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# The task at hand: fatigue-associated changes to corticospinal excitability during writing

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# The task at hand: Fatigue-associated changes to corticospinal excitability during writing

by

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## ABSTRACT

Corticospinal excitability measured via transcranial magnetic stimulation (TMS) is highly dependent on the task being performed at the time of stimulation. As such, this study measured corticospinal excitability during the functionally relevant task of writing and compared it to the conventional laboratory isometric abduction task. We used single-pulse motor evoked potentials (MEPs) to provide a measure of CSE and cortical silent period (CSP) duration, and paired-pulse conditioned MEPs to assess short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) recorded from the right first dorsal interosseous (FDI) of 19 participants on two randomized and counter-balanced days. On one day, participants performed the writing task and on the other day performed the abduction task. Each day consisted of a pre-fatigue test where participants performed the designated task and corticospinal excitability was measured, a fatiguing task, and a post-fatigue test which was identical to the pre-fatigue test. SICI was increased during the writing task and a trend towards a fatigue and task interaction for ICF was observed ($F=3.4$, [1,18], $p=0.07$). We found that not all participants were able to write in cursive. Accordingly, we compared fatigue-induced changes in CSE in printers (n=8) and cursive writers (n=8). Following fatigue, ICF increased (35%±46%) in the printers but did not change in the cursive writing group (5%±13%). This study is the first to assess measures of corticospinal excitability during a handwriting task. Given that changes in intracortical excitability after a fatigue protocol depend on motor task used to assess CSE, future studies should use paradigms that mimic functionally relevant motor tasks to better understand the role that CSE may play in the neural control of movement.

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## LIST OF ABBREVIATIONS

**AMT**: active motor threshold

**CSP**: cortical silent period

**ECR**: extensor carpi radialis

**EMG**: electromyography

**FCR**: flexor carpi radialis

**FDI**: first dorsal interosseous (muscle)

**ICF**: intracortical facilitation

**MEP**: motor evoked potential

**MVC**: maximal voluntary contraction

**TMS:** Transcranial magnetic stimulation

**TS**: test stimulus (AKA test pulse)

**SICI**: short-interval intracortical inhibition

# CHAPTER I: INTRODUCTION

## OVERVIEW

Transcranial magnetic stimulation (TMS) has been used to measure corticospinal excitability for over three-decades. A magnetic stimuli is placed over the primary motor cortex and upon stimulation activates cortical neurons. This can lead to the activation of cortico-spinal neurons and later spinal neurons, exciting a particular muscle of interest. The amplitude of the resultant motor evoked potential (MEP) in the recorded muscle gives a global measure of corticospinal excitability, the excitability of the pathway from the site of cortical stimulation to the muscle. Single-pulse TMS utilizes a single suprathreshold test stimulus to evoke an MEP. In addition, during voluntary contraction of the target muscle, a period of electrical silence is visible following the MEP, known as the cortical silent period (CSP). The CSP is a valuable TMS measure that represents cortical inhibition (Fuhr, Agostino, & Hallett, 1991). Paired-pulse TMS utilizes a subthreshold conditioning stimulus that precedes the suprathreshold test stimulus. When the conditioning stimulus is presented 1 to 5 ms before the test stimulus, effects of inhibitory interneurons are seen as a reduction in MEP amplitude. This is known as short-interval intracortical inhibition (SICI). In contrast, when the conditioning stimulus is presented 8 to 30ms before the test stimulus, effects of facilitatory interneurons are seen as an increase in MEP amplitude. This is knowns as intracortical facilitation (ICF).

Neuromuscular fatigue can be divided into central and peripheral mechanisms of fatigue. TMS has been used to identify specific central intracortical mechanisms of fatigue following exhaustive exercise of upper extremity muscles. Following fatiguing exercise of the FDI, levels of SICI decreased and levels of ICF increased (Maruyama, Matsunaga, Tanaka, & Rothwell, 2006). However, it is important to appreciate the task used to measure levels of excitability.

Corticospinal excitability is highly dependent on the state of the brain and descending pathways to the muscle at the time of stimulation – whether the muscle is at rest or active. During resting protocols, participants are instructed to keep the target muscle completely relaxed while cortical stimuli are presented. Though there are benefits to a resting protocol such that it controls for the activation of synergist and antagonist muscles, variations in attention and other sensory inputs can alter corticospinal excitability (Darling, Wolf, & Butler, 2006). In addition, as the muscle is at rest during measurements, this task is not representative of a motor state.

In place of resting protocols, many studies instead use isometric contraction tasks to measure corticospinal excitability. In such a protocol, participants are instructed to hold a low-level contraction, often abducting the index finger against a force transducer. An active protocol has been shown to decrease MEP amplitude variability (Darling, Wolf, & Butler, 2006). However, corticospinal excitability is highly dependent on the task being completed. For example, during voluntary index finger abduction, FDI MEP amplitudes are significantly reduced compared to FDI MEP amplitudes during a power and a precision grip (Tinazzi et al., 2003). Compared to the power and precision grips, index finger abduction utilizes the first dorsal interossei (FDI) muscle in isolation of other intrinsic hand muscles making the task significantly different from tasks we often use in daily life.

Writing is a task that demonstrates similar aspects to that of the precision grip. However, writing is a much more complex task compared to a simple grip. Writing requires the coordination of intrinsic and extrinsic hand muscles while also incorporating the postural shoulder muscles for movement across the writing surface. In addition, greater involvement of brain structures is necessary to allow fluid writing of a desired statement (Horovitz, Gallea, Najee-ullah, & Hallett, 2013).

Though conventional abduction tasks offer stable measures of corticospinal excitability, the task-dependent nature of this measure requires that findings are presented within the context of the task completed. Moving toward more natural, everyday tasks will allow researchers to draw more relevant conclusions from measures of corticospinal excitability as they pertain to different pathologies and disorders.

## PURPOSE AND SPECIFIC OBJECTIVES

The primary purpose of this study is to assess the task-dependent nature of fatigue-induced changes in corticospinal excitability. To do so, we will measure corticospinal excitability during the functionally relevant task of handwriting and compare this to measures of corticospinal excitability during a convention laboratory task before and after fatigue. In doing so, several objectives are to be met:

1. To determine the differences in corticospinal excitability between index finger abduction and writing.
2. To compare the fatigue-associated changes to corticospinal excitability when assessed during a simple finger abduction task compared to a writing task.
3. To compare the variability in measures of corticospinal excitability between the two tasks.

## HYPOTHESES

It is hypothesized that:

1. Measures of corticospinal excitability will be increased during the writing task in comparison to abduction.
2. There will be a task-dependent effect of fatigue.
3. Variability will be greater during the writing task than during the abduction task.

# CHAPTER II: REVIEW OF LITERATURE

## MEASURING CORTICOSPINAL EXCITABILITY (TMS)

Successful initiation and completion of voluntary movement relies on an appropriate balance between inhibitory and facilitatory systems within cortical networks such that an appropriate amount of excitability is expressed (Badawy, Loetscher, Macdonell, & Brodtmann, 2012). These networks rely on interactions between different neurotransmitters and their cellular receptors along with the ions and second messengers they facilitate. Transcranial magnetic stimulation (TMS) has been used over the past three decades as a non-invasive method for examining the integrity of this system by measuring corticospinal excitability. For the purposes of this literature review, the term *corticospinal excitability* will refer to the net excitability of the pathway from the cortical site of stimulation to the targeted muscle (Kalmar, 2018). During TMS protocol, a magnetic stimulating coil is placed tangentially on the scalp targeting the primary motor cortex. The hand region is commonly targeted due to its superficial and lateral location in the somatotopic organization of the motor cortex. Muscle recordings are often taken from the first dorsal interosseous (FDI) muscle due to its involvement in various hand and finger movements as well as its location on the hand. Upon stimulation, the magnetic field produced by the coil creates an electric field that is tangential to the cortex. This electric field then induces electric currents, which act upon and excite nearby cortico-cortical neurons (Hallett, 2007). If a single, suprathreshold stimulus (test pulse) is presented, cortical neurons are brought to threshold, which then activate corticospinal neurons. The signal can then travel from corticospinal neuron to spinal motor neuron and, finally, to the targeted muscle giving a global measure of corticospinal excitability when peripheral transmission is taken into account (Kalmar & Cafarelli, 2004). The response to the stimulus is dependent upon the efficacy of synaptic transmission of both cortico-cortical neurons and corticospinal neurons. In addition, the intrinsic excitability and the net

inhibitory and excitatory input of the corticospinal neuron and the spinal motor neuron will impact the response. The response to the stimulus is expressed as a motor evoked potential (MEP) in the targeted muscle and is recorded via electromyography (EMG) electrodes. The amplitude of the resultant MEP gives a global measure of corticospinal excitability.

