching task. Additionally, there were no significant task-specific differences in the total amount of change in excitability that developed between baseline and task failure for all of the neurophysiologic outcome measures. Although the same magnitude of change in the measures of supraspinal and spinal excitability were achieved in a mean shorter period of time during the force-matching task (i.e. because the force-matching task was 42% shorter than the position-matching task for the entire
subject set), the statistical analyses comparing the individual slopes used as the measure of rate of change were not significant. Together, these results suggest that the shorter duration force-matching task required an overall greater magnitude of corticospinal excitation in order to perform the task as compared to the position-matching task, but the net change in excitation that occurred as fatigue developed during task performance, did not differ between the two tasks.

The only prior study comparing cortical and spinal excitability measures found equivalent changes in corticospinal excitability, as measured by MEP amplitude, and a task specific difference in spinal excitability, measured with the H-reflex, such that the shorter duration position-matching task had both a greater and faster decline in spinal excitability (168). Therefore, because the same level of descending drive had to overcome differing levels of spinal resistance, the difference in TTF between the two tasks have been attributed to spinal mechanisms in general, and then specifically to the role of the stretch reflex in position-matching task performance (13, 104, 168, 202). The shorter duration of the position-matching task has been ascribed to a decline in neural activation of the muscle secondary to a decrease in peripheral sensory afferent drive to the motor pool from the muscle spindle Ia afferent fiber as opposed to a reduction in descending motor drive or adaptations intrinsic to the motorneuron that modulate firing rates (13, 17, 104, 153, 168). Specifically, during the position-matching task, due to the effect that load compliance has on the sensitivity of the stretch reflex, it is thought that there is a withdrawal or reduction in Ia afferent fiber facilitation to the motor pool, as opposed to direct reflex inhibition of the motor pool from group III and IV afferents from muscle metaboreceptors. This disfacilitation is suggested to be mediated by presynaptic inhibition of the Ia afferent fiber by descending inputs thereby permitting more sensory
feedback to be delivered to supraspinal centers which can then be used to adjust the drive to the motor pool via long loop reflex control (17, 168). Evidence to support this hypothesis include the task-specific differences in H-reflex amplitude (168), which involves direct stimulation of the Ia fiber to evoke a response, and in measures of Ia presynaptic inhibition which were found to decrease during the longer duration force-matching task (17). The purpose of the presynaptic inhibition is suggested to permit greater cortical influence over the motor pool in order to minimize force fluctuations (104, 297). Therefore, the question generated by this data that needs to be addressed is: *Why was there a greater amount of corticospinal excitability required during the force-matching task?* Prior studies using the force-matching/position-matching task paradigm to investigate neural mechanisms associated with task failure have suggested that there are fundamental differences in central neural control strategies that are driven by the task demands, specifically the compliance or stiffness of the load (13, 104, 106, 152, 153, 202, 286, 288, 338). This same rationale of different neural control strategy most likely explains the shorter duration and enhanced level of corticospinal excitability found in this study for the force-matching task and, in addition to differences in load compliance, could be driven by two specific elements of the experimental setup used in this study: 1) the absence of stabilization and limb constraint during task performance and 2) the sensitivity of the visual feedback.

It is well understood that less stabilization requires that more muscles are used to perform the task and if more muscles perform the task, then there is an overall greater level of central neural drive (13, 186, 286, 288). Greater stabilization has been associated with less muscle activation of prime movers and accessory muscles as well as a longer TTF for the force-matching task (153, 286, 288, 290). It should be noted,
that to date, co-activation ratios between the agonist prime movers and antagonists have been found to be the same between the two tasks and therefore do not contribute to the differences in time to task failure (153, 168, 192, 201). In this study, every effort was made to ensure equivalent mechanical demands during task performance (Figure 19). Therefore, external supports (i.e. straps) were not used to restrict motions at the shoulder or the torso in order to equalize the demand placed on synergists, proximal joints, and postural stabilizers between the two fatigue-tasks. Additionally, the arm was free to move in all degrees of freedom, with the tether used in the force-matching task limiting elbow flexion to 90° but not holding the arm securely in place unlike the commonly used setup that clamps the arm in place during the force-matching tasks (Compare Figure 6 and 7 with Figure 19) (16, 17, 152, 168, 201, 286, 288-290, 338). Accordingly, the increase in cortical excitability combined with the shorter task duration found in this study for the force-matching task could be related to the overall amount of muscle activity needed within the upper extremity and torso to perform the task.

Two studies using lower limb muscles have compared the TTF across three conditions: the typical free-motion position matching task, a more restrained position-matching task, and the typical setup for the force-matching task (265, 338). As expected, with a greater the amount of restraint provided to the limb during the position-matching task, the difference between the force-matching and position-matching tasks was reduced by half (Figure 6) (265, 338). With more restraint there were less degrees of freedom to control during the position-matching task as well as less compensatory movements to prevent at other joints. One additional “benefit” of restraint and stabilization from external supports during task performance is that it is easier for
synergist muscles from both proximal and distal joints to assist in isometric task performance. Indeed, the intention of effective stabilization during isometric task performance is to minimize joint motion that could occur at other joints; however, just because the joint motions are restricted does not mean that these other muscles are not producing force. For example, greater activation was recorded in the rectus femoris muscle during the force-matching task performed by the dorsiflexors. It was suggested that the hip flexion action of the rectus femoris could assist in task performance as both the foot and leg were restrained (153).

In this study, because the subjects were unrestrained, they were closely monitored and were specifically instructed that no other joint or body motions were permitted that would put tension through the tether connecting the wrist to the force transducer (e.g. no lateral trunk lean, no shoulder shrugging), they could only bend the elbow aiming the thumb towards the ceiling. Because subjects were not stabilized and the limb was not restrained in either fatigue task, the demands placed upon postural stabilizers and accessory muscles, in order to maintain postural alignment and to prevent limb motions in the transverse and frontal planes of motion, were most likely equivalent in this study. Thus, the difference in cortical excitability—as well as TTF—may be more related to the degree of cortical control needed to manage these multiple degrees of freedom within the body. In other words, in addition to the quantity of muscles that needed to be activated for task performance, the two tasks may have required different amounts of corticospinal inputs to the motor pool in addition to the elbow flexors to achieve the correct task performance. This type of control, since constant throughout task performance, would be independent from the amount of
change needed to overcome declines in spinal excitability, as fatigue developed which did not differ between the two tasks.

The input from direct corticospinal inputs to the motor pool during task performance is important for accurate motor control of distal limb motions (190, 191, 280). The MEP amplitudes recorded from the muscles involved in performing a precision grip were significantly greater than those recorded during a power grasp (139). The evoked potential in response to a TMS pulse delivered to the motor cortex is produced primarily through conduction of the stimulus through the large diameter corticospinal neurons that have monosynaptic excitatory connections with motoneurons (91, 170). Therefore, the change in motor control demanded by the setup used in this experiment may have required a greater amount of cortical control rather than spinal control during the force-matching task based upon the requirements set for task performance that could be separate from or in addition to the need to provide adequate output in order to override spinal resistance to continue task performance.

In general it can be argued that sustained submaximal contractions are more challenging tasks for the nervous system to not only sustain but also to control when compared to sustained maximal contractions (28, 123). This is one reason why neural mechanisms are considered to have greater influence in submaximal task failure. Unlike in maximal contractions where the defined performance criteria is the individual’s maximum force output, in sustained submaximal contractions subjects are required to sustain a particular amount of force output and also to stay within a particular bandwidth that is set around that target level, “the Goldilocks” value, not too much or too little. In addition, depending upon the amount of stabilization provided, the output needs to be sustained without using other movement strategies to compensate for fatigue in order to
prolong task performance. Therefore, task failure for sustained submaximal contractions is defined by a combination of both kinetic and kinematic performance criteria that are influenced by the amount of stabilization and output accuracy, as opposed to merely a decline in maximum force output.

The second potential source for the longer duration position-matching task may be due a difference in the sensitivity of or resolution of the visual feedback to detect fluctuations in output. From a motor control perspective, both of these tasks can be considered to be analogous to a sustained visuomotor tracking task because the only way the subject knows that the force output is correct is through constant visual feedback (185, 187, 188, 264). The shorter duration task is considered to be the more difficult task by subjects during task performance even though the mechanical demands, torque output, and amount of muscle fatigue at task failure are equivalent between the two tasks (104, 202). Indeed in this study, subjects anecdotally reported that the force-matching task was “harder” specifically because it was more challenging to keep the feedback line steady. For both tasks, the verbal instructions given to the participant were to “keep the line as close to the target line for as long as you possibly can without using compensations at other joints.” As reported previously the position-matching task ended suddenly and the force matching task ended more gradually (152, 202). More specifically, at task failure for the position-matching task, subjects commonly noted that they had to stop because they could not keep the arm in this position any longer whereas, in the force-matching task, subjects noted over a considerable period of time that it was getting harder and harder to get the muscle to give enough force to keep the feedback line on the target line.
A prior study comparing the effect of visual feedback signal gain during the position-matching task found an increase in TTF for a wider bandwidth of performance (227). This suggests that had the boundary be wider, performance could have lasted longer. Perhaps it is not just the boundary but also the sensitivity inside that boundary that matters (187, 188). The on-screen bandwidth was set as the criteria for defining task failure was the same for the two tasks such that the decline in performance output resulted in a similar drop in the net elbow flexor torque (i.e. force output or moment arm length set by joint position) for each task. However, the sensitivity of the force transducer to detect fluctuations in force output within that bandwidth and thus project those fluctuations on screen as visual feedback to the subject may have been greater than the sensitivity of the eletrogoniometer for detecting the effect of those force fluctuations had on joint angle position. Therefore, during the position-matching task, slight fluctuations in motor output may not be as obvious to the participant as compared to the force-matching task and therefore would not merit the need for corrective action by the subject in order to maintain their feedback line close to the target line. This suggests that the two tasks may have differed not only in load compliance but also in the demand for feedback-driven corrections in motor output requiring greater cortical control.

The overall increase in cortical excitability could be from excitatory inputs provided by the posterior parietal cortex in response to the heightened visual feedback. The posterior parietal cortex has extensive excitatory intracortical connections with the primary motor cortex that are activated during visually guided motions where the accuracy of the motor output depends upon visually identified targets (171). To explore this possibility, data regarding fluctuations in vertical and horizontal acceleration, both amplitude and frequency, during task performance would be beneficial. Prior studies
comparing force fluctuations between the force-matching and position-matching tasks have found greater amplitude and variability in force output at task failure for the position-matching task (104, 202). This is consistent with the hypothesis about differential regulation of the stretch reflex afferent feedback to the spinal cord and the motor cortex (104, 297). Additionally force fluctuations at task failure have been associated with increased muscle activation (222). Because of the transient involuntary effect that the evoked potentials have on force output and position (i.e. spike in force and “jump” in position) combined with the frequency of the stimuli delivered during task performance, the choice was made to not add accelerometers to the cast in order to detect fluctuations in vertical and horizontal acceleration associated with performance. Therefore it is not possible to determine if in addition to causing the same amount of muscle fatigue, both tasks ended with the same amount of fluctuations in output. Together these results, in combination with others investing differences in proximal stabilization and the effect of visual feedback on force control, suggests that there is something more than/other than load compliance that make the time to task failure for these two tasks differ.

**Supraspinal Contributions to Task Failure**

Although there were no task-specific differences found for the changes in excitability, the data from this experiment adds to the growing understanding of the neurologic mechanisms involved in the decline in force output that limits the duration of a sustained submaximal contraction by investigating the contribution of supraspinal adjustments stemming from changes in intracortical and corticospinal excitability relative to concurrent changes in spinal excitability. At task failure for both the force-matching
and position-matching tasks, a similar amount of decline in motorneuron excitability
developed as measured by the amplitude of the CMEP elicited in the SP. Additionally,
the amount of increase in corticospinal excitability, as measured by the single pulse
MEP, was also similar at task failure for both tasks. Therefore, consistent with prior
research, both fatigue-tasks ended secondary to a decline in motorneuron excitability
coupled with a failure of supraspinal input to successfully sustain motorneuron activity
(168, 214, 218). That task failure occurred for both the force-matching and position-
matching tasks after a similar mean decline in motorneuron excitability coupled with a
similar mean increase in corticospinal excitability suggests that, in general, the motor
cortex is able to compensate for changes in spinal excitability until a particular amount of
change develops. At that point, unless more drive is provided from the motor cortex,
failure occurs. These findings are consistent with the general mechanism for task fail
ure proposed from single motor unit studies, namely task duration is determined by the rate
of recruitment of the motor pool by descending drive to compensate for the declining
force output from active motor units (17, 202, 214, 218).

The next question to answer then is why is the motor cortex eventually unable to
sustain activation of the motor pool? To address this question, two competing
hypotheses/questions posed in the literature (104, 123, 279) were addressed by the data
in this experiment: 1) Is there evidence to support that the cortex itself becomes
inhibited, analogous to the spinal cord, which would then decrease the amount of
descending drive? 2) Is there evidence to suggest that there is a lack of excitatory drive
provided from upstream sources to the motor cortex that would be needed to sustain
descending drive?
During the performance of both fatigue-tasks, the duration of the silent period increased (Figure 25B and 29B) which would suggest an increase in intracortical inhibition; however, the direct measures of intracortical excitability do not support this interpretation. First, the amount of intracortical inhibition, as indexed by the value of the SICI ratio, progressively decreased throughout fatigue-task performance by nearly 30% for both tasks (Figure 27A and 29A). In general, SICI is considered to be mediated locally within the motor cortex such that changes in SICI are interpreted to reflect selective focusing of cortical excitability and corticospinal outputs involved in task performance in the muscle used for voluntary contractions (253, 273). In addition, prior studies that have used SICI to assess the intracortical changes that develop during fatigue associated with sustained or intermittent MVCs found significant decreases in intracortical inhibition localized to the muscle participating in the task (20, 209, 330). Second, the amount of intracortical facilitation, indexed by the ICF ratio did not change throughout either fatigue-task (Figure 27B and 29A). This indicated that there was neither an increase nor decrease in the amount of facilitation within the motor cortex. The ICF ratio, like the SICI ratio, is thought to reflect changes in local motor cortex excitability (92, 270). One prior study investigating fatigue associated with the performance of intermittent MVCs reported the same result as found in this experiment (209). Because of the way that that SICI and ICF are evoked through the paired-pulse protocol that investigates the effect of a subthreshold stimulus, that selectively activates the intracortical neurons, on the amplitude of the MEP evoked by the second stimulus, the values for SICI and ICF reflect the excitability of the intracortical circuitry within the motor cortex that synapse upon the corticospinal projections to the motor pool (60, 91, 179, 284). Therefore, when the normalized values for SICI and ICF were compared to
each other (Figure 29A), there was a significantly lower amount of intracortical inhibition at task failure; however, the amount of intracortical facilitation did not increase as fatigue progressed.