***Paired-pulse TMS and Cortical Excitability***

Paired-pulse TMS paradigms utilize a conditioning pulse which precedes the aforementioned suprathreshold test pulse. This conditioning stimulus is subthreshold, such that it is not strong enough to activate descending corticospinal neurons, instead only activating nearby cortico-cortical interneurons. When conditioning and test pulses are presented 8 to 30ms apart, effects of facilitatory interneurons are seen through facilitation of corticospinal neurons and a larger MEP amplitude. This is known as intracortical facilitation (ICF) (Hallett, 2007). In contrast, when the conditioning pulse precedes the test pulse by 1 to 5ms, monosynaptic inhibitory interneurons are activated, which hyperpolarize corticospinal neurons. This results in an MEP with a smaller amplitude relative to a single-pulse MEP and is known as short-interval intracortical inhibition (SICI). It is suggested that SICI consists of two phases. The initial phase occurs at interstimulus intervals of 1ms and are suggested to represent neuronal refractory periods of interneurons (Roshan & Paradiso, 2003). The second phase occurring at longer interstimulus intervals of 2 to 5ms in contrast is mediated by gamma-aminobutyric acid (GABA) on $GABA_A$ receptors. Roshan and colleagues (2003) found that interstimulus intervals of 1 and 2.5ms provided maximum amounts of inhibition. However, measures during this experiment were taken while the target muscle was at rest. Comparing the variability of MEP amplitudes at different interstimulus intervals using paired-pulse techniques, Matamala and colleagues (2018) found an interstimulus interval of 3ms provided a lower standard error of the mean compared to 1ms.

Also important to the measure of cortical inhibition and facilitation is the intensity at which each stimulation occurs. Two methods can be used to set the stimulation intensities for the conditioning and test pulses for the duration of the protocol. The first method sets the stimulator intensity to a percentage of stimulator output that produces a baseline MEP with a peak-to-peak amplitude of 1mV (absolute method). The second method sets the stimulator output based on a percentage relative to the subject's motor threshold (relative method) (Pitcher et al., 2015). In comparing each method to stimulus-response curves, the relative method presented as being superior. Comparing stimulator outputs given from each method to the stimulator output at which 50% of the maximum MEP amplitude was obtained, the relative method provided a more consistent measure across all participants, while the absolute method underestimated this intensity (Pitcher et al., 2015). Measuring levels of SICI across variations in test pulse stimulus intensity, stimulus intensities of 110% to 120% of resting motor threshold provide the greatest measure of SICI. Intensities below 110% did not result in inhibition, while intensities above 120% reduced levels of inhibition (Garry & Thomson, 2009).

The cortical silent period (CSP) is another valuable TMS measure of cortical inhibition and is represented as a period of electrical silence during voluntary EMG activity following a single suprathreshold stimulus (Fuhr, Agostino, & Hallett, 1991). The CSP is made up of spinal and cortical components. In contrast to SICI, from 50ms onward, the CSP reflects the effects of cortical $GABA_B$ receptors (Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999).

## NEUROMUSCULAR FATIGUE

Neuromuscular fatigue is defined as any reduction in the ability to exert maximal force (Gandevia, 2001). This neuromuscular fatigue can be broken up into central and peripheral fatigue.

Peripheral fatigue refers to failure at the location of the muscle beyond the site of neural stimulation, including the neuromuscular junction, muscular fibers and sarcolemma, and cross-bridge formation (Gandevia, 2001). Central fatigue, in contrast, refers to any failure upstream of the muscle, and can be described as mechanisms that ultimately result in the failure to drive motor neurons (Gandevia, 2001). Central fatigue can be further divided into spinal sites of failure such as the spinal cord, propriospinal inputs, spinal motor neurons, and motor axons, and supraspinal mechanisms such as motor cortex and corticospinal outputs (Gandevia, 2001). TMS has been used to measure the effects of fatigue on corticospinal excitability. Following non-exhaustive muscular contractions, MEP amplitudes show an initial transient post-exercise facilitation (Brasil-Neto et al., 1993; Kalmar & Cafarelli, 2004). However, once the muscle fatigues following prolonged exercise, a marked decrease in MEP amplitude occurs, lasting 12 (Brasil-Neto et al., 1993) to 15 minutes (Kalmar & Cafarelli, 2004). Brasil-Neto and colleagues (1993) found that a change in M-wave and H-reflex amplitudes did not accompany MEP depression, suggesting the observed post-exercise depression involves supraspinal mechanisms. Further, there was little to no observed decline in MEPs evoked by transcranial electrical stimulation (TES), suggesting a cortical mechanism of depression (Brasil-Neto et al., 1993). In addition, cortical measures of inhibition and facilitation post-fatigue show an increase in ICF and a decrease in SICI (Maruyama, Matsunaga, Tanaka, & Rothwell, 2006), which may result as a compensatory mechanism to the reduction in corticospinal excitability following fatigue. However, following sustained MVCs of the elbow flexors, evoked potentials elicited by cervicomedullary electrical stimulation are depressed immediately following fatiguing exercise, suggesting an additional subcortical, supraspinal contribution to fatigue (Gandevia, Petersen, Butler, & Taylor, 1999). Further, following an index finger abduction fatiguing task, M-wave amplitude and total wave area of the

first dorsal interosseous muscle (FDI) are significantly declined, introducing peripheral mechanisms of fatigue (Kalmar & Cafarelli, 2004). Thus, neuromuscular fatigue is often a combination of central and peripheral mechanisms.

**STATE-DEPENDENCY**

Often resting tasks, where TMS stimulation is presented while the participant keeps the targeted muscle completely relaxed, are used to assess corticospinal excitability following fatigue protocols. The advantage of a resting protocol is the ability to control for unwanted activation of the target muscle, its synergists, and its antagonists. However, the effect of an external stimulus on the brain is not only dependent on the stimulus itself but also on the activation state of the targeted brain region (Silvanto, 2008). Though the participants are instructed to maintain minimal activation in the targeted muscle, fluctuations in the excitability of cortical and spinal neurons can often occur and contribute to altering the inputs of the complex pathway leading to the muscle (Darling, Wolf, & Butler, 2006). These state changes would go undetected in baseline EMG activity, but ultimately can result in a change in MEP amplitude that is unrelated to the intervention or experimental population. For instance, motor imagery can alter corticospinal excitability in the absence of muscular activity. Upon imagination of a sequence of finger oppositions, MEP amplitude increased compared to resting conditions (Abbruzzese, Trompetto, & Schieppati, 1996). As MEP amplitude is our best estimate of corticospinal excitability, these variations in attention and sensory input throughout resting protocol can make it difficult to draw relevant conclusions about our measures. In addition, the resultant MEP only gives an estimate of corticospinal excitability at the exact time of stimulation. At rest, the various inputs that contribute to the pathway from cortex to muscle are very different from those during a motor task where the targeted

muscle is voluntarily active (Bestmann et al., 2008). As corticospinal excitability is state-dependent and the participant keeps the target muscle relaxed with no plan to contract, measured corticospinal excitability is not accurately expressive of corticospinal excitability in a motor state. Therefore, it is difficult to draw conclusions regarding corticospinal excitability outside of the laboratory setting in a true motor state.

To obtain more consistent measures by minimizing variations in attention and other sensory inputs, it is suggested that participants sustain a low-level contraction with the muscle of interest during stimulations (Darling, Wolf, & Butler, 2006). The task most often utilized due to its simplicity and use of the FDI muscle is isometric index finger abduction. This contraction is visually-guided on a screen in front of the participant, allowing their attention to focus on maintaining a certain level of force, thus, minimizing attentional changes. By maintaining these low-level contractions, MEP amplitude variability decreases (Darling et al., 2006). In addition, further increasing the force of contraction results in a greater decline in MEP variability (Darling et al., 2006). Having more consistent MEP measures provides a more precise account of corticospinal excitability, allowing more relevant conclusions to be drawn. Additionally, this submaximal isometric contraction has the benefit of being a motor task, compared to the aforementioned resting task. However, though an active task has the advantage of minimizing sensory and attentional variations in MEP measures, this low-level contraction sustained over time can fatigue the muscle of interest that may contribute to changes in corticospinal excitability that are unrelated to the intervention of interest.

## TASK-DEPENDENCY

Not only does corticospinal excitability depend on state, but it also depends on the task being completed. In the monkey, corticospinal neurons are more active during a precision grip compared to a power grip, despite increased EMG activity in the latter (Muir & Lemon, 1983). This suggests that corticospinal excitability is not simply related to the force of contraction, but rather, is related to the specific task at hand. During voluntary index finger abduction, MEP amplitudes in the FDI are significantly reduced compared to MEPs during a power and a precision grip (Tinazzi et al., 2003). In addition, CSPs are shorter during more natural power and precision grips compared to index finger abduction. These measures indicate that there is increased facilitation and decreased inhibition during manual tasks, such as the power and precision grip, compared to simple finger abduction often used in the laboratory setting (Tinazzi et al., 2003) (Figure 1). Flament and colleagues (1993) compared isolated finger abduction to simple manual tasks including precision grip, power grip, grasping of a petri dish, and rotation of a bottle cap. Compared to isolated finger abduction, which was restricted to FDI use, all other tasks required activation of at least one additional muscle including the second dorsal interosseous, abductor pollicis brevis, abductor digiti minimi, and flexor digitorum superficialis. Further, index finger abduction is an unnatural task that is not commonly performed on a daily basis. Being an unpracticed task that requires the use of an isolated finger muscle, it is suggested that due to the divergent nature of cortical and spinal projections to differing motor neuron pools, some level inhibition is required to produce this motion (Flament, Goldsmith, Buckley, & Lemon, 1993). As well, during these isolated finger movements, different cortical and spinal contributions are present. From cutaneous nerve stimulation, isolated finger abduction is characterized by a large long-latency excitatory component (Evans, Harrison, & Stephens, 1989). This component of the

cutaneomuscular reflex is of supraspinal origin compared to the short-latency excitatory component often dominant in non-isolated hand and finger grips, which is of spinal origin (Jenner & Stephens, 1982). Isolated index finger abduction shows increased inhibition in the cutaneomuscular reflex compared to tripod and power grips. (Evans et al., 1989). This is in line with the aforementioned increase in inhibition during isolated, non-natural finger tasks presented by Flament and colleagues (Flament et al., 1993). In contrast, Bunday and colleagues (2014) found MEP amplitude was increased during index finger abduction compared to a precision grip task. The observed differences between studies is likely due to differences in methodology, as the diameter of the object in each respective study varied (Bunday, Tazoe, Rothwell, & Perez, 2014).

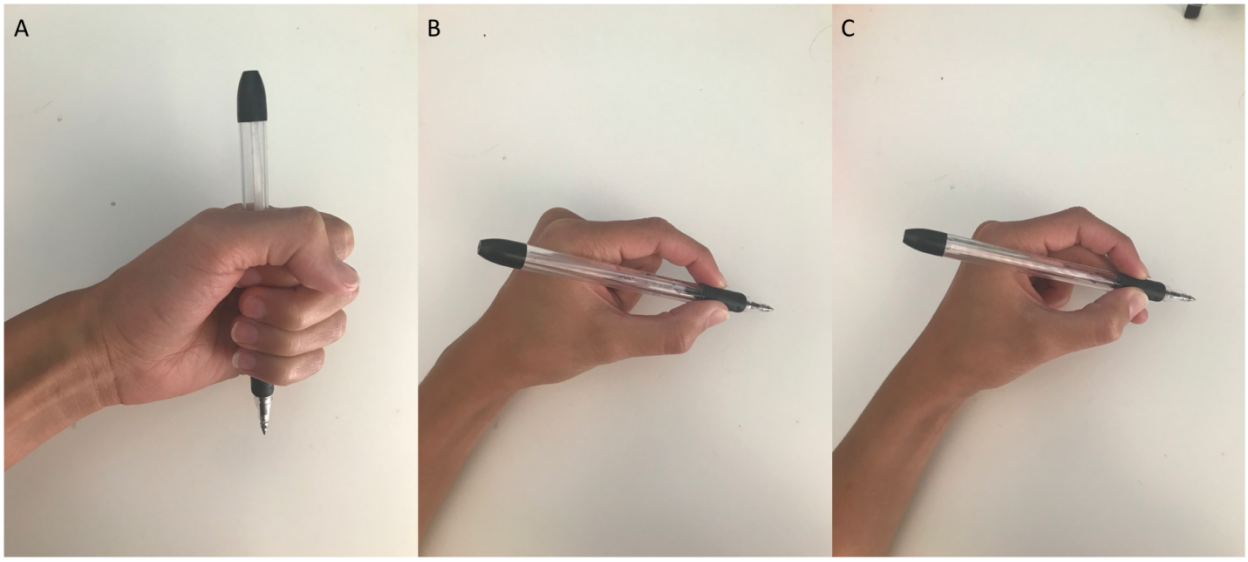


**Figure 1. Task schematics**
A) power grip, B) precision grip involving index and thumb opposition, and C) dynamic tripod grip involving index and thumb opposition with digit-III support. For the precision and tripod grip, the hand is in a neutral posture.

Writing demonstrates similar patterns in the cutaneomuscular reflex of the FDI to that during different types of gripping, suggesting that the FDI contributes to the gripping of the utensil

during writing (Evans, Harrison, & Stephens, 1989). Studies have thus shifted to using precision and power grip tasks in order to study task-dependent modulation of corticospinal excitability. These differing tasks provide a better account of corticospinal excitability due to their applicability and relevance given their resemblance to daily tasks. Similar to Flament and colleague's findings, Geevasinga and colleagues (2014) found MEP amplitudes to increase during a precision grip compared to a power grip as well as at rest. Due to the increased coordination required between different muscles in the precision grip, it is suggested that a greater amount of corticomotorneuronal drive to spinal motor neurons is required, leading to the increase in corticospinal excitability (Geevasinga, Menon, Kiernan, & Vucic, 2014). During various tasks, there are changes that occur in the population of corticomotoneuronal cells that project to the motor neuron pool of the FDI (Flament, Goldsmith, Buckley, & Lemon, 1993). These cells appear to be more active during precision versus power tasks (Muir & Lemon, 1983). As these task-dependent changes were not evident in the power task, the importance of specific neuronal drive and coupling to the control of fine finger movements and the task-dependent nature of corticospinal excitability is evident.

**WRITING**

Although the FDI is involved in writing in a similar way during precision and power grips, writing is considered a fine motor skill that requires higher-order brain structures to perform (Horovitz, Gallea, Najee-ullah, & Hallett, 2013). While in a precision or power grip, the FDI works simultaneously with other muscles of the hand. Similarly, this occurs during writing as someone grips the writing utensil. However, writing requires the coordination of the intrinsic and extrinsic hand muscles along with the postural muscles of the shoulders to allow steady movement up and

down and across the writing surface. These muscles also work together to manipulate the object both spatially and temporally to allow for fluid writing (Horovitz et al., 2013). A combination of shoulder, elbow, wrist, and finger movements are used to properly position and guide the utensil across the surface. In addition, with the hand held in a tripod grip, the joints involved in the activation of the intrinsic and extrinsic hand muscles also include those that are not directly mechanically linked to those specific muscles (Weiss & Flanders, 2004).

In assessing the effects of shoulder posture on the corticomotoneuronal output of the FDI and the abductor digiti minimi (ADM), abduction nor adduction of the shoulder had an effect on FDI output, whereas 30-degree abduction depressed ADM excitability (Dominici, Popa, Ginanneschi, Mazzocchio, & Rossi, 2005). These observed differences suggest that due to the various roles each muscle plays in hand function, there might also be differing amounts of corticospinal innervation to each muscle (Dominici et al., 2005). In contrast, in the FDI, corticospinal excitability is affected by the positioning of the wrist. In comparison to wrist extension, wrist flexion resulted in MEP facilitation as well as a reduction in CSP duration during a precision grip (Gagné & Schneider, 2007). Furthermore, FDI MEP amplitude is decreased when precision grip is maintained with the forearm in supination and pronation compared to neutral positioning, whereas MEP amplitudes recorded from the abductor pollicis brevis and ADM are not significantly different between each hand position (Perez & Rothwell, 2015). In contrast, MEP amplitude is unaffected by hand posture during unopposed finger flexion. These findings suggest the effect of hand posture is dependent on the muscle involved as well as the 0task being performed (Perez & Rothwell, 2015).

In addition to the motor component of the precision grip, the coordinating muscles must also receive input from other structures of the cortex and cerebellum in order to write the

appropriate statement. Not only must the motor cortex activate the FDI muscle in a precision or tripod grip, but the motor cortex must relay and coordinate sensory feedback and must use memory and higher-order writing programs. For example, during voluntary finger tapping, a smaller brain network is activated compared to when actively writing a standardized sentence as seen through functional magnetic resonance imaging (fMRI). Additionally, the common areas activated by the two distinct tasks show higher levels of activation during writing than when tapping (Horovitz, Gallea, Najee-ullah, & Hallett, 2013). Though commonly activated during tapping, drawing a zigzag, and writing a given sentence, the dorsal premotor cortex (PMd) shows the highest levels of activation during writing (Horovitz et al., 2013). Comparing writing tasks in both the dominant hand, non-dominant hand, and the foot, the anterior component of the PMd plays a significant role in writing, regardless of the limb used (Rijntjes et al., 1999). Further evidence for the importance of the PMd in writing is the fact that it is increasingly activated during imagined writing in those diagnosed with writer's cramp (Delnooz, Helmich, Medendorp, Van de Warrenburg, & Toni, 2013). Writer's cramp is a task-specific dystonia where patients lose the ability to perform writing tasks but maintain the ability to complete other tasks with the same hand (Goldman, 2015). As the PMd maintains involvement in motor imagery of writing in those with writer's cramp, it is clear that it plays a key role in the planning and transformation of an imagined or desired outcome into physical action (Delnooz, Helmich, Medendorp, Van de Warrenburg, & Toni, 2013). The anterior component of the PMd is associated with preparation for movement, in comparison to the posterior component, which is associated with movement execution (Rijntjes et al., 1999). The anterior component of the PMd is indirectly connected to the primary motor cortex by way of the posterior component (Barbas & Pandya, 1987). This increased activation of the PMd during writing tasks would suggest greater input to the primary motor cortex.

In comparison to a simple precision grip, writing also involves a visual component, whether the person is physically writing or imagining writing (Delnooz, Helmich, Medendorp, Van de Warrenburg, & Toni, 2013). Similar areas are activated during signature writing and zigzagging, however, writing uniquely activates the posterior parietal cortex as well as the occipitotemporal junction (Rijntjes et al., 1999). The occipitotemporal junction contains a visual area (V5), which is key for the perception of visual motion (Zeki, 2015). Other areas of the brain have been uniquely identified to a dominant-hand writing task compared to a dominant-hand zigzagging and tapping and other-hand writing, including areas in the left ventral premotor cortex, left anterior putamen, left anterior parietal cortex, and right cerebellum. Involvement of the left anterior putamen was present for all studied tasks, however, was only actively sustained for the full duration of the dominant-hand writing task (Horovitz, Gallea, Najee-ullah, & Hallett, 2013).