The amount of change that occurred in corticospinal excitability assessed in the presence of voluntary drive, indexed by the single, unconditioned MEP, did not significantly differ from the amount of change in corticospinal excitability measured during the silent period when volitional drive was temporarily suspended during both fatigue tasks (MEP elicited in the SP). Both values increased by ~175% (Figure 28A). If the motor cortex were becoming progressively inhibited as the traditional interpretation of the increased duration of the SP implies, then the amount of change in excitability for the MEP elicited in the SP would not have increased as much as the single MEP evoked in the presence of volitional drive. Additionally, the magnitude of change for the single, unconditioned MEP was not greater than the magnitude of change for the MEP elicited in the SP suggests that upstream input to the motor cortex remained consistent relative to the level of ongoing output from the motor cortex as fatigue developed. Further support for this result comes from the lack of change in the value for the LII ratio throughout task performance (Figure 27C and 29B). Recall that this value is the ratio of the two MEP values: the value for the MEP elicited in the SP independent from volitional drive to the value for the MEP evoked in the presence of volitional drive. Therefore, the LII ratio could be considered to represent the effect of volitional drive on corticospinal excitability. Taken together, when compared to the amount of change in the amplitude of the CMEP elicited in the SP (Figure 28B), these results indicate that increases in corticospinal excitability are not accompanied by inhibition within the motor cortex. Instead these results indicate that the increase in intracortical excitability that drives the
amount of descending drive needed to overcome spinal cord resistance is mediated by decreasing intracortical inhibition that exceeds the amount of change in intracortical facilitation and excitation delivered to the motor cortex from upstream drive. Therefore, the supraspinal mechanisms that limit task duration is most likely mediated by inadequate upstream excitatory drive to the motor cortex, as opposed to increased intracortical inhibition, as the increased SP duration would imply. Upstream drive can be influenced by the level of motivation as reflected by the RPE (102, 123). It can also be affected by sensory afferents from the periphery to the cortex including both Ia proprioceptive afferents as discussed in the previous section about task differences as well as inputs from the group III and IV metaboreceptors (13, 123, 202). Recent evidence suggests that the group III and IV afferents have a greater effect on cortical excitability compared to spinal excitability (208). Finally, when the normalized values for the changes in LII ratio were compared to the normalized SP duration, there was no interaction. Instead, when the normalized SP was compared to the normalized values for the cortical and spinal measures evoked during the silent period the results suggest that as the duration of the SP increase, the amount of spinal excitability decreases while the amount of cortical excitability independent from ongoing volitional drive increases. Therefore, these results also support the conclusion that the change in SP duration that occurs during fatigue is most likely mediated by the progressive decline in spinal excitability and not to an increase in intracortical inhibition (Figure 30).
Conclusion

Together, these results suggest that as fatigue develops prior to task failure, the increase in corticospinal excitability observed in relationship to the decrease in spinal excitability results from a combination of decreasing intracortical inhibition and constant levels of intracortical facilitation and upstream excitability which eventually fails to provide the input to the motor cortex necessary to overcome the spinal cord resistance, thereby contributing to task failure. Therefore, rather than the development of a global non-specific increase in the membrane excitability of cortical neurons, which would permit the concurrent development of opposing intracortical inhibition and excitation within the motor cortex as the previous interpretations of increased SP duration and increased MEP amplitude have implied (19, 104, 123, 293), these results suggest that the upstream drive to the motor cortex eventually limits the supraspinal capacity to endlessly override spinal resistance,. These results also support the conclusion from McNeil et al. that the increase in duration of the silent period that occurs during fatiguing contractions is most likely due to spinal mechanisms reducing motorneuron excitability and therefore, would be best viewed as a measure of corticospinal inhibition and not intracortical inhibition when measured during fatigue (216, 218). Additionally, although task-specific differences in the neurophysiologic variables were not found in this study, these results do add to a growing body of work that supports the efficacy of the two-task approach to explore the neural mechanisms of task failure. That the opposite task was found to have the shorter TTF (i.e. force-matching < position-matching), supports the prior conclusion of a task specific difference in central neural command in motor unit recruitment (13, 17, 227); however the source of the task specificity may be due to
factors other than load compliance, including the amount of stabilization provided to the body and limb and the corrective demand driven by the sensitivity of the visual feedback within the same range of gain (187, 188).
CHAPTER 4: ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION

ENHANCES TIME TO TASK FAILURE OF A
SUSTAINED SUBMAXIMAL CONTRACTION

Abstract

As fatigue develops during isometric submaximal contractions, the amount of excitatory descending drive from supraspinal regions to the spinal motorneuron pool increases to sustain task performance through motor unit recruitment. This suggests that task duration could be prolonged if supraspinal excitability could be specifically manipulated. Transcranial direct current stimulation (tDCS), a form of non-invasive neurostimulation using weak direct electrical currents (1-2mA) delivered to the brain through surface electrodes, is one of the major tools used to modulate cortical excitability in studies investigating mechanisms of neural plasticity. Anodal tDCS transiently increases motor cortex excitability both during and after stimulation and has been found to improve the speed and accuracy of motor skill performance when applied during practice. This suggests that tDCS may also improve performance of sustained submaximal contractions. Therefore, the purpose of this study was to determine whether delivering anodal tDCS during the performance of a sustained submaximal contraction would increase task duration compared to a sham tDCS condition. Eighteen healthy volunteers (9 men and women; 25±6 yrs) performed two sustained contractions at 20% of maximum voluntary contraction (MVC) strength with the elbow flexors on two separate visits (7.6±1.5 days). During fatigue task performance, either anodal or sham stimulation was delivered to the motor cortex for up to 20 minutes, per published
recommendations for safe administration of tDCS. The order of the stimulation conditions was counterbalanced and both subjects and lead investigator were blinded to stimulation condition. Single pulse transcranial magnetic stimulation (TMS) was used to assess changes in corticospinal excitability induced by tDCS during task performance. Outcomes included time to task failure (TTF), amount of muscle fatigue, rating of perceived exertion (RPE), and motor evoked potential (MEP) amplitude. There was no systematic effect of the anodal tDCS stimulation on the TTF for the entire subject set (n=18; p=0.64 ES 0.01). Accordingly, subjects were divided into two tDCS-time groups: Full-Time (n=8, 2 women, 6 men), where the TTF occurred prior to the termination of the tDCS, and Part-Time (n=10, 7 women, 3 men), where the TTF extended beyond the termination of the tDCS. The TTF for the Full-Time was 31% longer for the anodal tDCS stimulation condition when compared to the sham stimulation condition (p=0.04; ES 0.47) whereas the TTF for the Part-Time group did not change (p=0.81; ES 0.01). Therefore, the remainder of the analysis focused on the outcomes for the Full-Time group. The amount of muscle fatigue was 6% greater at task failure with anodal tDCS compared to sham (p=0.05; ES 0.44) for the Full-Time group. The anodal tDCS also increased the amount of time that the Full-Time group was able to perform the task at an RPE between 8-10 (“very hard”) by 38% (p=0.04; ES 0.47). There was no difference between the stimulation conditions for the amount of change in corticospinal excitability measured during the first 8:30 minutes of the contraction for the Full-Time group (n=7, MEP amplitude biceps p=0.56; brachioradialis p=0.31). That the targeted delivery of anodal tDCS (i.e. an intervention known to increase excitability to supraspinal structures) during task performance both prolonged the time to task failure and increased the amount of muscle fatigue suggests that augmenting cortical excitability enhanced
descending drive to the spinal motorpool to recruit more motor units. Therefore, even in the absence of a change in direct measures of corticospinal excitability, these data provide evidence to support the conclusion that upstream drive to the motor cortex is a key mechanistic component in task failure. Finally, the results suggest that the application of tDCS during performance of fatiguing submaximal contractions has the potential to enhance the capacity to exercise under conditions required to derive benefits due to overload, which has significant applications for rehabilitation.

Introduction

In healthy individuals, fatigue is an expected and normal physiologic reaction to sustained and to intense activity (123, 169). The human experience of fatigue is both physical and perceptual (107, 169, 310). The physical experience of fatigue in healthy individuals involves observable decrements in performance such as a decline in force output or deterioration in the kinetic or kinematic accuracy of movements over time (13, 123, 202, 310). The associated perceptual experience of fatigue during performance is described by the increased sense of effort required to sustain the force or difficulty in meeting the goal of an activity (13, 48, 107, 314). Fatigue, like the generation of a voluntary contraction, involves a multi-factorial physiologic process involving the nervous system and the muscle both of which undergo functional adjustments as a contraction continues (13, 28). The major question in fatigue studies has been “which of these events determine performance and which are simply incidental by-products” because “finding those which are not responsible is as valuable as investigating those that are” (28, p. 693). The assumption being that if the limiting physiologic mechanisms can be
found, then perhaps interventions can be used to effectively reduce fatigue and prolong performance.

It is well accepted that the mechanisms of fatigue are task specific and therefore, there is no single cause of fatigue (28, 102, 107, 123). In general, it has been shown that the nervous system's failure to maintain sufficient activation of the muscle is a significant contributor to the decrease in force output and to the eventuality of task failure in sustained submaximal contractions as compared to maximal contractions (13, 27, 98, 123 #97, 125, 135, 196, 303). Recent work investigating spinal mechanisms has provided convincing evidence that as the task duration progresses, the spinal excitability declines as the motorneurons become progressively resistant to activation (168, 214, 218) (See also Chapter 3). In order to sustain task performance as fatigue develops, the amount of excitatory descending drive from supraspinal regions increases to compensate for the reduced excitability of the spinal region (13, 21-23, 123, 125, 129, 135, 196, 279, 303). However, the fatigue will progress to a degree such that it will eventually prohibit effective task performance despite the compensatory mechanisms from supraspinal inputs (104, 214, 218). This suggests that task duration could be prolonged if supraspinal excitability could be specifically manipulated.

Unlike pharmacologic manipulation with substances like caffeine that have a systemic affect on all levels of the neuromuscular system (159), transcranial direct current stimulation (tDCS) is a form of non-invasive neurostimulation that involves the application of weak direct electrical currents (1-2mA) to the brain through sponge electrodes (25-35cm²) placed on the on the scalp (78, 145, 260, 331). tDCS differs from other brain stimulation techniques, such as transcranial magnetic stimulation (TMS), as the density (mA/cm²) of current delivered is not sufficient to directly stimulate axons
causing them to discharge (182, 243, 267), instead the current acutely modifies the resting membrane potential by either tonically depolarizing or hyperpolarizing it at a sub-threshold level thereby adjusting the ongoing firing activity of the neurons during stimulation (33, 237, 281, 331). Numerous studies in recent years have demonstrated that anodal tDCS (i.e., where current flows from the anodal electrode located over the motor cortex to the cathode placed over the contralateral forehead) acutely increases motor cortex excitability, as measured by TMS, both during and after stimulation (235-237, 240, 241, 243-245, 267, 305). The degree and duration of the after-stimulation effects of tDCS on both cortical excitability and motor performance have been found to depend upon current strength, electrode size, and stimulation duration, as well as the timing of stimulation (i.e. before or during) relative to motor practice (15, 271). For example, anodal tDCS delivered for a minimum of 13 minutes using 35cm² electrodes has been shown to increase measures of intracortical facilitation and simultaneously decrease intracortical inhibition for up to 90-minutes after the stimulation (240, 241, 243, 245, 305).

Because of the sustained but transient changes in cortical excitability combined with the ease in administration and the ability to do sham controlled double-blind experiments, tDCS has become one of the major tools to investigate the cortical mechanisms of neural plasticity and motor learning in the past two decades (33, 42, 127, 181, 270, 271, 281). In healthy subjects and individuals after stroke, anodal tDCS (1.0-2.0mA, 25-35cm² electrodes, 10-20 minutes) applied over the motor cortex during task practice has been shown to improve the speed and accuracy of performance of motor tasks, to enhance the rate of learning new motor tasks, and to facilitate recovery of function after CNS lesions (15, 145, 235, 242, 270, 271, 281, 305). It is interesting to
note that the majority of the studies evaluating the effects of tDCS to date have rarely examined changes in motor function and cortical excitability concurrently or during the same experiment; thus, the direct relationships between changes in motor performance and excitability induced by tDCS remain largely unexplored (15, 235, 242).

The findings about the capacity of non-invasive brain stimulation using tDCS to both increase cortical excitability and improve motor performance suggest that it also has the potential to inform the mechanistic study of muscle fatigue as well as to enhance muscle performance (i.e. endurance time) during sustained fatiguing contractions. Presently, only one study has examined the effects of anodal tDCS as an experimental means to modulate cortical excitability on muscle fatigue performance measures (70). In this cross-over design study, subjects completed two submaximal fatiguing contractions with the elbow flexors during the same test session and received either anodal (excitatory) or cathodal (inhibitory) tDCS between the two contractions. A second group of different subjects received sham stimulation. Although all subject groups had a shorter time to task failure for the second contraction in the session relative to the first, individuals who received the anodal tDCS before the second contraction had a significantly longer endurance time compared to both the cathodal and sham conditions.

The purpose of this study was to determine whether delivering anodal tDCS during the performance of a sustained, submaximal elbow flexion task would enhance the time to task failure when compared to a sham tDCS condition. I hypothesized that anodal tDCS would prolong the time to task failure relative to sham stimulation. In addition to measuring the effects of tDCS on the time to task failure, I also examined its influence on neurophysiologic measures of cortical excitability as assessed by single pulse TMS (i.e., motor evoked potential amplitude) during the fatiguing contraction.
Methods

Subjects

Eighteen healthy, right-handed, adult subjects (25 ± 6 years; 9 men and 9 women) participated in the two testing sessions. Prior to participation, each subject attended an orientation session where they completed a series of questionnaires to confirm they were free from any known neurologic disorder, cardiovascular disease, or musculoskeletal injury in the upper extremities. Handedness was evaluated using the Edinburgh Handedness Inventory (80±22%) with scores greater than 40% indicating right hand dominance (250). Subjects were also familiarized to the activities of the experiment by practicing maximum voluntary contractions (MVC) and the 20% MVC force-matching task used during the fatiguing contraction with the elbow flexors. The Institutional Review Board at Ohio University approved the study protocol, and all study participants provided written informed consent.

General Overview of the Experiment Protocol and Testing Sessions (Figure 31)

Subjects completed two experimental sessions separated by a minimum of 7 days (range: 7-13 days; average: 7.61 ± 1.46 days). Both visits were conducted at the same time of day for each subject. During each test session, subjects performed a sustained, submaximal isometric contraction for as long as possible (i.e. to volitional task failure) with the elbow flexors of the non-dominant (i.e. left) arm that was equal to 20% of their MVC. Subjects were provided with visual feedback of their force output relative to the target force throughout the contraction. Either anodal tDCS stimulation or sham
stimulation was delivered to the motor cortex for up to 20 minutes while the subjects performed the fatiguing contraction. Because previous studies have found that the TTF can increase in certain individuals across sessions (149), the order of the tDCS stimulation conditions (anodal or sham) were counterbalanced (Anodal visit-1 → Sham visit-2: 3 men and 5 women; Sham visit-1 → Anodal visit-2: 6 men and 4 women). Single pulse TMS was used to measure changes in corticospinal excitability (MEP peak-to-peak amplitude) induced by tDCS and the fatiguing contraction at two absolute time points during fatigue task performance. Outcomes included the time to task failure (TTF), muscle fatigue which was quantified as the difference in elbow flexor MVC before vs. after the fatiguing contraction, rating of perceived exertion (RPE) using the modified Borg 10-point scale (34), and MEP amplitude. Both the subjects and the primary experimenter (PSW) were blinded to the tDCS stimulation condition and subjects were not informed of their time to task failure until both visits were completed.