At the same time, language content must also be accessed. Different language regions are located in the frontal and parietotemporal lobes of the brain, which each serve different language functions (Ojemann, 1991). Most recognized are Wernicke's area located in the posterior temporal lobe, important in language development, and Broca's area located in the inferior frontal lobe, important for language processing and expression (Ojemann, 1991). There is increasing evidence for connections between language areas of the brain and the motor system (Pulvermüller, 2005). In physically producing repetitive tongue, arm, and leg movements, similar somatotopic brain regions were activated as seen in fMRI imaging as when the participant read the same action (Hauk, Johnsrude, & Pulvermüller, 2004). In applying TMS to the tongue region of the primary motor cortex, MEP amplitude increased when participants listened to words with a double-R sound compared to a double-T sound (Fadiga, Craighero, Buccino, & Rizzolatti, 2002). The double-R sound requires greater use of the tongue muscle, suggesting that participants subliminally activated

their motor cortex while listening to spoken language. Thus, a writing task is a more complex fine motor skill, compared to conventional tasks such as tapping, abduction, and power and precision grips, and differs in the cortical and spinal mechanisms for performance.

The fact that writing utilizes a larger range of brain networks compared to simplistic tasks again points to the importance of considering the task used in TMS protocols. The differing modulatory inputs on the motor cortex that are associated with writing should result in different levels of corticospinal excitability compared to a simplistic hand task such as abduction or precision grip. The power and precision grip, requiring more coordination between muscles, showed increased facilitation compared to index finger abduction as well as decreased inhibition. Further, precision grip requiring even more coordination, showed additional facilitation compared to the power grip (Tinazzi et al., 2003). Writing, involving coordination of intrinsic and extrinsic hand muscles, postural muscles, and various brain networks, is considered an even more complex task when compared to precision and power grips, and thus may present with increased corticospinal excitability. In previous studies of fatigue, injury, aging, and disease, corticospinal excitability has typically been measured during simplistic, conventional finger abduction paradigms. While these paradigms are highly controlled and easy to reproduce, they do not reflect motor tasks performed outside the laboratory. As it is clear that corticospinal excitability is highly task-dependent, this poses a problem when trying to generalize findings to real life. Thus, if consistent measures of corticospinal excitability can be made during a natural motor task such as writing, then results obtained from such studies would be more applicable to situations outside the laboratory.

## RELEVANCE AND APPLICATION

The findings of TMS studies are dependent on the task being completed during measurements. Being able to elicit consistent measures of corticospinal excitability during a highly relevant task, such as writing, will allow stronger and more specific conclusions to be drawn and will allow application of findings to activities of daily living. Most studies measuring corticospinal excitability utilize conventional laboratory tasks such as index finger abduction, and it could be that we need to change this approach. Completion of this study will enhance our understanding of the neural control of movement during complex motor tasks. This study will address the potential limitations of measuring corticospinal excitability during simplistic isometric tasks and instead use a task that better reflects the demands of functionally-relevant daily activities. Studies of corticospinal excitability in diseases such as Alzheimer's disease (Lazzaro et al., 2004) and stroke (Badawy et al., 2012), disorders such as epilepsy (Badawy, Macdonell, Berkovic, Newton, & Jackson, 2010) and depression (Steele JD, Glabus MF, Shajahan PM, 2000), aging (Oliviero et al., 2006; Peinemann, Lehner, Conrad, & Siebner, 2001), and neuromuscular fatigue (Brasil-Neto et al., 1993) have solely focused on TMS measures made with muscles at rest (a nonmotor state) or during isometric contractions. Descending drive from the cortex and brainstem, and afferent input from the periphery are state- and task-dependent, therefore, measures of corticospinal excitability during more relevant tasks will improve our understanding of the neural mechanisms of diseases, disorders, aging, and fatigue. For example, in studying the effects of stroke on motor cortex excitability and recovery, stroke patients had reduced inhibition compared to healthy controls. However, these measures were made with the muscle at rest. Corticospinal deficits during relevant motor tasks are unknown. Writing is a relevant task that employs the hand muscles that are typically used in TMS studies (due to the ease with which the hand region of the motor cortex is

stimulated). Deficits in writing present an interesting model to study the role of corticospinal excitability in movement. For example, children with developmental coordination disorder (DCD) often present with effortful, inconsistent, and illegible writing (Prunty, Barnett, Wilmut, & Plumb, 2014). Similarly, stroke patients often present with agraphia, or the disruption of previously intact writing skills along with many other neuromuscular impairments (Osman, 2015). Comparing corticospinal excitability between populations of disorders during functionally relevant tasks such as writing may uncover specific neural mechanisms for these impairments, which may then improve specific rehabilitation strategies by modifying current strategies or switching to a new approach altogether. In addition to these clinical applications, assessing corticospinal excitability during natural motor tasks will improve our basic understanding of the neural control of movement in healthy people and the central mechanisms which underlie neuromuscular adaptions during fatigue and training.

# CHAPTER III: MANUSCRIPT

**ABSTRACT**

Corticospinal excitability as measured via transcranial magnetic stimulation (TMS) is highly dependent on the task being performed at the time of stimulation. As such, this study sought out to measure corticospinal excitability during the relevant, daily task of writing and compare it to the conventional abduction task often utilized. We used single-pulse motor evoked potentials (MEPs) to provide a measure of corticospinal excitability and cortical silent period (CSP) duration, and paired-pulse conditioned MEPs to assess short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) recorded from the right first dorsal interosseous (FDI) of 19 participants on two randomized and counter-balanced days. On one day, participants performed the writing task, which consisted of writing the word *name* on a graphic tablet whose screen refreshed every 5-seconds. On the other day, the abduction task was performed and consisted of participants isometrically abducting their right index finger at a level that matched EMG levels during writing. Each day consisted of a pre-fatigue test where participants performed the designated task and corticospinal excitability was measured, a fatiguing task, and a post-fatigue test which was identical to the pre-fatigue test. There was a main effect of task on SICI, such that we saw greater inhibition during writing ($F=4.91$, [1,16], $p=0.04$). The writing task was further broken down into a printing task and a cursive writing task based on participant's self-selected writing styles. Accordingly, we compared fatigue-induced changes in CSE in printers (n=8) and cursive writers (n=8). Following fatigue, ICF increased (35%±46%) in the printers but did not change in the cursive writing group (5%±13%). This study is the first to assess measures of corticospinal excitability during a handwriting task. Given that changes in intracortical excitability after a fatigue protocol depend on the motor task used to assess excitability, future studies should

use paradigms that mimic functionally relevant motor tasks to better understand the role that CSE may play in the neural control of movement.

**Key Words:** Transcranial magnetic stimulation · corticospinal excitability · task-dependent · motor control

## INTRODUCTION

Voluntary movement of the body is modulated by the nervous system's complex network of communicating circuits. Transcranial magnetic stimulation (TMS) is used to assess intracortical and corticospinal excitability. Studies often employ resting or submaximal contraction tasks that are simple to control and manipulate to standardize levels of muscle activation when the TMS stimuli are applied. However, the neural mechanisms that govern corticospinal excitability are both state- and task-dependent. Magnetic stimuli activate cortico-cortical neurons, which send a descending volley from the motor cortex to the spinal motor neuron pool. The motor neuron pool receives various cortical, brainstem, and afferent inputs at the time of stimulation (Silvanto, 2008). Corticospinal excitability will differ depending on the net excitability of the targeted brain region at the time of stimulation and net excitatory input to spinal motor neurons, which depend on the task being completed during magnetic stimulation. Whether the participant is voluntarily contracting the targeted muscle in an abduction, a power grip, or a precision grip, for example, will have an effect on corticospinal excitability (Geevasinga, Menon, Kiernan, & Vucic, 2014; Tinazzi et al., 2003). Thus, the tasks used during stimulation and the conclusions drawn from these measures should be considered when making general statements about corticospinal excitability outside the laboratory setting. As such, more functionally-relevant tasks that can be carried out in the laboratory and translated into real life warrant investigation. This will allow the application of findings to specific task-related differences in disease populations and studies of performance, motor control, aging, fatigue, and injury. Therefore, the purpose of this study was to assess corticospinal excitability during handwriting (a functionally relevant task) and compare this to corticospinal excitability during a conventional isometric finger abduction task. In addition, we also sought to determine whether there is a task-dependent change in corticospinal excitability

following neuromuscular fatigue. We hypothesized that corticospinal excitability would be increased during the writing task compared to the simple isometric abduction task. We also hypothesized that the effect of fatigue on corticospinal excitability would be task-dependent, such that fatigue would effect corticospinal excitability less during the writing task.

## METHODS

### *Subjects*

Twenty-one right-handed adults with a mean age of 22.6±1.1 were recruited from the Wilfrid Laurier University student population. Twenty participants completed both testing sessions, however, one participant was excluded from analysis due to inconsistent MEPs. These findings represent data from nineteen participants (six male). All participants completed the Annett Handedness Questionnaire to measure handedness (Dragovic & Hammond, 2007) (Appendix D) and had an average handedness score of 9.5±2.7 out of 12. All participants completed a TMS contraindications questionnaire (Appendix C) to ensure their safety to participate. The exclusion criteria included the following conditions. Participants with cortical or cochlear implants were excluded from the study as the magnetic stimuli can disrupt the implants (Rossi, Hallett, Rossini, & Pascual-Leone, 2012). As musculoskeletal pain can affect TMS parameters, those with arthritic pain, carpal tunnel syndrome, or other pain in the arms and hands were also excluded from the study. In addition, those with past or present diagnosed neurological disorders, such as epilepsy, were excluded from the study. All participants provided written informed consent (Appendix B) prior to participating and the study was approved by the Wilfrid Laurier University Board of Ethics under REB #5381.

***Experimental Design***

In this repeated measures study design, each participant attended two testing sessions 2-8 days apart, and were tested at the same time on both days to decrease between session variability (Matamala et al., 2018). On one day, participants completed a writing task and on the other day, participants completed an abduction task (Figure 2). The order of the two days was randomized and counterbalanced between participants. On both days the participant began with a short familiarization to each task. Following familiarization, the participant completed 90 pre-fatigue trials of the selected task (writing or abduction), a fatigue protocol of intermittent isometric abduction contractions, and finally, repeated the neuromuscular battery of 90 post-fatigue trials of the same task (writing or abduction) (Figure 3).

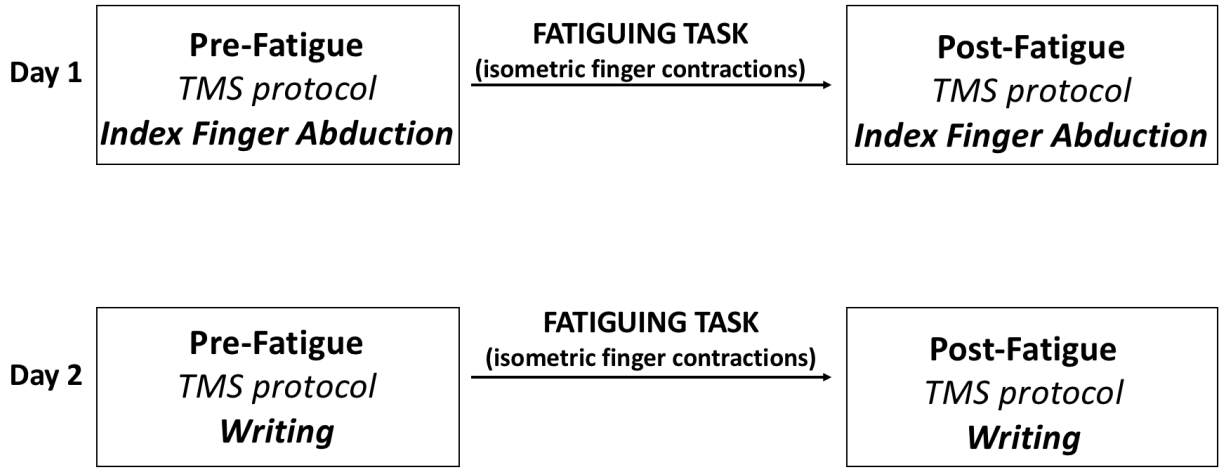


**Figure 2. Experimental design**
In this randomized and counterbalanced repeated measures experiment, testing days 1 and 2 consisted of the same pre- and post-fatigue tests (described below). The fatiguing tasks on both days consisted of isometric index finger abductions until task failure.

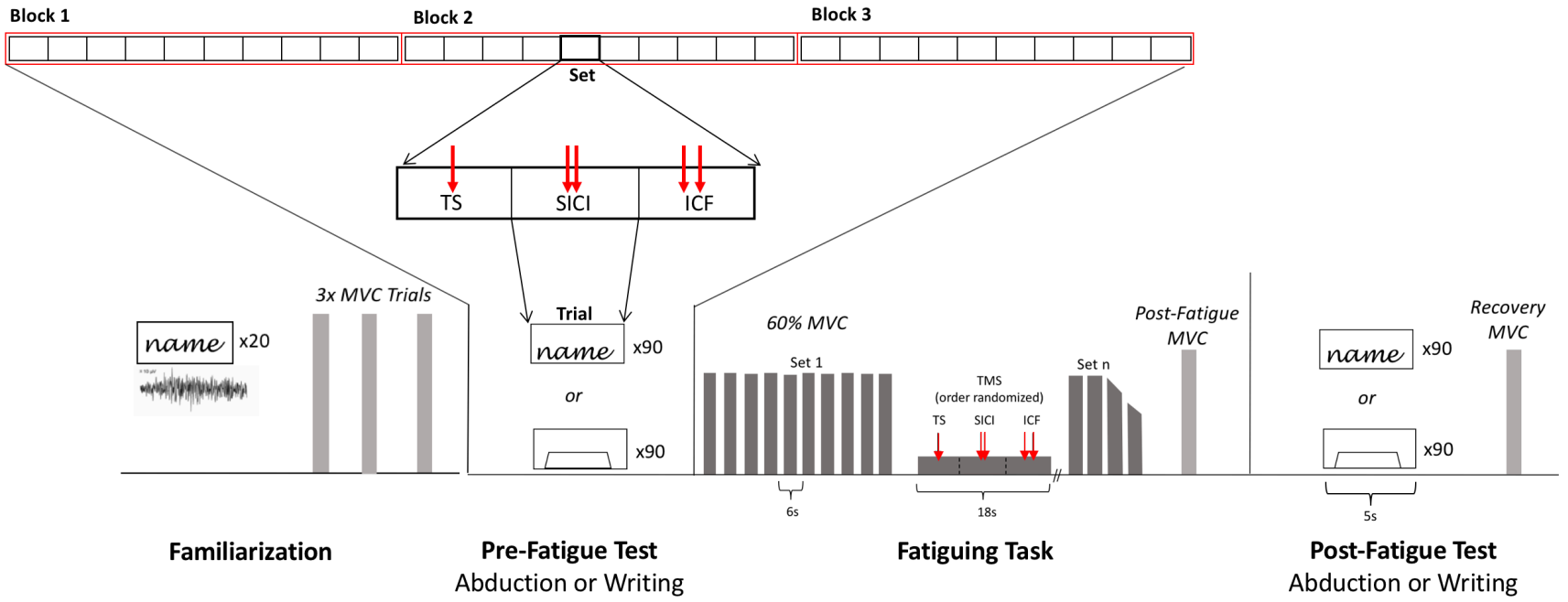


**Figure 3: Experimental protocol**
Testing days began with a familiarization session where 20 writing trials were completed. Next, three MVC trials were completed indicated by the light-grey rectangles. This was followed by a pre-fatigue test, a fatiguing task, and a post-fatigue test. TMS protocol used in the pre- and post-fatigue tests was identical (illustrated in this figure above the Pre-Fatigue Test). Briefly, this TMS protocol included 3 blocks, with each block consisting of 10 sets. Each set consisted of 3 trials for a total of 90 trials in each of the pre-fatigue and post-fatigue tests. One trial lasted 5 seconds during which time the selected task (writing the word "name" or performing an isometric finger abduction to a target force) was completed and TMS stimulation was delivered (red arrows). TMS stimulation (TS, SICI, and ICF) were randomized within each set so that they were pseudorandomized across each block. On both days, the fatiguing task consisted of sets of 10 4-second contractions at 60% MVC. There were 18 seconds between fatiguing sets during which one set of 3 TMS trials (TS, SICI, ICF in a randomized order) were presented while the participant held a contraction at a level that matched writing EMG. Task failure occurred when the participant's force fell below 60% MVC for longer than 3-seconds.

Familiarization included the writing task, the abduction task, and maximal voluntary contractions (MVCs). The *writing task* included 20 trials where the participant repetitively wrote the word "name" on an graphic tablet with a stylus pen. The graphic tablet screen presented a blank 7x2 cm rectangle as the boundaries within which the participant was encouraged to remain during writing. These writing boundaries allowed minimization of finger and wrist deviations. The use of a graphic tablet allowed automatic refreshing of the writing surface, again minimizing wrist and finger deviations, compared to writing down or across a piece of paper for multiple trials. The screen of the graphic tablet refreshed every 5 seconds. The position of the graphic tablet was marked to help maintain body position between trials, blocks, and testing days. As well, participants were instructed to maintain the same self-selected grip of the pen for the duration of the protocol. However, writing grips were not standardized between each individual. The *abduction task* consisted of the participant voluntarily abducting their right index finger for 3-seconds with a 2-second rest. The level of contraction during the abduction task was set to the average RMS amplitude of FDI EMG activity over the 20 familiarization writing trials (Figure 4). This level of activity was marked with horizontal cursors (±2.5%) to allow the participant to match it using a real-time EMG biofeedback channel. When abducting, the participant kept their hand in a pronated position, with the arm rested comfortably on the table. Participants also performed three MVCs by maximally abducting the index finger against a custom-built force transducer. The highest of these trials was taken as the participant's MVC.

Following familiarization, the participant was set up for TMS. The pre-fatigue and post-fatigue neuromuscular battery consisted of 90 trials. Each trial was 5-seconds in duration. On the writing day, TMS stimulation occurred 1.5-seconds into the 5-second trial while the participant wrote the word "name" on the graphic tablet. On the abduction day, the TMS stimulation occurred 2-seconds into the 5-second trial while the participant held a submaximal, isometric, finger-abduction contraction.