Each test session started with testing elbow flexor MVC. Subjects then performed 2 bouts of short duration (3-5 second) non-fatiguing 20% MVC contractions during which the motor hotspot for the biceps was located, the tDCS electrodes placed, and the TMS test stimulus intensity determined. Subjects began the fatigue task with no tDCS (anodal or sham) being delivered. At 1-minute into the fatigue task, RPE was obtained and 6 motor evoked potentials were elicited using TMS (5-sec between pulses). Immediately after the TMS measures were completed, the tDCS stimulation was initiated (i.e. after 1-min 30-sec of the fatigue task). After 7 minutes of tDCS (at 8-min 30-sec of the fatigue task), subjects were again asked their RPE and another 6 single TMS pulses were delivered. This time frame was chosen for two reasons: 1) it was anticipated that all subjects would be able to sustain the 20% MVC contraction at
least 8-min 30-sec (and all subjects were able to perform the task through this point) and 2) anodal tDCS delivered for 7 minutes has been shown to be sufficient to modify cortical excitability with changes that persist for 5-10 minutes after turning off the current (236, 243, 245). Regardless of the subject’s fatigue task contraction time, the tDCS stimulator was programmed to deliver current for a maximum of 20 minutes (anodal or sham), consistent with maximum stimulation durations currently reported in the literature examining motor function (15, 242). Knowledge about the safety boundaries for current density and duration is limited; therefore, it is recommended that tDCS current density and duration stay within those used in already tested protocols (235, 238, 242). To date, sham-controlled studies investigating changes in motor performance (e.g. dexterity) or MEP amplitude induced by anodal tDCS with electrodes over the motor cortex and contralateral orbit have not used a current density greater 0.043 mA/cm² for more than 20 minutes (15, 242). Therefore, it was expected that the contraction time for some subjects would exceed the tDCS stimulation time. Subjects were not informed as to the timing for the tDCS (i.e. start time or duration) or when RPE and TMS would occur during the fatiguing contraction. Just prior to task failure, subjects performed a maximal contraction (prior to relaxing), and a final RPE was obtained. After finishing the protocol, subjects answered a series of questions about any transient adverse effects they may have experienced during the tDCS (41, 78).

Experimental Setup and Mechanical Recordings (Figure 32)

Subjects were seated upright in an adjustable chair with the left arm positioned next to the body in 10-15° of abduction and the upper arm supported at the elbow (Biodex System 4, Biodex Medical Systems Inc., Shirley, NY). The elbow joint was
flexed to 90° and aligned with the axis of rotation of the torque motor with the forearm positioned in neutral (0° rotation) and the thumb pointing towards the ceiling. To obviate the use of the hand and wrist muscles during testing as well as to provide a secure and consistent attachment to the lever arm from the torque motor, subjects wore a prefabricated Wrist-Hand-Thumb orthosis (Model 1000, Orthomerica, Newport Beach, CA). The lever arm length was adjusted so that the point of application for the resistance was located just proximal to the wrist joint on the superior surface of the forearm. The orthosis was then securely strapped to the lever arm thereby maintaining the elbow in 90° and forearm in neutral throughout the testing session. Individuals were also securely strapped to the chair over both shoulders and at the waist in order to minimize the demand on proximal segments during task performance and to restrict motion in other planes (265). The resolution of the signal representing the isometric torque output of the elbow flexors was scaled to 39.1 mV / ft lb. (Biodex Researchers Tool Kit Software), sampled at 625 Hz and smoothed over a 10 pt median epoch (MP150, BioPac Systems, Inc.). This processed signal was provided as visual feedback representing the subject’s elbow flexor force output in ft-lbs (this unit of measurement provided a meaningful frame of reference for the subject) and displayed on a 14-inch computer monitor located within 1 meter in front of the subject. To create a 0 value baseline indicating that the arm was indeed relaxed between contractions, the extension torque value created by the weight of the relaxed arm strapped to the torque motor lever arm was added as a constant to the smoothed torque signal. Arm weight was confirmed at the start of the second session to ensure that the mechanical demands between testing sessions were identical (Arm weights Visit-1 and Visit-2 ICC_{(3,1)} = 0.966).
**Electrical Recordings**

Voluntary and evoked electromyographic (EMG) signals were recorded from the biceps brachii and the brachioradialis muscles using bipolar surface electrodes (Ag-AgCl, 8-mm diameter, Trace 1, interelectrode distance 25-mm, Nikomed, Huntingdon Valley, PA) located longitudinally over the muscle bellies on shaved, abraded and cleaned skin. The reference electrode was placed on the medial epidicondyle. EMG signals were amplified (1,000x), band-pass filtered (10-500 Hz), and sampled at 2,500 Hz (MP150, BioPac Systems Inc., Goleta, CA).

**Strength Testing of the Elbow Flexors**

Elbow flexion strength was defined as the MVC value of the elbow flexors. The MVC was calculated as the difference between the maximum value and the 0 value resting baseline. Subjects performed a minimum of three maximum isometric contractions against the stationary lever arm at the start of each testing session and then one final maximal contraction at task failure for each fatiguing contraction. To establish the baseline MVC, subjects were instructed to gradually increase their elbow flexion force to maximum over 3-sec and then hold that maximum force for 3-sec before relaxing. Standard verbal encouragement was provided (123) throughout the contraction and subjects were given visual feedback of their force output on the computer monitor. There was a 1-2 minute rest period between each contraction. If the MVC trials were not within 5% of each other or if subjects produced more torque with each trial, subjects performed additional contractions. The highest torque output was
used as the baseline MVC measure for each visit and was compared to the final MVC performed at task failure of the fatiguing contraction.

**Muscle Fatigue Task and tDCS**

The fatiguing contractions were performed at a target force of 20% of the MVC measured at the start of the first test session. Therefore, the same target force was used for both testing sessions. It should be noted that the MVC force measured at the start of each session did not differ between Visit-1 (171.47 ± 57.71 N) and Visit-2 (168.91 ± 57.06 N, *P* > .05, ICC$_{3,1}$ .981). Visual feedback of the force output was presented as a horizontal line across the computer screen whose position would shift up or down based on the force output from the elbow flexors. The gain of feedback was set to 2% MVC/cm with the time display set to 100 msec. The subject was instructed to keep the force output line as close to the target force line located in the middle of the screen for as long as possible. Verbal encouragement was provided to subjects to restore the position of the feedback line if they drifted away from the target force. The same experimenter (PSW) monitored the subject’s arm and body position and provided verbal feedback to correct any shifts in upper arm position on the elbow support. Task failure was declared if the feedback line drifted below 50% of the target force (i.e. ± 10% MVC) for longer than 3 seconds or when the subject decided to discontinue the task. At the end of the fatigue task, but prior to relaxing, the subjects were instructed to contract maximally and hold it for 2-3 seconds (Figure 31 provides an overview of the experimental protocols timeline.)

Anodal or sham tDCS was delivered to the right motor cortex, opposite of the left non-dominant arm, using a constant current stimulator (NeuroConn Eldith I Channel DC
Stimulator Plus, Rogue Resolutions, Cardiff, United Kingdom). For both conditions, two conductive-rubber electrodes (35 cm²) each enclosed in sponge pouches soaked with normal 0.9% saline solution (McKesson USP Normal Saline Sterile 0.9%, McKesson Medical-Surgical, Richmond, VA) were placed on the subject’s pre-moistened scalp with the stimulating electrode on the right motor cortex centered over the hotspot for the biceps and the active reference electrode on the left forehead just above the left eyebrow/orbit (Figure 32). During the anodal stimulation condition, a continuous current (1.5 mA) was delivered (35 cm² electrodes) for a current density of 0.043 mA/cm². The maximum duration for current delivery was 20 minutes with an 8-second ramp at the start and end; therefore the total charge did not exceed 0.051 C/cm² during anodal stimulation (average: 0.044 ± 0.008 C/cm²; range: 0.023 – 0.051 C/cm²). For the sham stimulation condition, current was delivered for just 30 seconds at the start and then the device stopped the current. At the conclusion of each testing session, all subjects were asked if they experience transient adverse effects resulting from the tDCS, using the questionnaire recommended by Brunoni et al. 2012. A total of 12 subjects in both the sham and anodal conditions subjects reported feeling either itching, tingling, burning, stinging, or warmth at the onset of current flow that typically resolved during the session or experienced skin redness underneath the electrodes. All were directly attributed to the tDCS and described as mild or moderate. No subjects reported any form of discomfort (i.e. headache, neck pain, scalp pain).

Transcranial Magnetic Stimulation

Single pulse TMS was used to evaluate the effect of tDCS on corticospinal excitability during the fatiguing contraction. A hand-held 70-mm diameter figure-of-8
focal coil connected to a BiStim\textsuperscript{2} stimulator (Jali Medical Inc., Woburn, MA) attached to two Magstim 200\textsuperscript{2} stimulators (The Magstim Co. Ltd., Whitland, United Kingdom) was used to deliver a monophasic magnetic pulse. The coil was positioned tangentially to the lateral surface of the scalp in the region of the right motor cortex with the handle pointing backwards and laterally 45° from midline. With the coil in this location and position; current is expected to flow from a posterior-lateral to anterior-medial direction in the cortex (37, 342). To find the optimal location that consistently elicited the largest peak-to-peak amplitude motor evoked potential (MEP) in the biceps (i.e. the motor hotspot), suprathreshold single TMS pulses (~60-90% of stimulator output) were delivered while subjects performed short duration (2-5 seconds) submaximal isometric contractions at 20% MVC. Subjects received the same visual feedback as they would during the fatiguing contraction. The coil was systematically moved in 1 cm increments around the anatomical location on the scalp corresponding to the upper extremity distribution in the underlying brain based upon EEG 10/20 measurements (78). After identifying the biceps motor hotspot, the two tDCS sponge electrodes were placed on the subject’s scalp (see below). From this point forward, all TMS pulses were delivered through the tDCS electrode located over the motor cortex. The motor hotspot position was confirmed and marked on the tDCS sponge for coil placement throughout the fatiguing contraction. To determine active motor threshold (AMT), subjects performed 4 of the short 20% MVC contractions during which a single pulse was delivered while the subject maintained the force output at the target force line before and after the TMS pulse. The maximum EMG peak-to-peak amplitude was quantified across the 500 milliseconds prior to the stimulus artifact and averaged across the 4 trials. AMT was defined as the minimum stimulator intensity, reported as percent of stimulator output
(%SO), that evoked an MEP with a peak-to-peak amplitude twice the amplitude of the averaged EMG baseline in at least 50% of the MEPs (75). The stimulator intensity was then varied by 3-5% to confirm AMT. To evaluate corticospinal excitability during the fatiguing contraction, the TMS stimulus intensity was increased to 130% of the AMT. AMT was not significantly different between sessions (AMT mean Visit-1: 63±16%SO, range: 40-100%SO; AMT mean Visit-2: 62±16%SO, range: 35-100%SO; ICC(3,1) = 0.927); therefore, the test stimulus intensity calculated for Visit-1 was also used during Visit-2 (test stimulus intensity mean: 78±15%SO, range: 52-100%SO).

Data Analysis

Data were analyzed offline using AcqKnowledge software package version 4.2.0 (Biopac Systems Inc., Goleta, CA). The TTF was measured from the recorded torque output signal starting from when the torque signal reached the target force and ending at the onset of the final MVC. MVC values were converted from ft-lbs to N for analysis. The peak-to-peak amplitudes for the 6 evoked MEPs were measured from the EMG signals for the biceps and the brachioradialis and averaged together for each muscle at minute-1:00 (baseline MEP) and minute-8:30 (tDCS MEP).

Statistical Analysis

SPSS version 20 for Mac (SPSS Inc, Chicago, IL) was used for the statistical analyses and an α of 0.05 was required for statistical significance. Data are reported with mean±SD in the text and as means±SE in the figures, and when appropriate, effect size (ES: partial η²). Paired t-tests were used to compare TTF between stimulation conditions. For data with serial observations, repeated measures analysis of variance
(RM-ANOVA) procedures were performed for within subject’s factors for STIMCONDITION (2-levels: anodal tDCS vs. sham tDCS) and TIME (2 levels: Pre-Stim vs. Post-Stim; minute-1:00 vs. minute-8:30; 4 levels: Baseline, minute-1:00, minute-8:30, Task Failure). Post-hoc testing was used to investigate main effects with Sidak correction for multiple comparisons.

**Pilot Experiment (Figure 33)**

Prior to the main experiment, a pilot experiment was conducted with 4 subjects (3 men, 1 woman) to ensure that the anodal tDCS stimulation protocol as performed in this study would, with the subject relaxed, produce the anticipated after-effects on cortical excitability as reviewed in the introduction. It was also important to determine if the changes could be successfully detected in the biceps muscle as the vast majority of studies have used the distal hand muscles to explore the effects tDCS (235, 242). Therefore, using the technique described above, single pulse MEPs were evoked in the biceps using TMS stimulus intensities of 130 and 150% of motor threshold before and after 20-min of anodal tDCS (1.5mA, 35cm² electrodes) with the subject’s arm relaxed. On average, MEP amplitude was nearly twice as large at 10-minutes following anodal tDCS compared to baseline (ES=0.24). There was no change in the MT stimulus intensity and the inter-individual variability in response to tDCS stimulation paralleled previously published results (241, 245). These data did indeed confirm that the anodal tDCS protocol used in this study can increase cortical excitability with the subject relaxed, consistent with the literature, and that the change in MEP amplitude can be successfully recorded from the biceps (70, 144, 309, 318).
Results

Neuromuscular Performance (Figures 34-36)

There was no systematic effect of the anodal tDCS stimulation for altering the time to task failure for the entire subject set (n=18; p=0.64 ES=0.01) (Figure 34). Recall, that because of the safety recommendations regarding the duration for tDCS delivery, the maximum amount of time a subject received tDCS stimulation was 20 minutes. Accordingly, the subjects were categorized into two tDCS-time groups: Full-Time (n=8, 2 women and 6 men) and Part-Time (n=10, 7 women and 3 men). The Full-Time group included subjects whose time to task failure, for both testing sessions, occurred prior to the termination of the tDCS (i.e. they received tDCS throughout the entire fatigue task) (n=8, 2 women and 6 men). The Part-Time group included subjects whose TTF, for both testing sessions, extended beyond the termination of the tDCS (i.e. they did not receive tDCS throughout the entire fatigue task). Figure 35A illustrates the individual subject TTF response by stimulation condition. Note that 7 of the 8 subjects in the Full-Time group experienced an increase in the TTF during the anodal tDCS condition. An analysis of these sub-groups indicated that the Full-Time group exhibited a 31% longer TTF with anodal tDCS stimulation when compared to the sham stimulation condition (Full-Time Anodal tDCS TTF: 16.48±2.87 min vs. Sham tDCS TTF: 13.13±1.34 minutes, p=0.04 ES=0.47) (Figure 35B). Conversely, the Part-Time group did not exhibit a differential effect in TTF between stimulation conditions (Part-Time Anodal tDCS TTF: 33.34±14.56 min vs. Sham tDCS TTF: 34.23±17.46 min, p=0.81 ES=0.01). An examination of the visit order for the subset of subjects in the Full-Time group revealed
that 63% of this subset (5 of 8) performed the anodal tDCS condition during Visit-1, whereas 37% (3 of 8) performed the sham tDCS during Visit-1. It is also important to note that there was no significant difference in the mean strength between the two groups.

At the end of the fatigue task subjects were asked to perform an MVC and the absolute decline (N) from baseline MVC was calculated. Interestingly, the Full-Time group had a greater decline in MVC force in the anodal tDCS condition compared to the sham tDCS session (Full-Time Anodal tDCS MVC decline: 53.8±12.5%, Sham tDCS MVC decline: 47.9±16.1%; STIMCONDITION X TIME INTERACTION: \( p=0.05, \text{ES}=0.44 \)) (Figure 36). The Part-Time group exhibited a similar level of decline in MVC in both conditions (Part-Time Anodal tDCS MVC decline: 67.7±18.4% vs. Sham tDCS MVC decline: 72.1±23.7%, STIMCONDITION X TIME interaction \( p=0.56, \text{ES}=0.01 \)). It is also important to note that there was no significant difference in the mean target force exerted by both groups during fatigue-task performance (Target Force Full-Time: 11.44±3.76Nm, Target Force Part-Time: 9.38±3.13Nm; \( p=0.23 \)).

Due to the inability to know whether the lack of a prolonged TTF in the Part-Time group is due to the subjects not receiving the tDCS stimulation throughout the entire contraction or whether other confounding factors explain this lack of effect (e.g., anodal tDCS may only influence TTF in individuals with lower levels of endurance) the remainder of the results will be limited to the data derived from the Full-Time group only.