The *fatigue protocol* consisted of sets of ten 4-second isometric finger-abduction contractions at 60% of the participant's MVC, with two-seconds between each contraction. Between each fatiguing set, participants maintained a low-level contraction matched to that during the abduction task. During this time, three TMS stimulations were presented every 6 seconds, which allowed measurement of corticospinal excitability during fatigue. Each TMS stimulation-

type was randomized throughout each set. Task failure was defined as the point at which the contraction level held by the participant fell below 60% MVC for more than three seconds (Kalmar & Cafarelli, 2004). Submaximal contractions with intermittent rest periods were selected in order to elicit greater central fatigue rather than peripheral fatigue resulting from ischemia. Immediately following task failure, participants completed a post-fatigue MVC before beginning the post-fatigue test. Finally, one MVC was completed immediately following the post-fatigue test (recovery MVC) (Figure 3). It is important to note that on both days, pre-fatigue and post-fatigue measures of corticospinal excitability were made during handwriting or abduction before and after the same finger abduction fatigue protocol. In this way, we examined the task-dependent nature of corticospinal excitability rather than the task-dependent nature of neuromuscular fatigue.

The pre-fatigue and post-fatigue tests consisted of 3 blocks, each block containing 10 sets. Each set consisted of 3 trials for a total of 90 trials across the three blocks (Figure 3). TMS stimulations occurred within each trial and were one of three types: (1) test stimulus (TS), (2) short-interval intracortical inhibition (SICI) stimulus, and (3) intracortical facilitation (ICF) stimulus. The stimuli were randomized within each set so that they were pseudorandomized within each block.

***Experimental Set-up and Recordings***

*Electromyography*

Participants were seated at table with an adjustable headrest situated in front of the forehead to allow the body and head to be supported and rest in a comfortable position (Figure 5). Participants were asked to position themselves in a comfortable position to write, and they maintained this posture with the aid of the headrest. The table surface contained engraved angles beginning at 0-degrees (parallel to the right edge of the table) to 80-degrees. The angle of the arm during the writing task was recorded. Creation of a custom designed table allowed the force transducer to work at angles ranging from 10-degrees to 70-degrees from the right edge of the table. The angle of the arm during the abduction task was then matched to that during the writing task (Figure 5). The skin over the right FDI muscle was cleaned with isopropyl alcohol and two disk EMG electrodes (0.5 cm recording surface, 11mm diameter) were placed over the muscle belly secured by double-sided adhesive (BIOPAC Systems, Inc. QC, CA). Electrodes were placed

at a consistent inter-electrode distance of 1 cm. The EMG signal was pre-amplified 300x (Motion Lab Systems, Inc. LA, USA). A 40 mm reusable ground electrode (DELSYS Inc., MA, USA) was placed on the dorsal aspect of the right hand after being shaven, abraded, and cleaned with alcohol to reduce the signal-to-noise ratio. To allow the hand to rest comfortably while writing on the electronic tablet, a glove covering the hand as well as digits IV and V was worn by participants. Parallel bar surface EMG electrodes were also placed on the extensor carpi radialis (ECR) and the flexor carpi radialis (FCR) (10x1mm Ag contacts with 1cm inter-bar distance, DE-2.1) (DELSYS Inc., MA, USA) and a 40 mm reusable ground electrode (DELSYS Inc., MA, USA) was placed on the elbow or collar bone after being cleaned with alcohol and shaven. To measure force for obtaining MVCs, the index finger was placed against a custom-built force transducer and the arm was secured comfortably with wooden pegs. The force signal was amplified 10x using a custom-built, variable-gain amplifier. EMG and force signals were digitized at 2000 Hz using the Micro 1401-3 data acquisition unit and Signal 6.0 waveform acquisition software (Cambridge Electronics Design, Cambridge, UK). EMG data was band-pass filtered from 20 Hz to 450 Hz.

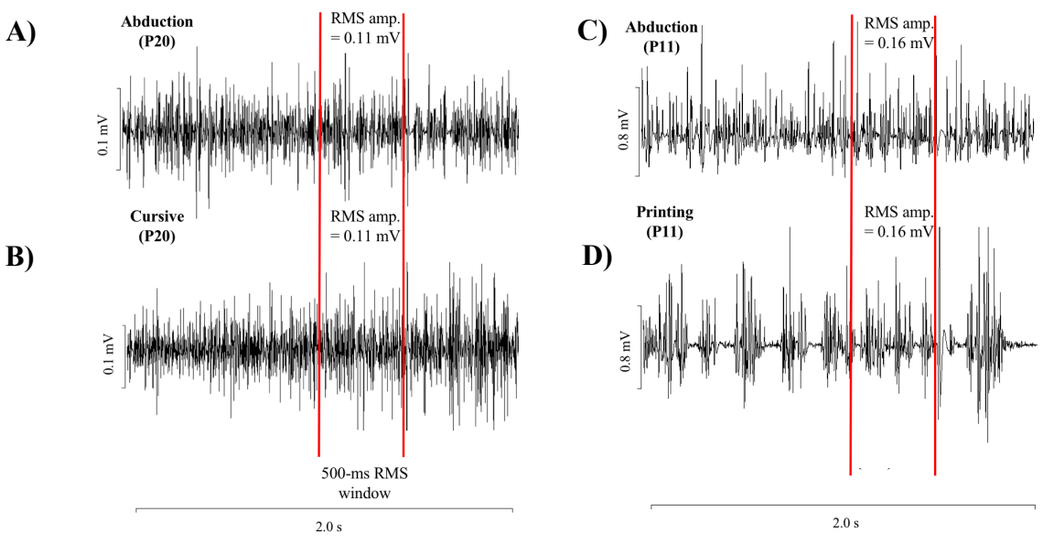


**Figure 4: EMG activity between tasks for a printer and a cursive writer**
EMG activity differed between participants, however the abduction target for each participant was matched to the EMG activity during a writing sample acquired at the beginning of the each experimental day. Participant 20 (P20, panels A and B) completed the writing task using a cursive writing strategy. The RMS amplitude of EMG activity is shown for one abduction trial (A) and one writing trial (B) sampled during a 500-ms window (red bars). RMS amplitude for both abduction and writing are 0.11 mV for this participant. Participant 11 (P11, panels C and D) completed the writing task using a printing strategy. The RMS amplitude of EMG activity is shown for one abduction trial (C) and one writing trial (D). RMS amplitude for EMG during the 500-ms pre-stimulus epoch was 0.16 mV for this participant. Although distinct bursts of activity in the EMG activity occurred during printing, but not cursive or abduction, trials were excluded from analysis if the TMS stimulation fell between bursts.

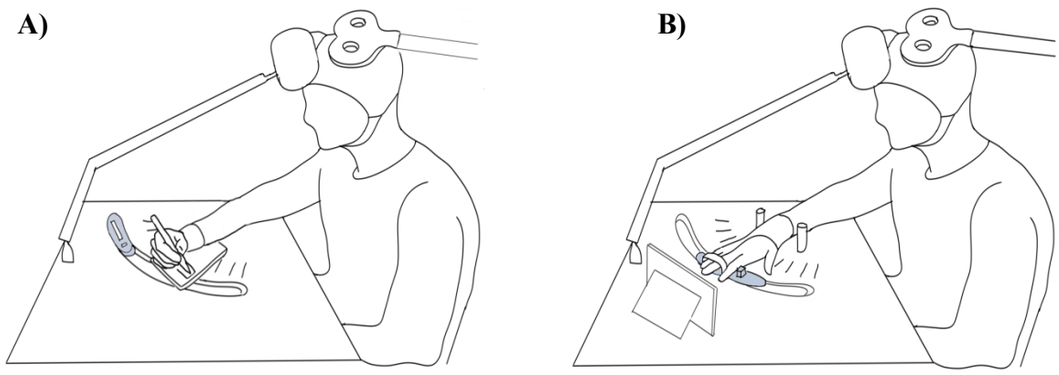


**Figure 5: Experimental setup**
The figure above represents the setup of participants during an experimental session. The head rest was the brought to the forehead so the participant could rest comfortably in a natural writing position for both tasks. During the *writing task* (A), participants set the tablet where most comfortable to write and completed the allotted writing trials. During the *abduction task* (B) the angle of the arm was matched to that during the writing task using a protractor etched into the table. Participants completed the abduction task with their index finger against a force transducer and the other fingers strapped together. The thumb was positioned to rest behind a piece of tape, to maintain a consistent joint angle without allowing the participant to exert force with the thumb. Their wrists were stabilized with pegs as shown above. The window of EMG for which they were to trace was presented on an electronic tablet placed in front of the participant.