**Rating of Perceived Exertion (Figure 37)**

There were no differences in the values for RPE between stimulation conditions for the Full-Time group prior to starting the fatigue task, at minute-1:00, minute-8:30 and
at task failure (Anodal tDCS 0.0±0.0, 3.5±1.5, 8.1±0.8, 10.0±0.0 vs. Sham tDCS: 0.0±0.0, 3.8±1.3, 8.3±0.5, 10.0±0.0, StimCondition X Time Interaction p=0.78) All subjects reported being at their maximum level of exertion (i.e. RPE 10 = “extremely hard”) at task failure in both conditions (Figure 37A). It is meaningful to note that because the anodal stimulation increased the TTF by a mean of 30% (equivalent to 3:21 minutes), the absolute time points when RPE was assessed (i.e. minute-1:00 and minute-8:30) correspond to different time points relative to the total TTF for each stimulation condition. Therefore, minute-8:30 corresponds to 68±17% of the TTF for the sham condition and to 53±12%, or to just over half of the TTF for the anodal condition (% of TTF: StimCondition X Time Interaction and StimCondition Main Effect p=.08 ES=0.37). This means that at 53% of the time to task failure with anodal tDCS, the Full-Time subjects reported the same level of effort (8.1±.08; RPE 8 = “hard”) as they did after nearly 68% of the time to task failure with sham tDCS (8.3±0.5; RPE 8 = “hard”). The anodal brain stimulation did not reduce the rate of change in perceived effort during the first 8:30-min of the two contractions; therefore, the subjects felt that they were exerting the same degree of effort earlier in the contraction time with anodal stimulation. However, the average rate of change in RPE between minute-8:30 and task failure was significantly slower for the anodal condition compared sham (Slope RPE/Time between 8:30 and Task Failure: Sham 0.38±0.11, Anodal 0.24±0.1; p=0.03) meaning that after 8:30 minutes, it took significantly longer time to reach the same RPE at task failure with anodal tDCS (RPE_{TaskFailure}-RPE_{8:30}: Sham 1.8±0.5, Anodal 1.9±0.8; p=0.57) (Figure 37A). Therefore, the subjects in the Full-Time group were able to work for an average of 8.0-min at an effort of 8-10 with anodal stimulation compared to 4.6-min with sham stimulation (Sham tDCS time at 8-10 RPE: 4.6±2.9min; Anodal tDCS time at 8-10 RPE:
8.0±2.9min; p=0.04 ES 0.47) (Figure 37B). This is equivalent to a 38% difference between conditions.

**Motor Evoked Potential Amplitude (Figure 38)**

The data for 7 of the 8 subjects in the Full-Time group were analyzed because MEPs could not be obtained in one subject. Stimulation condition × Time interactions were not observed for changes in MEP amplitude for either the biceps brachii or brachioradialis muscles (STIMCONDITION × TIME INTERACTION: biceps p=0.27 and brachioradialis p=0.90). As expected, a Time main effect was observed for both muscles indicating an increase in MEP amplitude as the fatiguing contraction progressed (TIME MAIN EFFECT: biceps: p=0.02 and brachioradialis: p=0.00). A Stimulation Condition main effect was observed for the biceps brachii (STIMCONDITION MAIN EFFECT: biceps p=0.04), as the MEP amplitudes prior to applying the anodal stimulation as well as after 7-min of delivering the anodal stimulation were significantly lower than those evoked during the sham condition (p=0.05), although the percent change in amplitude between the two conditions was not significantly different (p=0.56). No such stimulation condition main effect was observed for the brachioradialis (STIM MAIN EFFECT: brachioradialis p=0.31). Unfortunately, the inconsistent baseline measures between the anodal and sham sessions, despite having consistent baseline assessed between visit 1 and visit 2, for the biceps muscles as well as the low subject number in the Full-Time group preclude any meaningful interpretation of the difference in MEP amplitude between conditions.
**Discussion**

The purpose of this study was to determine if excitatory brain stimulation with anodal tDCS delivered *during* a sustained submaximal contraction (i.e. 20% MVC) could increase the duration that the contraction could be sustained. In agreement with the hypothesis, anodal brain stimulation dramatically increased the time to task failure by more than 30% and also increased the amount of muscle fatigue by 6% in individuals whose time to task failure occurred prior to the termination of the anodal stimulation protocol. Additionally, the anodal stimulation prolonged the period of time that the subjects could sustain a high degree of effort (i.e. between RPE 8-10) by 38%. Together, these novel findings suggest that 1) motor cortical excitability plays a crucial mechanistic role in the time to task failure of sustained submaximal fatiguing contractions, and 2) that anodal brain stimulation has the potential to enhance human muscle performance, which has obvious implications for rehabilitation medicine. Below, these findings are discussed in further detail.

**Physiologic Interpretation of Findings**

In contrast to TMS, the direct current that passes through the cortex between the two surface electrodes during tDCS is too weak to elicit action potentials in cortical neurons (300, 331). Instead, tDCS has been shown to modulate neuronal membrane potential by either depolarizing it at subthreshold levels if anodal tDCS is used or hyperpolarizing it with cathodal tDCS (31, 236, 239, 331). When tDCS is delivered at rest, the shifts in membrane potential that underlie the measured after-effects on cortical excitability develop gradually throughout the tDCS stimulation period and can persist for
a period of time after the stimulation stops based upon the duration of the stimulation protocol (240-242). The physiologic mechanisms of anodal tDCS that underly the immediate changes in cortical excitability during stimulation include voltage-mediated modulation of sodium and calcium ion channel conductance (237, 305, 331). These ion channel changes together with modulation of NMDA receptor function have been found to mediate the after-effects of tDCS, or the prolonged change in cortical excitability measured after the stimulation has stopped (237, 305). However, as with TMS, the effect of tDCS to produce measurable changes in cortical excitability has also been found to depend upon the functional state of the stimulated cortex such that the after-effects of tDCS can be eliminated when an individual performs a motor or cognitive task while anodal tDCS is delivered (10). At this time, little is known about the mechanisms of tDCS to modulate cortical excitability during an active contraction as no studies have directly measured cortical excitability during the delivery of tDCS during a contraction.

The observation that a neuromodulatory protocol designed to increase motor cortical excitability (i.e., anodal tDCS) prolongs the time to task failure of a sustained submaximal contraction, in individuals who receive the stimulation throughout their entire fatigue task, clearly indicates that supraspinal mechanisms are mechanistically involved in task failure of fatiguing contractions. The greater decline in post-task failure MVC, as a measure of muscle fatigue, suggests that the brain stimulation may have enhanced motivation and/or facilitated descending drive in the Full-Time group throughout the contraction time (28). It should be noted that this enhancement in the time to task failure and associated force decline was not observed in the individuals whose time to task failure exceeded the anodal brain stimulation duration (i.e., individuals in the Part-Time group). This finding raises the question of whether the Part-Time group did not exhibit
enhanced endurance capacity simply because they did not receive the anodal brain
stimulation throughout the entire fatigue protocol or whether the effects of anodal brain
stimulation are only beneficial for individuals who have a low initial endurance capacity.
Based on the current data it is not possible to ascertain the answers to these questions;
however, I will discuss options for future studies to address these questions below.

As mentioned previously, the rationale for limiting the brain stimulation duration
to 20-minutes was based on recommendations from Nitsche and colleagues (235, 238,
242) that tDCS current density and duration stay within those used in already tested
protocols in order to prevent any risk for acute neuronal damage from hyperexcitability
as well as prolonged excitability after-effects (i.e. greater than 1 hour) that could lead to
unwanted synaptic remodeling in healthy subjects (238). However, knowledge about the
safety boundaries for current density and duration is still limited as there have been no
studies specifically aimed at defining protocol limits (235). To date, sham-controlled
studies investigating changes in motor performance (e.g. dexterity) or MEP amplitude
induced by anodal tDCS with electrodes over the motor cortex and contralateral orbit
have not used a current density greater 0.043 mA/cm² for more than 20 minutes (15,
242). In this study, the maximum time to task failure for the subjects in the Part-Time
group was 70.55 minutes—nearly 3.5 times longer than the longest stimulation duration
over the motor cortex reported in the literature (235, 242). It has been established that
the degree and duration of the after-effects induced by tDCS depend upon current
density (i.e. current intensity mA / electrode size cm²) and duration of stimulation in
subjects at rest (15, 235). Increasing current density has been found to produce
stronger polarizing effects but the duration determines the persistance of after-effects
and therefore the potential for synaptic remodeling (239, 240). To begin to address the
questions stated above regarding the performance differences between the Full-Time and Part-Time group it will be necessary to establish if increasing the duration of the stimulation is viable by measuring the degree and persistence of after-effects of the combined stimulation/contraction protocol used in this experiment.

The changes in performance suggest that the anodal brain stimulation increased intracortical excitability in the Full-Time group; however, the actual direct measures of corticospinal excitability taken during the contraction with brain stimulation did not show a change in MEP amplitude relative to the sham condition after 7 minutes of tDCS. Measuring cortical excitability during stimulation but after a period of time found sufficient to induce short-term after-effects (183, 241) would be expected to show an increase in MEP amplitude relative to the sham condition. However, physiologically speaking, increases to neural excitability cannot be unlimited (243). In this study there were two sources of excitability to the nervous system: the sustained submaximal contraction and the tDCS. MEP amplitude has been shown to progressively increase as fatigue develops during sustained submaximal contractions (123, 293, 310, 312). This finding was demonstrated in this study for both conditions and for both the Full-Time and Part-Time groups. Therefore, a lack of difference between stimulation conditions may be due to a “ceiling-effect” in membrane excitability reached by the already high background level of excitation from the contraction (236, 245).

Perhaps the more significant finding of this study is that there was not a decrease in MEP amplitude. Homeostatic plasticity is a central nervous system regulatory mechanism for keeping neuronal mechanisms within a reasonable physiologic range such that the amount and direction of added stimulation is inversely correlated to the amount of background excitation (33, 117). Based on the work investigating
homeostatic plasticity, it is likely that the addition of external excitatory stimulation during a fatiguing contraction, which is already well known to increase the levels of excitation in an activity dependent manner within the neural regions involved in performing the contraction, could be expected to cause a rebound inhibitory effect to keep neuronal modulation within a physiologic range (236). Finally, even though the effects of tDCS have been found to be primarily intracortical (237, 239, 245, 305), it is worth questioning whether the tDCS increased descending drive to the motorneurons thereby minimizing the need to increase cortical excitability to compensate for motorneuron resistance (214) (See also Chapter 3). Therefore, while not conclusive, the during-stimulation TMS results of this study do not exclude the possibility that the anodal tDCS modulated cortical excitability during the fatiguing contraction in the Full-Time Group.

The other significant finding in this study is the observation that the anodal tDCS also slowed the rate of increase in perceived effort during the last half of the fatiguing contraction such that the subjects in the Full Time group were able to work at a high level of effort (i.e. 8-10) 38% longer than without the anodal tDCS. These RPE results may provide some insight into the mechanisms of tDCS behind the increases in task duration and muscle fatigue. During the performance of a sustained submaximal contraction, the level of force output remains the same but the sense of effort progressively increases as fatigue develops (214, 216). Although RPE is subjective, it is attributed to the corollary discharge or replica of the central motor command delivered to the muscle during task performance but instead is sent to sensory regions. Thus the value for RPE is thought to reflect the ongoing amount of neural drive needed to perform the task (107, 123, 157). Because the task duration at which individuals were able to sustain the contraction while perceiving a high degree of effort increased by 38%, this
suggests that the tDCS was able to provide the additional excitatory input to the motor cortex needed when task failure was eminent in order to overcome the increase in spinal resistance that could not otherwise be met by volitional drive. Therefore, it seems plausible that the anodal tDCS added enough excitability to essentially provide a "boost" to the volitional drive exerted by the subjects themselves when it was most needed (i.e. effort 8-10) as spinal resistance was increasing. Because there was an increase in muscle fatigue (i.e., reduction in MVC) measured at task failure, the excitatory input provided by the anodal tDCS increased task duration most likely through the recruitment of additional motor units. This finding supports the mechanistic relationship between the perceptual and physical components of fatigue in healthy individuals: “…the fatigue related adjustments in motor unit activation also underlie the sensations that accompany fatiguing contractions and there is typically a strong association between fatigability (loss of force) and the rating of perceived exertion” (102).

This interpretation of the RPE results may also help to explain why the individuals in the Part-Time group did not have a change in task duration. In other words, this interpretation suggests that by the time that the subjects in the Part-Time group needed the assistance from the anodal tDCS, when their RPE level was at an 8 or higher suggesting that their volitional drive was beginning to fail to overcome spinal resistance, the stimulation had stopped. Below the RPE level of 8, the stimulation may have had a negligible effect because the amount of volitional drive was sufficient to continue task performance. Finally, because of the relationship between RPE and motor command, the RPE data may also the help to explain why there was no difference found for the measures in MEP amplitude at the two time points measured but because corticospinal excitability was not measured beyond the 8:30 minute mark, it is not
possible to determine if cortical excitability changed in relationship to RPE. Below I review findings from previous studies that could shed light on these ideas and offer suggestions for future studies.

Two prior studies that have investigated the combined influence of anodal tDCS with sustained motor contractions performed either concurrently (10-min) or after stimulation for 2-min both report a decrease in MEP amplitude after-effects (10, 318). In the first study, both anodal (10 min, 1mA, 35cm²) and cathodal tDCS (using the reverse electrode placement to create intracortical inhibition) delivered *during* the performance of sustained, submaximal hand gripping contraction at 50% of maximum grip force resulted in equal depression of the MEP amplitude for both stimulation conditions. Although they did not set out to study fatigue, Antal et al. concluded that fatigue was a most likely explanation for their results because their changes in MEP amplitude mimic those reported during the recovery phase after a fatiguing contraction (36, 38, 292, 294). In the second study, when the stimulation was followed by a 2-min sustained 20%MVC, the excitatory effects of 20 minutes of anodal tDCS (1.0mA, 35cm²) on MEP amplitude were reversed and intracortical facilitation and inhibition were reduced (318) during the 8 minutes after the contraction. Like those reported by Antal et al., these results are also consistent for post-exercise depression in MEP amplitude for submaximal contractions (36, 38, 292, 294). While these prior studies suggest that the combination of tDCS with fatiguing contractions would lead to depression of the MEP amplitude as opposed to an increase, it is important to recall that I did not measure after-effects as was done in these studies.

The neurophysiologic mechanisms of tDCS behind the performance changes found in this study merit further exploration. In addition to exploring the degree and
duration of after-effects of this protocol as discussed above, two other approaches are worth considering to better understand the neurophysiologic effects of tDCS. First, the progression of the during-stimulation neurophysiologic measures of excitability, both at rest and during activity, remains largely unknown. In other words, it may worth investigating the journey (during-stimulation) as much as the destination (after-effects).

As previously noted, the majority of studies measure the changes and duration of neurophysiologic after-effects (i.e. the “destination”) and when both performance and excitability are measured, they are done in separate experiments in order to assess the capacity of the tDCS protocol to induce changes in excitability, much like the pilot experiment in this study (70, 144). Therefore, it is difficult to compare the outcomes of this study with prior work investigating tDCS. While a pilot study was done to evaluate the utility of the stimulation protocol to increase excitability as reported in the literature, the choice was made to measure cortical excitability during stimulation after 7-min of tDCS as this has been shown to be the minimum duration of time necessary to induce measurable short-duration increases in cortical excitation after-effects (240, 241). The few studies that have measured during-stimulation effects with TMS or functional magnetic resonance imaging (fMRI) have taken their measures immediately after very brief stimulation periods (e.g. 4, 10, and 20 seconds of tDCS) in order to keep the measures from being contaminated by after-effects (9, 236, 245, 267). Such measures, taken in relaxed subjects, have concluded that the during-stimulation effects are either not detectable (as in the case of fMRI), inhibitory, or significantly less pronounced than the after-effects (9, 236, 245, 267). While using TMS to measure ongoing neurophysiologic changes during fatiguing contractions is a well established experimental technique (86, 123, 125, 312-314, 322), to my knowledge, this is the first
study to have used this approach to examine the during-stimulation effects of tDCS with the stimulation still on as well as to combine neurophysiologic measures of cortical excitability with changes in performance. Therefore, it would be beneficial to study the development of neurophysiologic adjustments throughout the stimulation protocol both with and without a fatiguing contraction.

Second, it is assumed that the effects of tDCS were localized to intracortical neural structures. Single pulse TMS measures the excitability of the entire corticospinal-motorneuronal pathway; therefore changes in MEP amplitude cannot be attributed solely to supraspinal structures (123, 234, 270). In the relaxed state, there is compelling evidence to support that tDCS acts on intracortical interneurons from studies examining the after-effects using paired-pulse TMS, H-reflex, and transcranial electrical stimulation (237, 239, 245, 305). However during a fatiguing contraction, the neural changes associated with fatigue are distributed across the nervous system (104, 123). Thus to investigate the location of actions of tDCS it would be worthwhile to investigate changes in motorneuron excitability using cervicomedullary evoked potentials (CMEP) in combination with TMS measures to explore the functions of tDCS both at rest and during fatiguing contractions. This approach is feasible as single TMS pulses delivered at the frequency of 1 pulse every 4-10 seconds (e.g. the frequency used for measuring excitability) has not been found to independently alter cortical excitability (unlike rTMS) nor has it been found to alter the after-effects when used during tDCS stimulation (243).

**Implications for Rehabilitation Medicine**

The key finding in this study was that the addition of anodal brain stimulation provided throughout the entire performance of a sustained, submaximal contraction
increased muscular endurance and also prolonged the period of time that the subjects could sustain a high degree of effort, suggests that tDCS can increase exercise capacity. Specifically the observations that anodal tDCS increased time to task failure, increased muscle fatigue, and also slowed the rate of increase in perceived effort during the last 47% of the fatiguing contraction in healthy individuals who were mild to moderately active, indicate that tDCS facilitated sustaining the exercise performance, which is largely required to derive the classical benefits from exercise training. Exercise, as distinguished from motor training, is defined as physical activity done with the purpose of improving or sustaining components of health and physical fitness such as muscular strength, endurance, and power (128). To achieve improvements, the exercise demands must sufficiently overload or stress the neuromuscular system during the training session beyond that typically confronted in daily life (2, 128). This means that in order to successfully overload a muscle to increase endurance, the muscle needs to work for a longer period of time during the exercise session and experience a greater level of fatigue at the end of the session (97).

Although the subjects in the Full-Time group felt the same degree of perceived exertion earlier in the total contraction time with anodal brain stimulation compared to sham, they were able to sustain their force output with this high effort for the last 47% of the time to task failure, a difference of nearly 38% compared to the sham condition. It is important to remember that this effect was seen regardless of the sequence of testing sessions. In other words, these effects of anodal tDCS were seen as much during the first session as during the second session. During exercise training, the RPE scale is used as an indirect indicator of the physiologic demands of the exercise (34). The individual learns to associate her perception of effort with her target exercise intensity.
needed to derive improvements in performance (246, 275). In this study, the addition of anodal tDCS allowed the healthy subjects who were mild to moderately active to exercise at a high degree of effort for nearly twice as long as during the sham condition. This increase in time resulted in not only in an overall longer time to task failure but also a greater amount of muscle fatigue at the end of the session. Therefore, while the addition of anodal tDCS did not make the overall task performance feel easier, it did allow the subjects to work at overload conditions necessary to derive the benefits from exercise.

Along with motor skill training, exercise is also a key rehabilitation strategy and has been found to improve functional recovery in individuals with neurologic injuries (i.e. post stroke, TBI) and neurologic disease (e.g. AD, MS, PD) (11, 59, 74, 94, 177, 255, 315). Exercise has also been shown to be a valuable treatment for the symptoms of fatigue in neuromuscular disorders and is recommended as part of a multi-prong approach to manage the consequences of fatigue (43, 96, 177, 251). It is important to recognize that this experiment explored the effects of one session of anodal brain stimulation on the performance of a sustained, submaximal isometric contraction with the elbow flexors in healthy, mild to moderately physically active adults. Thus, it would be both naïve and presumptuous to assume that the findings of this study, which suggest that anodal tDCS can enhance exercise capacity in this healthy group, can be applied to clinical populations with neuromuscular diagnoses, or generalized to other muscle groups and motor tasks, or used to predict a response to repetitive training sessions. However, these stated limitations do most certainly suggest rich opportunities for future study. Below I discuss findings from previous studies that could inform hypotheses in these areas and offer ideas for future studies.
In addition to impaired speed and accuracy with motor skills, individuals after CNS injury like stroke, TBI and those with neurologic disorders such as PD and MS also have difficulty sustaining skill performance for the duration required for daily life activities (52, 59, 81, 88, 96, 118, 156). It is simply not enough to perform a skill accurately; to be functionally independent, a person must also be able to perform multiple repetitions of that skill (e.g. button a shirt, type a letter, climb stairs) within a reasonable time frame. Although fatigability is defined as the decrement in maximum force output whether or not the task can be sustained (28, 94, 169), it is likely that fatigability is underestimated in these individuals because the level of exertion required by most functional activities is rarely if ever maximal, thus the onset of muscle fatigue may not correlate with functional performance (94, 106, 169). Therefore a significant contribution to the loss of functional capacity and increased disability in this population is not just motor control or motor skill based but also endurance capacity based. The findings of this study, while done in healthy, mild to moderately active individuals suggest that tDCS could be an equally valuable tool for enhancing the exercise training capacity in individuals with neuromuscular disorders. Even though this study excluded individuals with impairments, it has been demonstrated that the responses to motor skill training with anodal tDCS are more robust in those who are more impaired to begin with (167, 271) thus, it is reasonable to consider that exercise with tDCS could improve their capacity to sustain performance of functional activities in daily life.

In neurologic rehabilitation, the practice variable “intensity” refers to the amount of practice (i.e. the number of repetitions of the skill or duration of practice) compared to exercise training where intensity refers to the amount of load (18, 96, 173, 184, 254). Practice intensity is a carefully controlled factor in studies that examine strategies to train
motor skills because the actual amount of practice is a key determinant to the acquisition and retention of motor skills (116, 173, 184, 328) however, the actual amount of practice that a person with a neurological injury can perform at one time can also be severely limited (95, 173, 254). Therefore, enhancing exercise capacity in this context can also refer to increasing the actual amount of practice that can be done in one treatment session. It would be very interesting, as well as pertinent, to explore whether tDCS combined with task-oriented progressive resistance exercise could even provide a “two-for-one” overload opportunity allowing individuals to increase their overall functional potential at a more rapid pace by practicing motor skills while simultaneously enhancing their capacity to practice.

Perceived fatigue is also reported by individuals without an associated decrement in physical capacity or performance fatigability. This “central fatigue” in the clinical literature, as compared to the definition of central fatigue used in physiology, refers to the subjective perception of increased difficulty initiating and sustaining voluntary activities (59) or the lack of physical and mental energy that interferes with usual activities (94). It is a primary symptom reported in a host of systemic diseases and neuromuscular disorders including those listed above; however this symptom is an experience distinct from fatigability—the expected decline in maximum force with activity is not seen nor required for diagnosis (59, 94, 156, 343). Individuals with clinical perceived fatigue frequently do present with reduced physical capacity that is the result of inactivity and disuse secondary to their symptoms of fatigue that hinder their participation in daily activities as opposed to a direct effect on neuromuscular performance (59, 81, 94, 169, 343). Although during activity and exercise, the perceptions of fatigue may be exacerbated, exercise is recommended as part of a multi-
prong approach including medication and activity modification to manage the effects of clinical perceived fatigue in these individuals (43, 59, 88, 94). One of the proposed mechanisms behind the symptomology reported in clinical perceived fatigue is the activation of many regions of the central nervous system during regular activity that is above and beyond that used by neurologically normal controls and when challenged by activity does not increase (58, 87, 172, 306). The results of this study in healthy adults found that the level of effort perceived during the fatiguing contraction with anodal tDCS was not reduced, but more importantly, the effort level did not limit the performance as they were able to exercise/work at the same level of effort for a longer period of time and developed a greater degree of muscle fatigue. The change in performance with RPE at an 8-10 suggests that the tDCS augmented the level of activation provided by the individual, when the assistance was most needed in order to prolong performance. It remains to be seen whether tDCS would not only enhance the capacity of individuals with clinical perceived fatigue to exercise but also if it has the potential to alter their ratings of perceived exertion during exercise; thereby making exercise more tolerable.

Conclusion

The novel finding that the targeted delivery of non-invasive brain stimulation known to increase excitability to supraspinal structures during sustained, submaximal contractions improved the time to task failure, even in the absence of a change in direct measures of excitability, suggests that changes in supraspinal excitability are mechanistically involved in neuromuscular fatigue. To date the primary clinical application of tDCS to modulate cortical excitability in studies that explore motor function
has been to facilitate motor control and motor learning as measured by a change in speed or accuracy of performance (15, 33, 144, 145, 269, 271). Therefore, this finding also indicates that tDCS can be as useful a tool to explore neural mechanisms of fatigue as it has become for understanding the neuroplastic mechanisms of motor learning. In order to further characterize the neurophysiologic mechanisms of tDCS, the experimental approach used in this study to assess during-stimulation changes in cortical excitability combined with motor performance outcomes will be valuable strategies to add to those traditionally used in tDCS experiments that assess its after-effects. Finally, that anodal tDCS delivered during the performance of a fatiguing submaximal isometric contraction increased endurance exercise capacity, as measured by the ability to continue to contract for a longer period of time at a high level of perceived effort, has tremendous clinical utility in neurologic rehabilitation and physical therapy practice. Future studies applying these results in patient populations will help to determine if tDCS will be as useful in enhancing exercise capacity in individuals with and without fatigue as it is for improving motor skill performance and motor learning. The potential for tDCS to not only improve the motor performance variables related to motor skill (i.e. speed and accuracy) but also, as this study suggests, to enhance exercise capacity permitting greater intensity of motor practice (i.e. the duration and repetitions of motor practice per session (180, 254) would provide the opportunity to address both aspects needed for functional independence in daily life. As others in the field of rehabilitation have stated: “The successful implementation of tDCS as an adjuvant strategy to physical therapy should rely on an improved understanding of the underlying plastic mechanisms and their functional interaction with activity-induced plasticity” (33, p.8). Clearly ongoing study is needed in both applied neurorehabilitation practice and
mechanistic neurophysiologic research to assess the therapeutic benefits of tDCS and to better understand how to target non-invasive brain stimulation techniques to optimize neural adaptations that underlie changes in multiple facets of motor function.
CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTIONS

Conclusions

During sustained submaximal isometric muscle contractions, numerous physiologic adjustments across all levels of the neuraxis occur in order to provide activation of the muscle sufficient to maintain force output as fatigue develops. A number of studies investigating the neural mechanisms behind the decline in force production during task performance, conducted in labs from across the world over the past 50 years, have provided convincing evidence that task failure occurs when supraspinal inputs can no longer compensate for the decline in spinal excitability (13, 27, 98, 123 #97, 125, 135, 196, 303). Multiple neurophysiologic techniques have been used and developed to assess the fatigue-induced changes in spinal and supraspinal excitability that occur during task performance. These studies have provided convincing evidence about the role of spinal mechanisms in task failure that, at the same time, have raised questions about the role of supraspinal excitability (19, 104, 123, 125, 312).

In particular, when a single suprathreshold TMS pulse is delivered to the motor cortex during a fatiguing contraction, a mechanical twitch is superimposed on the volitional contraction. Evidence of additional force output above that exerted volitionally is seen as evidence of supraspinal failure or inadequate supraspinal drive to the motor pool. However, the twitch does not provide information about the location or nature of neural adjustments behind the failure, whereas changes in the evoked potentials recorded from the muscle can provide this insight (125). The motor evoked potential (MEP) evoked by the TMS pulse is followed by an electrical silent period (SP) observed
as a transient cessation of ongoing EMG activity. During fatigue task performance, both the MEP amplitude, used to index corticospinal excitability, and the SP duration, traditionally interpreted to reflect an increase in intracortical inhibition, increase (293, 312). This interpretation implies that the source of failure in supraspinal descending drive is from growing inhibition within the motor cortex; however, recent work using a novel technique to assess spinal excitability by eliciting MEPs and cervicomedially evoked potentials (CMEP) during the silent period suggests that the change in SP duration is most likely due to spinal changes (214, 215, 218). This finding raises the possibility that the source of failure in supraspinal descending drive could also come from upstream inputs to the motor cortex. Therefore, the focus of this dissertation research was to delineate the specific contributions that supraspinal circuits have in determining the time to task failure using two different experimental approaches.

The first approach compared adjustments in multiple neurophysiologic measures of supraspinal and spinal excitability taken throughout the performance of two different fatigue tasks (i.e., force-matching and position-matching) to determine the functional significance of the changes to task duration. The concurrent use of single pulse, paired-pulse TMS and paired cortico-cervicomedullary stimulation provided a unique opportunity to both localize and compare adjustments in segmental excitability. In the first experiment, task failure occurred for both the force-matching and position-matching tasks after a similar mean decline in alpha-motoneuron excitability developed coupled with a similar mean increase in corticospinal excitability. Additionally, throughout fatigue-task performance, the amount of intracortical inhibition dropped while the amount of intracortical facilitation and upstream excitation of the motor cortex remained unchanged. The findings from experiment 1 indicate that, in general, the motor cortex is
able to compensate for changes in spinal excitability until a critical amount of change develops and, at that point, unless more neural drive is provided to the motor cortex, failure occurs.

The second approach examined the effect of experimentally manipulating cortical excitability during task performance on task duration for one fatigue task (force-matching). Thus, experiment 2 tested the conclusions made in experiment 1 by delivering external excitatory neuromodulatory brain stimulation to the motor cortex using anodal transcranial direct current stimulation (tDCS) compared to a sham control condition. Anodal brain stimulation dramatically increased the time to task failure by more than 30% and also increased the amount of muscle fatigue by 6% in individuals whose time to task failure occurred prior to the termination of the anodal stimulation. Additionally, the stimulation increased the duration of time that the subjects were able to exert a high amount of effort. This finding suggests that the anodal tDCS provided the additional excitatory input to the motor cortex needed when task failure was eminent in order to overcome the increase in spinal resistance that could not otherwise be met by volitional drive. Together the results from these two experiments provide complimentary evidence to support the conclusion that the capacity of supraspinal inputs to endlessly override the decline in spinal motoneuron excitability is eventually limited by the failure of upstream drive delivered to the motor cortex, and not the development of intracortical inhibition.

Despite the complimentary nature of these results, a key question needs to be addressed about corticospinal excitability: Why was an increased absolute magnitude of corticospinal excitability found for the shorter duration task in experiment 1 when deliberately increasing cortical excitability in experiment 2 prolonged task performance?
Before answering this question it is important to describe two distinct situations where MEP amplitude, as an index of corticospinal excitability, can be increased. First, during a sustained submaximal contraction, it has been demonstrated that the longer a motor unit stays active, the more the firing rate of the motorneuron decreases (17, 53, 109, 129, 196, 228, 274). The general strategy the nervous system uses to compensate for the decline in force is to recruit additional motor units (17, 29, 109, 228). This is reflected in the increase in MEP amplitude during fatigue task performance (293, 312). Thus, the increase in excitability is a measured change that occurs over time. Second, MEP amplitude has also been found to differ between two motor tasks based upon the demand for cortical control driven by the performance criteria for the task. The greater amount of cortical input needed to complete the task, the greater the MEP amplitude (46, 190, 191, 256, 261, 270, 280, 295). In this situation, an increase in excitability is based upon cortical control of the movement or task performed and therefore measures complexity, not change.