*Transcranial Magnetic Stimulation*

A figure-eight magnetic stimulating coil (Magstim Company Ltd., Whitland, UK) was positioned over the hand region of the primary motor cortex and held in place using a lighting-support arm and clamp (Manfrotto Supports, Italy) with additional support and position maintenance by the investigator. The TMS coil was moved in small increments in order to determine the optimal site for generating a motor evoked potential (MEP) in the FDI via suprathreshold stimulations from the BiStim$^2$ system (Magstim Company Ltd., Whitland, UK). Once located, this spot was marked on the cap worn by participants to maintain coil position throughout protocol. Stimulator output was then adjusted to find the minimum intensity that elicited a 50 μV MEP in 5 out of 10 of trials while a low-level contraction was held (active motor threshold (AMT)). Paired-pulse TMS was used to assess SICI and ICF. To elicit SICI, a conditioning stimulus of 80% AMT preceded the test stimulus (which was set to 120% AMT) by 3ms (Kujirai et al., 1993). To elicit ICF, a conditioning stimulus of 80% AMT preceded the test stimulus by 12ms. Test stimulus (TS) MEP amplitudes are reported in millivolts (mV). Conditioned MEP amplitudes (SICI and ICF) were normalized to the unconditioned test stimulus MEP amplitude (conditioned/unconditioned).

### *Data Analysis*

*Motor Evoked Potentials (MEPs)*

MEP peak-to-peak amplitudes were measured using an offline using Signal 6.0 (Cambridge Electronics Design, Cambridge, UK). Trials were excluded if (a) the participant responded incorrectly (i.e., delayed or no contraction) (b) TMS stimulation occurred between EMG bursts during writing, and (c) no MEP was elicited (MEP < 200 μV) (Campen et al., 2013). When inhibition of the MEP was expected (SICI), MEP amplitudes <200 μV were included only if there was a visible negative-positive peak at the appropriate latency for the evoked response. Exclusion criteria *a, b*, and *c* were based on trial by trial inspection of the waveform data. SICI and ICF MEPs were normalized to the corresponding TS MEP within the same set (each series of three randomized trials that include TS, SICI, ICF). If a TS trial was excluded, MEPs were normalized to the TS MEP in the next closest set such that the conditioned MEP was always normalized to an unconditioned MEP that was no further than three trials away (or 15 seconds).

*Cortical Silent Period*

Duration of cortical silent period (CSP) of the test stimulus was measured offline using a custom script on MATLAB (R2019a MathWorks, Inc., MA, USA). CSP duration was calculated from the point of the test-pulse stimulus delivery to the point at which EMG activity returned to pre-stimulus activity calculated over a 300-ms period prior to stimulation). CSP was calculated as the average for the 30 TS trials only (CSP following paired-pulses were not included). One participant was removed from CSP analysis due to inconsistency in EMG activity.

### *Statistical Analysis*

Analysis was performed using Statistica 13.2 (TIBCO Software Inc., CA, USA). Within each participant, TS MEPs were removed from analysis if they fell <2 standard deviations from the participant's TS all-trial mean. An average of 4 and 6 trials were removed per participant for the abduction and the writing task, respectively. Assumptions for the ANOVA were tested for each variable. The Shapiro-Wilk test for normality was used. Test stimulus (TS) MEP amplitudes were not normally distributed, thus, a 1/sqrt transformation was applied. 2x2 repeated-measures analysis of variance (ANOVA) were performed to examine the effect of task (abduction versus writing) as

well as the effect of fatigue (pre- versus post-fatigue) for each dependent variable. Fisher's LSD was used for *post hoc* analysis. An ANOVA identified no main effect of block for each dependent variable (raw TS MEP amplitude, normalized SICI, normalized ICF, CSP, coefficient of variation (CoV) of TS MEP amplitudes, as well as FDI, ECR, and FCR EMG). As such, all pre-fatigue trials were averaged and all post-fatigue trials were averaged for each participant. Dependent samples t-tests were used for all baseline measures (see below) to identify an order effect of testing session for this randomized and counterbalanced repeated-measures study.

*Secondary Analysis on Printers and Cursive Writers*

We had participants write the word "name" for the writing task because movements used to produce the letters are similar for both cursive and printing. Of the 19 participants included in the study, 8 wrote in cursive, 8 printed, and 3 used a combination of cursive and print. Accordingly, we included writing strategy (cursive vs. printing) as a categorical predictor (printer [P, n=8] or cursive writer [C, n=8]) in an *a posteriori* analysis. The three individuals who used both printing and cursive writing strategies were excluded from this secondary analysis. A factorial ANOVA (task x fatigue x writing style) was performed. Additionally, independent samples t-tests were computed to determine if there were differences in level of FDI, ECR, and FCR EMG activity between printers and cursive writers during the writing task.

## RESULTS

### *Baseline Measures*

Maximal voluntary contraction force and maximal FDI muscle activation (RMS amplitude), as well as the number of fatiguing sets completed did not differ significantly between testing sessions (day 1 or 2) nor between task days (abduction or writing day). Finally, the amplitude of FDI muscle activity during writing did not differ between testing sessions nor task days (Table 1). AMT was 3% lower on testing session two compared to testing session one ($t(18)=2.5$, $p=0.02$). However, this was a randomized and counterbalanced study and AMT did not differ between the two task days (Table 1).

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**Table 1. Baseline measures**
Baseline measures comparing MVCs, EMG, fatiguing sets, and AMT between task days. This was a randomized and counterbalanced repeated-measures study. Note, there was a significant effect of testing day but not task day on AMT ($t(18)=2.5$, $p=0.02$) (Mean±SD).

| | **Abduction Day** | **Writing Day** |
|---|---|---|
| **MVC Force (N)** | 0.31±0.04 | 0.31±0.04 |
| **MVC EMG (mV)** | 0.91±0.38 | 0.94±0.40 |
| **Writing EMG (% MVC)** | 18.7±6.88 | 20.5±9.62 |
| **# of Fatiguing Sets** | 4.32±2.55 | 4.81±4.36 |
| **AMT (%MSO)*** | 39.1±8.20 | 41.0±7.30 |

*MSO = maximum stimulator output

***Corticospinal Excitability***

*Abduction vs. Writing*

There was a main effect of fatigue on raw TS MEP amplitudes, such that TS MEPs were smaller following fatigue ($F=10.5$, [1,18], $p=0.005$, $\eta_p^2=0.37$, Figure 6). Examination of percent change scores identified two physiological outliers for SICI, which were removed for statistical analysis. Repeated-measures ANOVA identified that there was no interaction between task and fatigue on SICI, ICF, and CSP. SICI was greater during writing compared to abduction ($F=4.91$, [1,16], $p=0.04$, $\eta_p^2=0.23$). ICF did not differ between task nor fatigue (Figure 7), however, a trend was observed for a task x fatigue interaction on ICF ($F=3.6$, [1,18], 0.07, $\eta_p^2=0.17$). There was no effect of task or fatigue on duration of cortical silent period (CSP).

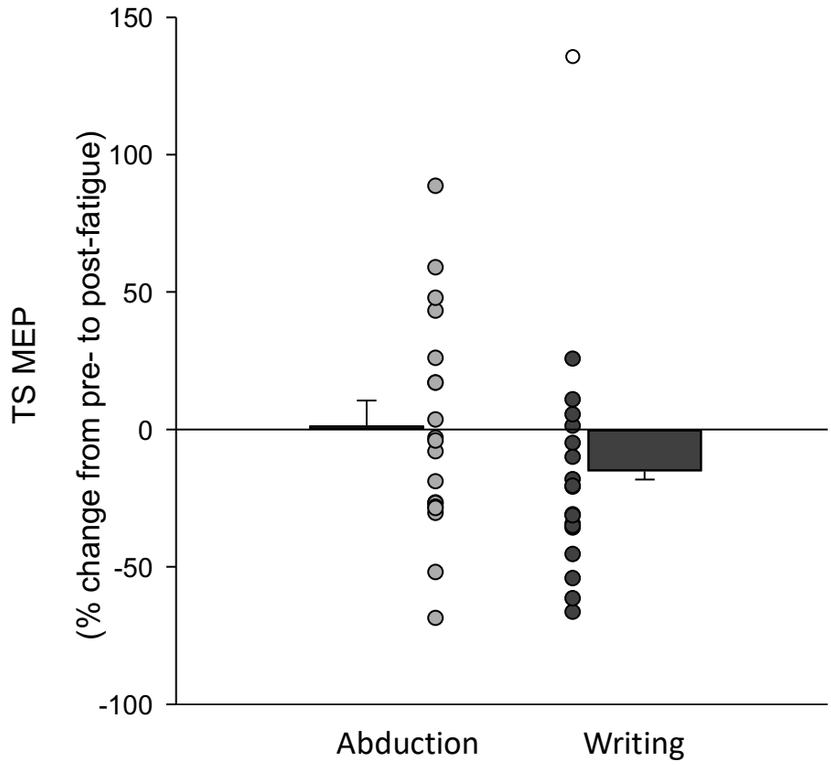


**Figure 6. TS MEP amplitude % change following fatigue** (Mean±SE)
Repeated-measures ANOVA showed no main effect of task or fatigue on TS MEP amplitude. Due to variability, percent change scores from pre- to post-fatigue were compared between tasks. One statistical outlier identified with an open symbol was removed. Writing showed a greater percent change following fatigue compared to abduction ($t(17)=2.12$, $p=0.05$).