In the first experiment, there was a task-specific difference in the absolute magnitude of corticospinal excitability for the shorter duration force-matching task, but this difference was independent from the fatigue-induced changes in excitability. In other words, the amount of change that occurred in response to fatigue did not differ between the two tasks. Therefore, this suggests that the differences in task duration, and also corticospinal excitability, are more likely due to the central neural strategy used in the motor plan for the two tasks. If there is a difference in central neural control strategies needed to meet the demands of the task, then this suggests that the recruitment and subsequent discharge behaviors of the spinal motor pool also differed. If the increase in corticospinal excitability, when viewed in relationship to all of the other
measures taken during the experiment, can be viewed to indirectly reflect the amount of
descending drive, then the increased excitability reflects the amplitude of the drive
needed to perform the force-matching task, as opposed to sustaining it.

During the second experiment, because the same fatigue-task was performed
with anodal tDCS and sham tDCS, it can be assumed that each subject used the same
neural control strategy to recruit the motor pool during the performance of both fatigue
tasks regardless of the tDCS protocol administered. Therefore, the development of
spinal resistance during task performance was most likely the same because the motor
plan was the same. What differed in experiment 2 was the amount of supraspinal
excitability available to perform this same task, and therefore overcome the same
amount of spinal resistance. With extra input to the motor cortex from the external
upstream source, when the critical value of change in spinal excitability was reached as
failure would typically occur (as seen in experiment 1 for both tasks) the descending
drive was adequate to maintain force output for a longer period of time. Because there
was an increase in fatigue measured at task failure, the excitatory input provided by the
tDCS task duration increased the task duration most likely through the recruitment of
additional motor units.

Even though the focus of this dissertation was on supraspinal mechanisms in
task failure, data from experiment 1 also included changes in spinal excitability via
eliciting a cervicomедullary evoked potential (CMEP) during a cortically evoked silent
period during both the force-matching and position-matching tasks. Therefore, a final
question to address is: \textit{What is the relationship between the changes observed in the
amplitude of the CMEP elicited in the SP in this experiment and prior fatigue studies that
developed this technique? And, do the results support the mechanism proposed for a}
faster time to task failure (i.e., disfacilitation of the motorpool secondary to presynaptic inhibition of the Ia afferent projection to the alpha-motorneuron) that is based upon task-specific differences found for the H-reflex amplitude?

The decline in the amplitude of the CMEP elicited in the silent period, observed in experiment 1 for both the force-matching and position-matching tasks, is consistent with results previously found for sustained submaximal EMG output-matching contractions (214) as well as for sustained maximal contractions (218) performed with the elbow flexors with this technique. Together with the results from this study, this indicates that the decline in spinal excitability, and specifically reduced alpha-motorneuron excitability, is a key mechanism of force decline and task failure for both sustained submaximal and maximal contractions. That there was not a task-specific difference found in changes of spinal excitability does conflict with the prior reports of a faster and greater decline in spinal excitability as measured by the H-reflex amplitude for the shorter duration task (which, in those studies, is most commonly the position-matching task) (168). However, the difference may be due to how these two techniques elicit responses from the neurons in the spinal cord (i.e., H-reflex during volitional drive vs. CMEP elicited during the temporary cessation of volitional drive) (1, 218, 232, 233, 263, 311, 326, 327). In other words, the difference in time to task failure for the two tasks could have been mediated by differences in descending presynaptic inhibition of the Ia afferent facilitation of the motor pool; however, the CMEP technique used in this study most likely would not be able to assess it.

Evidence supports that the amplitude of the CMEP recorded after cervicomedullary electrical stimulation of the spinal cord tracts reflects a monosynaptic connection between the descending spinal cord tracts and the alpha-motorneuron pool
When elicited during a voluntary contraction, the CMEP amplitude will represent the responsivity of the alpha-motorneuron to the external stimulus in the presence of multiple synaptic inputs to the motorneuron—descending as well as those from the periphery. However, when elicited during the cortically evoked silent period, all of the input to the motorneuron is assumed to be temporarily suspended (62, 120, 154, 252, 279, 332). Therefore, this suspension will most likely also interrupt presynaptic inhibitory inputs to the Ia fibers. There is evidence that the spindle afferents do mediate reflexive corrections within the muscle in response during the silent period as a response to the transient relaxation (and therefore muscle lengthening) that occurs because of the disruption in neural drive (47). However, this spindle response would occur prior to the restoration of descending drive and presumably, descending presynaptic inhibition. Thus, any effect of spindle input to the motor pool that may have occurred in the time frame when the CMEP was elicited in the silent period during experiment 1 (i.e. 75msec after the stimulus) would most likely not be modulated by presynaptic inhibition. Therefore, the results from this experiment provide support for the hypothesis that intrinsic motorneuron adaptations contribute to the decline in spinal excitability as fatigue develops during both fatigue-tasks. At the same time, the data do not rule out that fatigue is also mediated by presynaptic inhibition of the Ia afferent as a general mechanism as well as a specific mechanism that explains the difference in time to task failure between the force-matching and position-matching tasks.
Future Directions

Throughout the discussions sections for Chapters 3 and 4, as well as the conclusion sections above, numerous ideas for future studies have been suggested. Below I provide further insight on three broad areas of research that could be pursued based on the overall conclusion made from the results from this dissertation, with specific recommendations made for both clinical and mechanistic research questions. Future directions for the potential use of anodal tDCS are found in the Discussion for Chapter 4.

Clinical Diagnosis of Fatigability

Fatigue has been referred to as “the new pain” because the current understanding of its pathogenesis, mechanisms, and therefore, treatments are similar to the understanding of pain decades ago (131). One of the significant challenges to the effective clinical management of fatigue is accurate diagnosis of the underlying cause. By definition, physical or performance fatigability is not always associated with the clinical symptom of perceived fatigue (See Chapter 2: Defining Fatigue); however, aside from basic muscle strength testing of the different myotomes that is part of a standard neurologic screening exam (276), objective changes in physical performance caused by neuromuscular fatigue are frequently not examined in the clinical setting (85, 94, 169). Further, most clinical screening tools for fatigue do not include performance measures (52, 81, 94, 113, 131, 178, 329). A physical performance test of fatigability should be developed that identifies if clinically-meaningful changes in motor performance exist for the patient (e.g., excessive decrements in performance associated with repetitive or
sustained activity, such as a decline in force output or deterioration in kinematics). While clinical examination strategies consistent with this idea have been suggested (e.g., 94, 169) a test battery that uses the task-specificity principle of neuromuscular fatigue by having patients perform different types of contractions, whose fatigue mechanisms are known to stress different regions of the nervous and muscular systems, would be a valuable clinical tool. This would provide the basis for the development of targeted treatment strategies that would enhance the physiological capacities of these respective systems. Compared to maximal contractions (which are essentially what is assessed during the muscle strength screen portion of a neurologic exam), sustained submaximal contractions are more functionally relevant, as most activity done on a daily basis is submaximal. Submaximal contractions are also less intimidating for individuals to perform, and as this and other studies demonstrate, task failure is influenced by the capacity of supraspinal inputs to compensate for drops in spinal excitability.

For example, it would be interesting to examine the differences in task failure for sustained submaximal contractions between individuals with known CNS pathology (i.e., MS, PD) and known PNS pathology (i.e., GBS, post polio) who report fatigue. Mechanistically it would also be interesting to examine the changes in spinal and supraspinal excitability, in those who are willing, from these populations during task performance to determine if they have a similar “wishbone” presentation as that is observed in Figure 28B from Chapter 3. What is the presentation of the decline in spinal excitability relative to the compensatory increase in corticospinal excitability? Would there be a more rapid increase in cortical excitability for those with PNS pathology and a blunted response in those with CNS pathology? Recent work with individuals with MS found that even though they developed the same amount of muscle fatigue (as
measured by a decline in maximum force output) after a 2-minute sustained MVC as healthy controls, the neural mechanisms responsible for the force decline differed. The individuals with MS had a blunted compensatory cortical response, meaning that they had less force because they had less neural activation of the muscle compared to controls (306). Performance on these tasks, with evidence from mechanistic studies, could be adapted for bedside use, and could facilitate the process of diagnosis and therefore expedite treatment of the underlying cause for fatigue.

**Mechanisms Behind Task Duration**

The nervous system is capable of plastic changes in response to the demands placed upon it—whether it is from increased or decreased use (249, 256). Short-term changes in synaptic efficacy that underlie immediate improvements in skill during a 30-minute training session form the scaffolding for synaptic remodeling and plastic reorganization (161, 230 494, 256). Relatively permanent changes are driven by sufficient repetition of activity that support long-term retention and sustained improvements in motor performance (76, 161, 249, 256). This same mechanism is involved in the immediate improvements in performance associated with exercise training—specifically, central neural adaptations to increased use (44, 54-56, 69). The results from this study, placed in context with the larger body of work on this topic, suggest that both the spinal motoneuron and the motor cortex are stressed during the performance of sustained submaximal contractions because they demonstrated adjustments that were associated with task failure (experiment 1) and because manipulation of cortical excitability prolonged task failure. (experiment 2). However, to help confirm “which of these [physiologic] events determine performance and which are
simply incidental by-products” (28, p. 693), it is important to know whether or not the changes in task duration that could occur in response to training (or other prospective longitudinal interventions) support the proposed mechanism for task failure. Would practice or training of the two fatigue-tasks drive long-term adaptations in spinal and supraspinal excitability that would then prolong task duration? In addition, it would be worthwhile to use a prospective intervention design to also follow up on the “difference in central neural control strategy” which was provided as an explanation for the difference in time to task failure for the force-matching and position-matching task (e.g., have subjects train on one task and then test on both tasks, and determine if there is a task specific performance improvement that does not carry over into the other task).

The results from experiment 1 also provide reason for further motivation to determine the cause of task-specific differences in the time to task failure. The results from this experiment, in combination with the others discussed in Chapter 3, suggest that other factors, beyond the variable of load compliance, are contributing to the difference in the time to task failure between the force-matching and position-matching tasks. Aside from the study performed with the trunk extensors (321), this is the first study to find the position-matching task to be the longer task by an amount usually found for the force-matching task (i.e., ~40% difference) (16, 17, 152, 153, 168, 201, 265, 286, 288-290, 338). Two variables that merit further exploration are 1) the degree of stabilization, and 2) the effect of visual feedback. Stabilization for the position-matching tasks has been manipulated by other groups (265, 338), but this is the first study to not use any form of stabilization, per se; the key difference being the potential for movement in the contracting limb (i.e., the arm was free to move in all planes of motion in both tasks, where prior studies have clamped the arm in place during the force-matching task,
see Figures 5 and 19) (17, 152, 168, 286, 288). Thus the amount of stabilization for the force and position tasks were arguably more identical than that used in the majority of other experiments. In addition, although visual gain was initially thought to be a constant for the two tasks, there is concern that subtle difference in visual feedback could have contributed to the time to task failure differences between the two. Recall that the instructions for these fatigue-tasks suggest that these are visuomotor tracking skills because they require that the subjects keep a feedback line that represents their actions as close to the target line as possible, and that failure is experimentally defined by distance away from that line.

What seems to put all of these variables (i.e., limb compliance, stabilization, and visual feedback) under one “umbrella” is the perception of difficulty—as opposed to the perception of effort associated with the fatiguing muscle activity—reported by subjects for the shorter-task. In experiment 1, the majority of subjects specifically emphasized that it was much more difficult to keep the line steady during the force-matching task compared to the position-matching task. This difficulty was distinguished from the perception of effort the subjects felt in their arm muscles as it was offered spontaneously—as opposed to the RPE that was specifically measured during the tasks. In experiment 2, the mechanical setup was different (see Figures 19 and 30) and thus the issue of difficulty was not raised. The shorter-task in the work by Enoka et al. and Hunter et al. was also associated with a greater degree of difficulty during task performance. Although these studies did not describe to what the difficulty was attributed per se, perhaps the mechanisms for differences in time to task failure have to do with the combination of task-specific variables that comprise “difficulty” that include load compliance (i.e., “difficulty” between isoinertial vs. isometric), degree of proximal
stabilization (i.e., “difficulty” could be due to the number of degrees of freedom to control) and also the visual feedback (i.e., “difficulty” could be due to the demand for corrections in motor output in response to feedback in order to maintain accuracy in force output). Therefore, the difference in time to task failure between tasks could be attributed to the greater demand for cortical output to guide the task-specific activation of the motor pool determined by the level of accuracy demanded by the task driven by the combination of variables.

Summary

The focus of this dissertation research was to delineate the specific contributions that supraspinal circuits have in determining the time to task failure. In experiment 1 task failure occurred after a similar mean decline in motorneuron excitability developed coupled with a similar mean increase in corticospinal excitability. During task performance, as the amount of intracortical inhibition dropped, the amount of intracortical facilitation and upstream excitation of the motor cortex remained unchanged. The findings from experiment suggest that the motor cortex is able to compensate for changes in spinal excitability until a critical amount of change in both regions develops which implies that unless more drive is provided to the motor cortex to sustain or strengthen descending drive, failure occurs. In experiment 2 the application of anodal tDCS throughout task performance as fatigue developed prolonged task duration, increased the amount of muscle fatigue and the amount of time subjects could exert a high amount of effort. These results suggest that the anodal tDCS provided the additional excitatory input to the motor cortex needed when task failure was eminent in
order to overcome the increase in spinal resistance that could not otherwise be met by volitional drive. In summary, the results from these two experiments provide complimentary evidence to support the conclusion that the capacity of supraspinal inputs to endlessly override the decline in spinal motoneuron excitability is eventually limited by the failure of upstream drive delivered to the motor cortex and not the development of intracortical inhibition.
REFERENCES


152. **Hunter SK, Ryan DL, Ortega JD, and Enoka RM.** Task differences with the same load torque alter the endurance time of submaximal fatiguing contractions in humans. *Journal of Neurophysiology* 88: 3087-3096, 2002.


203. **Marey EJ.** *Theorie du myographe que inscrite le raccourcissement du muscle.* 1876.


Figure 1: Possible sites of fatigue along the neuromuscular pathway. This classic figure by Brenda Bigland-Ritchie from the CIBA symposium on muscle fatigue in 1981 depicts the chain of events involved in force production across the different levels of the neuromuscular system. There is no one single source of fatigue, rather the cause of the decline in force output that characterizes fatigue and leads to task failure is an interactive, dynamic process of physiologic adjustments in each of these regions that begin when the muscle contraction starts. Note #1: Excitatory drive to the motor cortex.

Figure 2: Decline in whole muscle force output (A) and motorneuron firing rates (B) associated with fatigue during a sustained maximum voluntary contraction.

A. Associated change in whole muscle twitch dynamics seen in this example of altered relaxation time after a 1-min maximum voluntary contraction (MVC). Twitch force (and differentiated force) and the unfused tetanus with a 7-Hz stim are reduced after the MVC.

B. Maximal discharge frequencies during a sustained MVC of adductor pollicis. Note the decline in motor unit firing rate throughout the contraction time. The increase in the relaxation time with fatigue is shown as a decline in the inverse of half-relaxation time.

Figure and content for figure legend adapted from Gandevia, S.C., Spinal and supraspinal factors in human muscle fatigue. Physiological Reviews, 2001; 81: 1725-1789. Used with permission.
Figure 3: Sources of synaptic input to the alpha-motoneuron.

Figure adapted from Gandevia, S.C., Spinal and supraspinal factors in human muscle fatigue. *Physiological Reviews*, 2001; 81: 1725-1789. Used with permission.
Figure 4: Proposed mechanisms for declines in motorneuron firing rates mediated by changes in synaptic input from peripheral afferents (A and B) and descending drive (C) during fatigue. A. Direct inhibition by group III and IV afferents from muscle metaboreceptors. B. Disfacilitation of the motorneuron mediated by presynaptic inhibition (arrow from descending drive) of the Ia afferent spindle input to the motorneuron. The spindle output to the motorneuron is excitatory, therefore presynaptic inhibition reduces the excitatory effect on the motorpool (as opposed to providing inhibitory synaptic input as the Group III and IV fibers do). C. Supraspinal influences of incoming sensory afference and their effect on descending drive to both the motorpool and the presynaptic axon terminals of the sensory afferents to mediate cortical control of movement (see text) in combination with their spinal effects.

Figure and content for figure legend adapted from Gandevia, S.C., Spinal and supraspinal factors in human muscle fatigue. Physiological Reviews, 2001; 81: 1725-1789. Used with permission.
Figure 5: Experimental setup of the mechanical demands used for the force-matching (A) and position-matching (B) fatigue-tasks from prior studies. Setup used for the two fatigue-tasks when performed with the elbow flexors in Baudry et al., 2009; Hunter et al., 2003; Klass, 2008; Mottram et al., 2005a; 2005b; Rudroff et al., 2007; Rudroff et al., 2011. A. To perform the force-matching task in these experiments the forearm is clamped into the vertical poles thereby preventing elbow flexion/extension and forearm pronation/supination. B. To perform the position-matching task in these experiments the arm is free to move.

Figure from Rudroff et al., Muscle activity and time to task failure differ with load compliance and target force for elbow flexor muscles. *Journal of Applied Physiology*, 2011; 110: 125-138. Used with permission.
Figure 6: Differences in limb stabilization for two different experiments with the knee extensors during the force-matching and position-matching tasks. A1. For the force-matching task the lower leg is clamped to the vertical supports. B1. For the position-matching task the lower leg is free to move. In both only the upper thigh is supported to minimize demand on the hip joint. Difference in time to task failure between the two tasks was ~50% and the position matching task was shorter. A2. Unconstrained position-matching task without thigh strap holding limb to apparatus. B2. Constrained position matching task has same amount of stabilization to the limb as that used in C2. for the force-matching task. Difference in time to task failure was ~18% for conditions B2 and C2, and 11% for conditions A2 and B2. Note the differences in position and therefore support provided by the bolsters between the top experiment and the bottom experiment.

Top figures from Rudroff et al., Muscle activity differs with load compliance during fatiguing contractions with the knee extensor muscles. Experimental Brain Research 2010; 203(2): 307-316. Used with permission from Springer.

Bottom figures from Poortvliet et al., Changes in constraint of proximal segments effects time to task failure and activity of proximal muscles in knee position-control tasks. Clinical Neurophysiology 2012: 732-739. Used with permission from Elsevier.
Figure 7: Etienne-Jules Marey around 1850 (A) and his myograph (B). Marey was the first individual to record the electromyogram signal. Marey, E. J. (1876). Théorie du myographe qui inscrit le raccourcissement du muscle.

Copyright on these images have expired and it is considered in public domain.
Figure 8: Two simulated motor unit action potentials discharging asynchronously, and the resultant EMG signal representing the sum of these respective motor units.
### Factors That Influence the Surface EMG

**Non-physiological**

- Shape of the volume conductor
- Thickness of the subcutaneous tissue layers
- Tissue inhomogeneities
- Distribution of the motor unit territories in the muscle
- Size of the motor unit territories
- Distribution and number of fibers in the motor unit territories
- Length of the fibers
- Spread of the endplates and node junctions within the motor units
- Spread of the innervation zones and tendon regions among motor units
- Presence of more than one propagation angle

**Anatomic**

- Skin-electrode contact (impedance, noise)
- Spatial filter for signal detection
- Inter-electrode distance
- Electrode size and shape
- Inclination of the detection system relative to muscle fiber orientation
- Location of the electrodes over the muscle

**Detection system**

- Conductivity of the tissue
- Amount of cross-talk from nearby muscles

**Physiological**

**Fiber membrane properties**

- Average muscle-fiber conduction velocity
- Distribution of muscle-fiber conduction velocities
- Distribution of conduction velocities of the fibers within the motor units
- Shape of the intracellular action potentials

**Motor unit properties**

- Number of recruited motor units
- Distribution of motor unit discharge rates
- Statistics and coefficient of variation for discharge rate
- Motor unit synchronization

---

*Figure 9: Factors that influence the interpretation of neural drive to the muscle from the surface electromyogram (EMG).*

Figure adapted from Farina, D. et al., The extraction of neural strategies from the surface EMG. *Journal of Applied Physiology*, 2004; 96: 1488-1495. Used with permission.
Figure 10: Schematic representation of a monopolar vs. bipolar electrode configuration. Monopolar recordings consist of a single electrode being placed on or in the muscle of interest while a second neutral (reference/ground) electrode being placed at an electrically quiescent site (e.g., bone), whereas bipolar recordings consist of two electrodes being placed on or in the muscle of interest along with a neutral electrode.
Figure 11: Example of the interference EMG signal recorded with bipolar surface electrodes from the vastus lateralis muscle during a maximal voluntary knee extension task. (Interference EMG signal shown in the top trace and the exerted force shown in bottom trace). Because the interference EMG signal varies in both the positive and negative direction the mean of the signal is zero. Thus, to quantify the amplitude of the signal mathematical processing is required. Common approaches involve averaging the full-wave rectified EMG (2nd trace from top), calculating the root mean squared value (3rd trace from top; over a 500-msec epoch in this example) or applying a linear envelope (4th trace from top; using a 10-Hz low-pass Blackman-61dB filter).
Figure 12: Compound surface EMG signal (A) from the soleus muscle in response to a single, supramaximal electrical stimulus to a peripheral nerve (tibial nerve) and intramuscular EMG recordings (B) obtained from the medial head of the biceps brachii. A. Evoked potentials are commonly quantified by the simple calculation of their peak to peak amplitude and/or the duration of a given potential. B. Fine wires were inserted into the muscle and a single motor unit was recorded discharging at a rate of 6 Hz during a low force isometric contraction (inset shows the single unit EMG with greater temporal resolution).
Figure 13: Neuropathway of the Hoffmann (H) reflex response and that of cervicomедullary junction stimulation. The H-reflex is evoked by electrically stimulating the peripheral nerve which elicits action potentials in the sensory Ia afferents that propagate to the spinal cord where they give rise to excitatory postsynaptic potentials and activate alpha-motoneuron axons. As such, this reflex response provides a global measure of spinal excitability as it can be modified by a number of factors such as presynaptic inhibition, the amount of Ia neurotransmitter released, and the excitability of the α-motoneurons. Conversely, magnetic stimulation at the level of the cervicomедullary junction evokes single descending volleys which activate alpha-motoneuron axons primarily through a monosynaptic connection, and can be used to more directly assess α-motoneuron excitability in vivo.

Figure modified from Aagaard et al., Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. J Appl Physiol, 2002; 92; 2309-2318. Used with permission.
Figure 14: Transcranial magnetic stimulation delivered to the motor cortex (A), the motor evoked potential followed by the silent period in response to a single magnetic stimulus during a voluntary contraction (B), and the difference in amplitudes for paired-pulse protocols that assess intracortical inhibition and facilitation. A. Transcranial magnetic stimulation (TMS) induces electrical currents in excitable tissue by electromagnetic induction (here being demonstrated in the brain). B. TMS to the cortex during a muscle contraction produces a motor evoked potential (MEP) followed by electrical quiescence before activity resumes that is indicative of corticospinal inhibition and commonly referred to as the silent period. C. The paired-pulse TMS technique involves coupling a conditioning stimulus with a test stimulus at different intervals. Specifically, the intensity of a conditioning pulse is set below motor threshold (the intensity where an MEP is not elicited), and the test pulse is set to a suprathreshold level. At short interstimulus intervals (e.g., 3-msec) the conditioning stimulus inhibits the MEP, whereas at longer interstimulus intervals (e.g., 15-msec) it facilitates the MEP. Paired pulses with inter-stimulus intervals (ISI's) between 1–5 milliseconds results in short-interval intracortical inhibition (SICI) and it provides a means of studying the activity of GABA_A inhibitory circuits within the primary motor cortex (decreases the MEP amplitude in comparison to a control pulse), whereas ISI's between 10-25 milliseconds results in intracortical facilitation (ICF) and it allows for the study of intracortical facilitation that is controlled by GABA_A and NMDA receptors.
Figure 15: 3-D contour map of cortical representation of skeletal muscle plotting the motor evoked potential amplitude relative to the spatial location of the TMS coil. The x–y grid represents the surface of the contralateral scalp, marked into 0.5 cm squares. The z-axis represents the peak to peak EMG amplitude (expressed relative to Mmax) evoked at each point on the scalp for 10 stimuli.
Figure 16: Changes in surface EMG characteristics of the interference signal relative to the force output (A) and the power density spectrum (B) during a sustained, submaximal contraction. A. Note the gradual increase in the amplitude of the interference EMG signal (top trace) as the force is continually maintained to task failure at 25% of maximum strength (bottom trace of panel A). B. The power density spectrum shifts towards the lower frequencies in association with fatigue. At the start of the contraction the median frequency was 88 Hz (gray trace) and by the end of the contraction this was reduced to 38 Hz (black trace).
Figure 17: Plots of the current density magnitudes on the cortical surface for the TMS (left) and tDCS (right) (A) and current density vector plots on the gray matter surface for the TMS and tDCS brain stim models (C). A. The location of the stimulation source is depicted to the right of the current density magnitude models, both graphically over the 3-D models and the source of the stimulation shown above the models. The figure-of-8 coil (gray) represents the TMS model, whereas the anode (red) and the cathode (black) represent the tDCS model. C. Note that the scales are normalized to the corresponding stimulation method, where the maximum for TMS is 2.9 A/m² and the maximum for tDCS is 0.103 A/m² at the anode.

Figure and legend adapted from Wagner, T et al. Noninvasive human brain stimulation. Annual Review of Biomedical Engineering, 2007; 9: 527-85.
Figure 18: Overview of the experimental protocol. **Phases:** Each test session had 4 phases: the set up phase (A), strength testing and TMS stimulus intensity determination phase (B), pre-fatigue baseline measurement phase (C), and the sustained, submaximal fatigue task phase (D). **Performance:** Representative trace of the recorded force signal. **Neurophysiology:** The brackets indicate when a subject received stimulation. **Stimulus Protocol:** The specific stimulation protocol corresponding to each phase is illustrated.

**AMT:** active motor threshold; **CMEP:** cervico-medullary evoked potential; **CS:** conditioning stimulus; **ICF:** intracortical facilitation; **LII:** long interval inhibition; **MEP:** motor evoked potential; **Mmax:** maximum compound muscle action potential; **MVC:** maximum voluntary contraction; **RPE:** rating of perceived exertion; **SICI:** short interval intracortical inhibition; **spCMEP:** cervico-medullary evoked potential elicited in the silent period; **TS:** test stimulus
Figure 19: Experimental setup of the force-matching (A) and position-matching tasks (B). Special care was taken to ensure that the mechanical demands of each task were identical, and no external restraints were used to restrict motions of the torso, shoulder, elbow, or forearm in either test session. A. During the force-matching task the orthosis was anchored to the chair base via an adjustable length tether that became taut with the elbow flexed to 90°. The force transducer (a), placed in series between the anchor and the orthosis, measured the amount of force exerted by the elbow flexors through the tether against the anchor. The force output (15% MVC) was displayed on a computer monitor to provide visual feedback. The elbow joint angle was determined and confirmed by an electrogoniometer (b), electromyographic signals were recorded from the biceps brachii and brachioradialis muscles (c), electrical stimulation was delivered at Erb’s point (d) and the cervicomedullary junction (e), and transcranial magnetic stimulation was delivered to the motor cortex (f). B. During the position-matching fatigue task the magnitude of the suspended weight was equivalent to 15% MVC confirmed by the force transducer (a), and the elbow joint angle, measured via an electrogoniometer, was displayed on a computer monitor to provide visual feedback (b). An identical electromyographic (c), electrical stimulation (d and e), and transcranial magnetic stimulation (f) setup as described for the force-matching task was also implemented for the position-matching task.
Figure 20: Stimuli used to elicit cortical, cervicomedullary, and peripheral evoked potentials. A combination of six single or paired stimuli were delivered to the motor cortex, the cervicomedullary junction, or the brachial plexus to elicit six evoked potentials. 

Top: Anatomy of the stimulus including the site of stimulation and the most direct pathway (see note below) activated by the stimulus. The large down arrows indicate if the evoked potential was elicited when volitional drive was present (A, B, and C) or with an X over the large down arrow when volitional drive was transiently suspended in the silent period (D and E). 

Bottom: Evoked potentials from a single subject elicited at pre-fatigue baseline for the force-matching task. Stimulus artifact is designated on the line below. 

A. Electrical stimulation to the brachial plexus with a single supra-maximal stimulus simultaneously activates all motor axons projecting to the biceps to evoke a maximal compound muscle action potential (M_{max}). The peak-to-peak amplitude of M_{max} depends upon transmission across the neuromuscular junction and muscle fiber membrane conduction. 

B. Single supra-threshold pulse transcranial magnetic stimulation (TMS) to the motor cortex evokes a descending volley of action potentials in the corticospinal neurons that are temporally summated by the motoneuron pool. The peak-to-peak amplitude of the motor evoked potential (MEP) is influenced by both cortical and spinal excitability. During a voluntary contraction, the MEP is followed by an electrical silent period (SP) observed as a temporary cessation of ongoing EMG activity caused by a transient interruption of volitional drive and motoneuron activity (represented by large down arrow with X). The duration of the SP can be influenced by both spinal and cortical mechanisms.

Note: It is important to recognize that the stimuli will activate other indirect pathways as well as travel antidromically. For clarity, only the most direct pathway is presented.
C. Paired pulse TMS over the motor cortex that uses a sub-threshold conditioning pulse (70% of active motor threshold) to activate the intracortical interneurons followed by a supra-threshold test pulse (at the same intensity as the single pulse TMS) evokes an MEP whose peak-to-peak amplitude is conditioned or adjusted by the pre-activation state of the intracortical neurons that synapse on the descending corticospinal projections. The amplitude of the conditioned MEP evoked with an interstimulus interval (ISI) of 3 msec is reduced consistent with the effect of short interval intracortical inhibition on MEP amplitude ($SICI$ conditioned MEP) when compared to the amplitude of the single pulse MEP (e.g. figure 20B). When evoked with an ISI of 15msec, the conditioned MEP is larger than the single pulse MEP and reflects the effect of intracortical facilitation on MEP amplitude ($ICF$ conditioned MEP).
D. Paired pulse TMS that combines two supra-threshold stimuli to the motor cortex separated by 75 msec ISI will evoke two MEPs, an unconditioned MEP evoked from a single pulse of TMS followed by a second conditioned MEP evoked during the silent period (SP) from the first stimulus. The amplitude of the first MEP, like the single pulse MEP (Figure 20B) depends upon the excitability of cortical and spinal circuits in the presence of ongoing volitional drive. The amplitude of the second MEP elicited in the SP reveals the state of excitability of both cortical and spinal circuits when volitional drive has been temporarily suspended. E. Paired cortico-cervicomedullary stimulation combines one suprathreshold TMS test stimulus to the motor cortex with a single suprathreshold electrical stimulus to the spinal cord descending tracts at the cervicomedullary junction separated by 75 msec ISI. This protocol will elicit an unconditioned MEP followed by a cervicomedullary evoked potential (CMEP) in the silent period. The electrical stimulus to the cervicomedullary junction simultaneously activates the descending tracts that project to the spinal motoneuron pool; therefore, the amplitude of the CMEP depends upon the synaptic activation of the motoneuron pool by the descending corticospinal tract. When elicited during the SP, the amplitude of the CMEP (CMEP elicited in the SP) reveals the state of excitability of the motoneuron pool when volitional drive as been transiently suspended.
Peripheral pathway:
1. Muscle excitability → Mmax amplitude

Corticospinal pathway:
2. Corticospinal excitability → MEP amplitude
3. Corticospinal inhibition → SP duration

Fatigue state of the corticospinal pathway and the spinal motor neurons (with volitional drive suspended):
4. Corticospinal excitability in the silent period → MEP amplitude elicited in the SP
5. Motoneuron excitability in the silent period → CMEP amplitude elicited in the SP

Intracortical circuits:
6. Intracortical inhibition → SICI ratio
7. Intracortical facilitation → ICF ratio

Effect of upstream input on corticospinal pathway:
8. MEP amplitude (1) compared to MEP amplitude elicited in the silent period (5) → LII ratio

Figure 21: Neurophysiologic outcome variables used as indices of corticospinal, intracortical, spinal and peripheral excitability quantified from electromyographic recordings of evoked potentials. 1. Muscle excitability was quantified by the peak-to-peak amplitude of a maximal compound muscle action potential (Mmax) elicited by a single supramaximal electrical stimulus to the peripheral nerve at the brachial plexus.*

2. Corticospinal excitability was quantified by the amplitude of the motor evoked potential (MEP) elicited from single pulse suprathreshold transcranial magnetic stimulation (TMS) to the motor cortex. 3. Corticospinal inhibition was indexed as the duration of the silent period (SP) and measured as the time between the stimulus artifact to the resumption of the EMG signal. 4. Because the SP reflects a temporary cessation of voluntary drive, stimuli delivered during the silent period were used to examine the fatigue state of the corticospinal pathway and spinal motor neurons. The fatigue state of the corticospinal pathway was quantified as the amplitude of the MEP elicited during the cortically evoked SP. 5. The fatigue state of the spinal motor neurons was quantified as the cervicomедullary evoked potential (CMEP) amplitude elicited during a cortically evoked SP. 6. To examine intracortical excitability, the amplitude of the single pulse MEP is compared to a conditioned MEP elicited by paired pulse TMS where a subthreshold conditioning pulse used to activate intracortical neurons is followed by a suprathreshold test pulse. Intracortical inhibition is the ratio of the amplitude of the conditioned MEP evoked with an interstimulus interval (ISI) of 3 msec to the amplitude of a single test pulse MEP (SICI ratio). 7. Intracortical facilitation is the ratio of the amplitude of the conditioned MEP evoked with a 15msec ISI to the single test pulse MEP (ICF ratio). 8. The effect of upstream drive to the motor cortex was examined by comparing the amplitude of the MEP elicited during the silent period to the amplitude of the single pulse MEP. This was also quantified as a ratio of long interval inhibition (LII ratio). *Note: Cortical and cervicomедullary evoked potentials were normalized to Mmax to control for changes in muscle excitability with fatigue.
Figure 22: Time to task failure (A) and percent decline in elbow flexor maximum voluntary contraction force (B) for the force-matching and position-matching fatigue-tasks. A. The time to task failure (TTF) for the position-matching task was longer than the TTF for the force-matching task (p<0.01). B. There was no difference between the two fatigue-tasks in the amount of decline in maximum voluntary contraction (MVC) force at task-failure (p=0.59).
Figure 23: Individual times to task failure for men (filled circles) and women (open circles) during the force-matching and position-matching tasks (A) and for the difference in time to task failure relative to absolute target force (B) sustained during both fatigue-tasks. A. When compared to the force-matching task, 80% of the subjects had a greater time to task failure (TTF) during the position-matching task. The dashed line represents an equivalent TTF for both fatigue-tasks. B. There was inverse relationship between the magnitude of the difference in TTF of the two fatigue-tasks and the absolute value of the target force ($r = -0.85, t_{(1,8)} = 21.52, p < 0.01$).
Figure 24: Ratings of perceived exertion during the force-matching and position-matching tasks. The values reported for rating of perceived exertion (RPE) were similar at task failure and for each 20% TTF time interval (p>0.05) during fatigue-task performance. *Significant increase in RPE from previous value (p<0.01).
Figure 25: The motor evoked potential amplitude (A) and silent period duration (B) during the force-matching and position-matching tasks. A. The motor evoked potential (MEP) amplitude (as % of \( M_{\text{max}} \)) was greater for the force-matching task compared to the position-matching task (**\( \text{TASK MAIN EFFECT: } p<0.01 \)) and increased during both fatigue-tasks (**\( \text{TIME MAIN EFFECT: } p<0.01; \text{ TASK X TIME INTERACTION: } p=0.46 \)). ***The pre-fatigue baseline force-matching task MEP amplitude was greater than that observed in the position-matching (\( p<0.05 \)). § The respective TTF interval was significantly greater than pre-fatigue baseline. §§ The respective TTF interval was significantly greater than the 20% and 40% TTF interval. B. Silent period (SP) duration increased throughout the fatigue tasks (**\( \text{TIME MAIN EFFECT: } p<0.05 \)), but did not differ with respect to the two tasks (\( \text{TASK MAIN EFFECT: } p=0.20; \text{ TASK X TIME INTERACTION } p=0.23 \)). **The pre-fatigue baseline position-matching task SP duration was greater than that observed for the force-matching task (\( p<0.05 \)).
Figure 26: Amplitudes of the cortically-evoked (A) and cervicomедullary-evoked (B) responses elicited during the silent period for the force-matching and position-matching tasks. A. The motor evoked potential amplitude elicited in the silent period (MEP in the SP) was greater during the force-matching task (**TASK MAIN EFFECT: p<0.05), and increased progressively to task failure during both fatigue-tasks (**TIME MAIN EFFECT: p<0.05). A TASK X TIME INTERACTION was not observed (p=0.79). B. The cervicomедullary-evoked potential amplitude elicited in the SP (CMERP in the SP) did not significantly differ between the two fatigue-tasks (TASK MAIN EFFECT: p=0.30; TASK X TIME INTERACTION: p=0.52) and progressively decreased throughout the fatiguing contractions to task failure (**TIME MAIN EFFECT: p<0.01).
Figure 27: Ratios for short-interval intracortical inhibition (A), intracortical facilitation (B), and long-interval inhibition (C) for the force-matching and position-matching tasks. A. The value of the short interval intracortical inhibition (SICI) ratio did not significantly differ between fatigue-tasks (Task x Time interaction: p=0.77; Task Main Effect: p=0.09) and progressively increased throughout the fatigue-tasks which is consistent with decreasing intracortical inhibition (Time Main Effect: p<0.01). **The respective TTF interval was significantly greater than the 20% TTF interval. B. The intracortical facilitation (ICF) ratio value did not differ between fatigue-tasks nor change during fatigue-task performance (Task x Time interaction: p=0.32; Task Main Effect: p=0.50; Time Main Effect: p=0.36). C. The value for long interval inhibition (LII) did not differ between the fatigue-tasks nor change during fatigue-task performance (Task x Time interaction: p=0.84; Time Main Effect: p=0.54).
Figure 28: Comparisons between normalized values of corticospinal excitability with and without volitional drive (A) and between normalized values of corticospinal and spinal excitability without volitional drive (B) during the fatigue-tasks. A. The amounts of corticospinal excitability both with volitional drive (MEP %pre-fatigue baseline) and without volitional drive (MEP elicited in the SP %pre-fatigue baseline) progressively increased throughout the fatigue-tasks to task failure (*TIME MAIN EFFECT: p=0.00). There were no differences found between values when compared by task or stimulation protocol therefore, values were pooled across tasks for clarity (TASK X TIME X STIMULUS INTERACTION: p=0.58; TASK X TIME INTERACTION: p=0.61; TASK X STIMULUS: p=0.49; TIME X STIMULUS: p=0.51; TASK MAIN EFFECT p=0.88; STIMULUS MAIN EFFECT: p=0.86). **Significantly greater than pre-fatigue baseline. ***Significantly greater than 20% TTF interval. § Significantly greater than 40% TTF interval. B. The amount of corticospinal excitability without volitional drive (MEP elicited in the SP %pre-fatigue baseline) progressively increased while the amount of spinal excitability without volitional drive (CMEP elicited in the SP %pre-fatigue baseline) progressively decreased throughout fatigue-task performance (*TIME X STIMULUS: p=0.00; **TIME MAIN EFFECT: p=0.00). There were no differences found for task therefore, values were pooled across tasks for clarity (TASK X TIME X STIMULUS INTERACTION: p=0.51; TASK X TIME INTERACTION: p=0.68; TASK X STIMULUS: p=0.71). ***Significantly decreased relative to pre-fatigue baseline.
Figure 29: Comparisons between normalized values for short interval intracortical inhibition and intracortical facilitation (A) and between normalized values for long interval inhibition and silent period duration (B) during the fatigue-tasks. A. The normalized value of short interval intracortical inhibition (SICI %pre-fatigue baseline) was significantly greater than the value for intracortical facilitation (ICF %pre-fatigue baseline) during the fatigue-tasks (*STIMULUS MAIN EFFECT: \( p=0.02 \); TIME X STIMULUS INTERACTION: \( p=0.057 \) Effect Size: 0.21) and remained >100% indicating a reduction in inhibition. There were no differences found between values when compared by task or time therefore, values were pooled across tasks for clarity (TASK X TIME X STIMULUS INTERACTION: \( p=0.31 \); TASK X TIME INTERACTION: \( p=0.88 \); TASK MAIN EFFECT: \( p=0.42 \); TIME MAIN EFFECT \( p=0.29 \)). B. Comparison of the normalized values for long interval inhibition (LII %pre-fatigue baseline) and silent period duration (SP duration %pre-fatigue baseline) did not demonstrate significance when compared by task, time and stimulation protocol therefore, values were pooled across tasks for clarity (\( p>0.05 \)).
Figure 30: Comparisons of the normalized value for the silent period duration with the normalized values for corticospinal and spinal excitability measured during the silent period. The duration of the silent period (SP %pre-fatigue baseline) progressively increased during the fatigue-tasks to task failure as the amount of corticospinal excitability measured during the silent period (MEP elicited in the SP %pre-fatigue baseline) progressively increased and the amount of spinal excitability measured in the silent period (CMEP elicited in the SP %pre-fatigue baseline) progressively decreased (**STIMULUS X TIME: p=0.00). ***Significantly different than pre-fatigue baseline (p<0.05). ****Significantly less than SP% pre-fatigue baseline and MEP elicited in SP %pre-fatigue baseline. Significantly less than MEP elicited in SP %pre-fatigue.
Figure 31: Experimental Protocol. Representative traces of biceps EMG (Top) and force signal (Bottom) from one subject during anodal tDCS. Resting arm weight was measured and added as a constant to the force signal to create a 0.0N baseline with the arm relaxed. Three flexion MVCs were followed by a series of brief (3-5 sec) 20%MVC contractions during which MEPs were measured in the biceps EMG. After locating the biceps motor hotspot, but prior to determining AMT, the tDCS electrodes were placed on the scalp. One minute after starting the fatigue task, 6 MEP’s were evoked over 30 seconds (Pre-tDCS MEPs), immediately after which the anodal tDCS was initiated (at time 1:30). The second set of 6 MEP’s were evoked at time 8:30 of the fatigue task which was after 7 minutes of tDCS (7-min tDCS MEPs). At time 21:30 of the fatigue task, the tDCS stimulation was stopped as the maximum duration for the tDCS protocol was 20 minutes. This subject’s time to task failure was 33:32 minutes. At task failure, one final MVC was performed prior to relaxing.
Figure 32: Experiment setup and subject positioning. Subjects were seated in an adjustable chair with the left elbow flexed to 90° and the forearm in neutral. With upper arm supported under the elbow, the wrist/hand were immobilized in an orthosis strapped to the adjustable length lever arm of the torque transducer. EMG recording electrodes were placed over the biceps and brachioradialis muscle bellies. tDPS electrodes, placed over the right motor cortex and above the right orbit, were secured under straps. The hand-held TMS coil delivered single pulses to the motor hotspot through the tDPS electrode over the right motor cortex.
Figure 33: Pilot study: After-stimulation effects of anodal tDCS on cortical excitability (n=4). MEP amplitude measured in the biceps 10 minutes after anodal tDCS (1.0 mA, 35cm², 20 minutes) increased by 105% and 82% relative to pre-stimulation baseline at TMS stimulus intensities of 130% MT and 150% of MT, respectively.
Figure 34: Time to Task Failure (n=18). Mean (± SE) time to task failure (TTF) for sustained, submaximal elbow flexor contraction did not differ between stimulation conditions (Sham TTF 25.85 ± 13.78 min; Anodal TTF 24.85 ± 16.77 min; p = 0.639).
Figure 35: Individual time to task failure by stimulation condition (n=18) (A) and percent change in time to task failure (B) with anodal stimulation for subjects in the Full-Time group (n=8; filled circles) and Part-Time group (n=10; open circles). A. Full-Time Group: subjects for whom tDCS stimulation was delivered through task failure in both stimulation conditions (n=8). Part-Time Group: subjects for whom the tDCS terminated before they reached task failure for one or both stimulation conditions (n=10). Solid line designates equivalent TTF for both conditions. Dashed lines signify maximum tDCS stimulation duration. Data points above the solid line indicate that the TTF for the Anodal tDCS stimulation condition was longer than the TTF for the Sham condition. Seven of the 8 Full-Time subjects had a longer TTF with Anodal tDCS. An equal number of Part-Time subjects (n=5 and n=5) are on both sides of the equivalence line. B. Percent change in TTF with anodal stimulation. Mean % change in time to task failure increased for the Full-Time group with Anodal tDCS but not for the Part-Time group (p <.05).
Figure 36: Percent decline in MVC Force for the Full-Time group. Average decline in MVC force was 6% greater after task failure in the Anodal stimulation condition compared to the Sham stimulation condition.
Figure 37: Rating of perceived exertion for the Full-Time group (A) and amount of contraction time spent at a rating of perceived exertion between 8-10 (B). A. Mean rating of perceived exertion (RPE) was the same before (baseline), during (minute-1:00 and minute-8:30), and at mean the TTF of the fatiguing contraction for both the Anodal and Sham tDCS conditions. From baseline to minute-8:30, the mean increase in RPE over time did not differ between the two stimulation conditions. Between minute-8:30 and the mean TTF, the rate of change for RPE was significantly slower during Anodal tDCS condition than the Sham tDCS condition (p=.03). B. Subjects sustained their contraction time while at an RPE level between 8 and 10 for an average of 8.0±2.9 minutes with anodal stimulation compared to 4.8±2.9 minutes with sham stimulation (p=.04).
Figure 38: During-stimulation effects of tDCS and fatiguing contraction on cortical excitability for the Full-Time group (n=7). Motor evoked potential (MEP) amplitude was obtained in 7 of 8 subjects in the Full-Time group. Simulation condition x Time interactions were not observed for changes in MEP amplitude for either the biceps brachii or brachioradialis muscles (STIMCONDITION X TIME INTERACTION: biceps p=0.27 and brachioradialis p=0.90). MEP amplitude increased in both muscles between the two times points in both muscles (*TIME MAIN EFFECT: biceps: p=0.02 and brachioradialis: p=0.00). A Stimulation Condition main effect was observed for the biceps brachii (**STIMCONDITION MAIN EFFECT: biceps p=0.04), as the MEP amplitudes prior to applying the anodal stimulation as well as after 7-min of delivering the anodal stimulation were significantly lower than those evoked during the sham condition (p=0.05), although the percent change in amplitude between the two conditions was not significantly different (p=0.56). No stimulation condition main effect was observed for the brachioradialis (STIMCONDITION MAIN EFFECT: brachioradialis p=0.31).