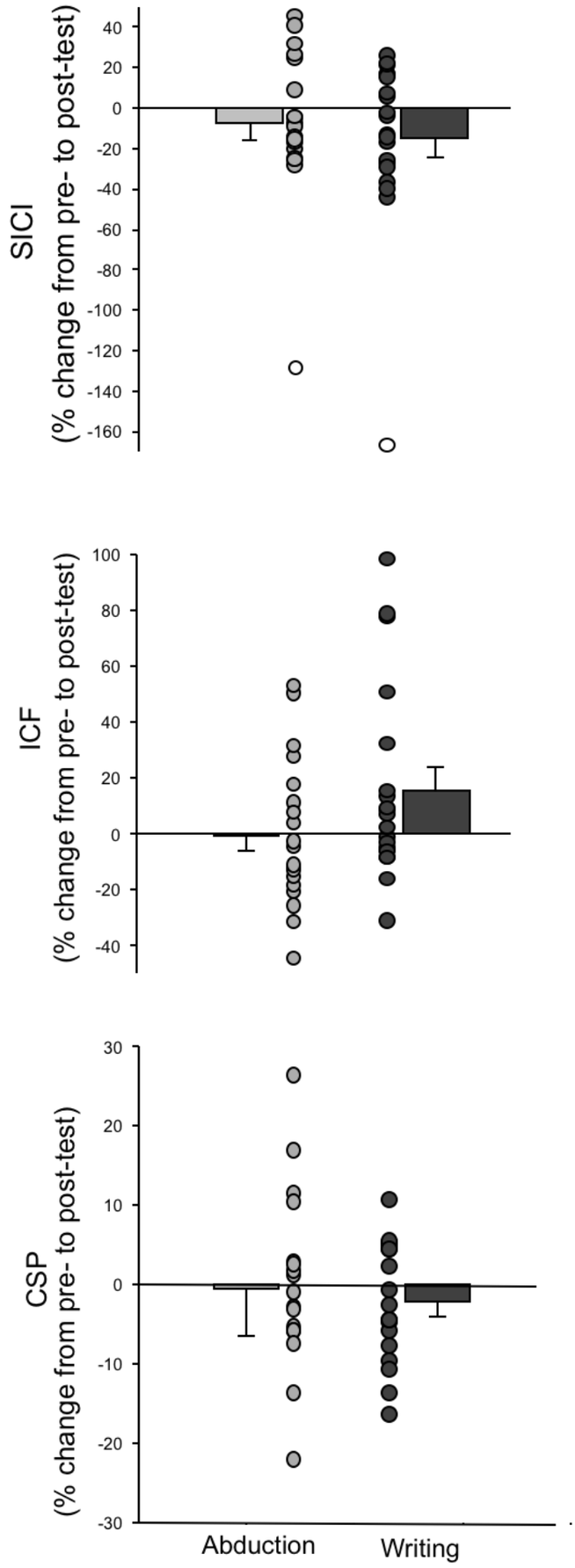


**Figure 7. SICI, ICF, and CSP % change following fatigue.** Repeated-measures ANOVA indicated that writing had greater levels of inhibition compared to abduction (F=4.91, [1,16], p=0.04). There was no effect of fatigue on levels of SICI, ICF, or CSP. A trend toward significance for a task x fatigue interaction was found (F=3.4, [1,18], p=0.07; Mean±SE).

*Printers vs. Cursive Writers*

The factorial ANOVA (task × fatigue × style of writing) was not significant for TS ($F=0.77$, [1,14], $p=0.40$, $\eta_p^2=0.05$), SICI ($F=0.56$, [1,13], $p=0.47$, $\eta_p^2=0.04$) or CSP ($F=0.28$, [1,14], $p=0.60$, $\eta_p^2=0.02$), but was significant for ICF ($F=9.9$, [1,14], $p=0.007$, $\eta_p^2=0.41$). The effect of fatigue was not significant for abduction or cursive writing, but there was a 35% increase in ICF following fatigue in printers ($p=0.003$, Figure 8).

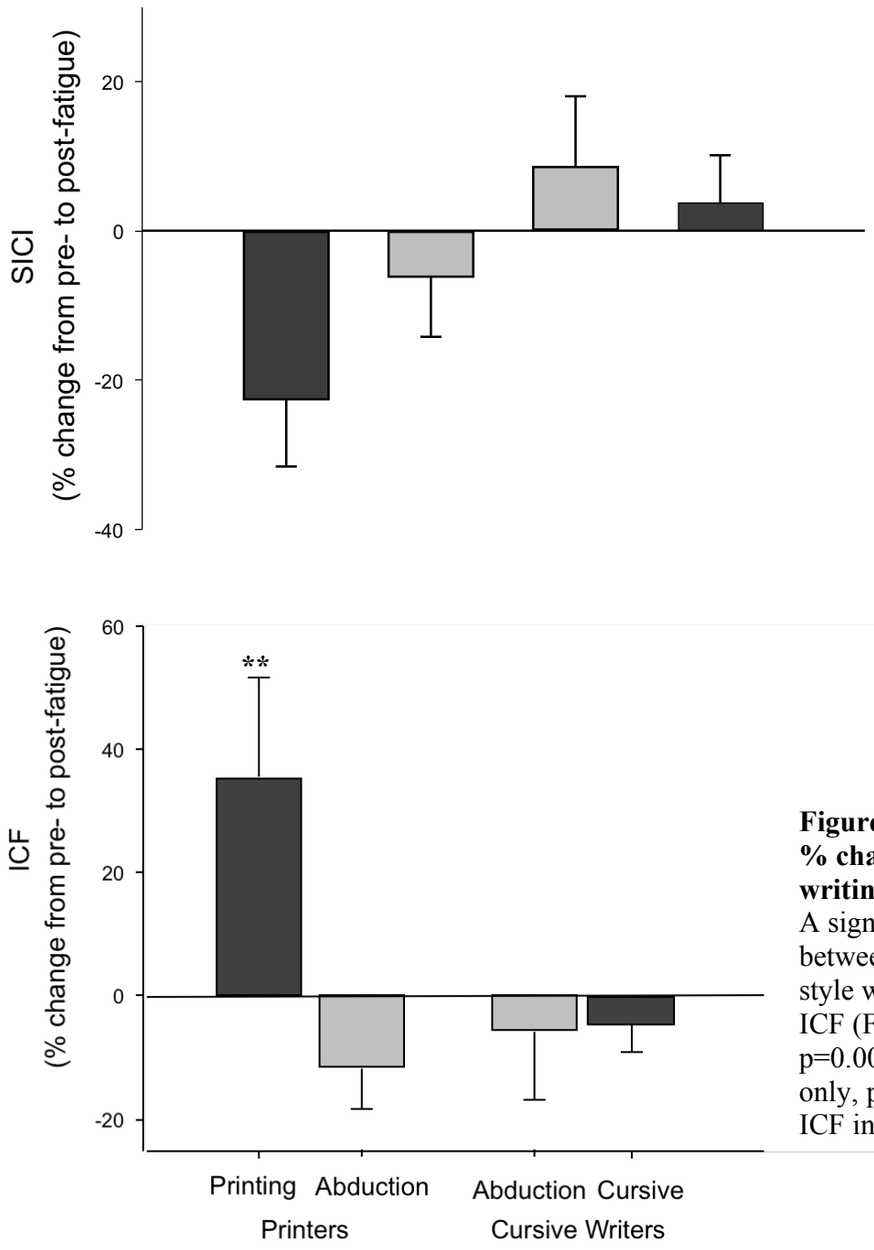


**Figure 8. SICI and ICF % change separated by writing style**
A significant interaction between task x fatigue x style was found for levels of ICF ($F=9.9$, [1,14], $p=0.007$**). In printers only, post-fatigue levels of ICF increased (Mean±SE).

***Muscle Activity***

Normalized FDI EMG activity 500ms prior to TMS stimulation was not different between tasks, pre-fatigue and post fatigue, and between printers and cursive writers (Figure 9). Total FDI muscle activity used for the entirety of each task was not significantly different between tasks. Total FDI activity and total time active was reduced following fatigue during the writing task only (task*fatigue interaction, $F=7.1$, [1,18], $p=0.02$, $\eta_p^2=0.28$; $F=21.7$, [1,18], $p<0.01$, $\eta_p^2=0.55$, Table 2). There was no effect of writing style on total muscle activity or total time active. ECR EMG activity was greater in the writing task ($F=7.95$, [1,18], $p=0.01$), whereas FCR activity was greater in the abduction task ($F=5.5$, [1,18], $p=0.003$). A trend was seen, such that printers used ECR more compared to cursive writers during the writing task ($t=2.03$, [1,14], $p=0.06$) (Table 3). There was no main effect of fatigue on ECR and FCR EMG activity. A simple regression was computed to determine if there was a correlation between the % change in TS MEP amplitude from pre- to post-fatigue and % change in EMG activity. The two were found to be uncorrelated for both tasks (Abduction: $r=0.13$, $p=0.14$; Writing: $r=0.18$, $p=0.47$).

***Variability***

There was a trend toward significance such that TS MEP amplitudes were more variable during the writing task (main effect of task, $p=0.07$) and were more variable pre-fatigue compared to post-fatigue during the writing task (task x fatigue Interaction, $p=0.07$). To assess whether this decrease in variability post-fatigue was due to a learning effect, an ANOVA was computed to compare effect of block, but significance was not reached. An independent samples t-test showed that TS MEP amplitudes were 15% more variable during printing in comparison to cursive ($t(30)= 2.18$, $p=0.04$) (Table 4).

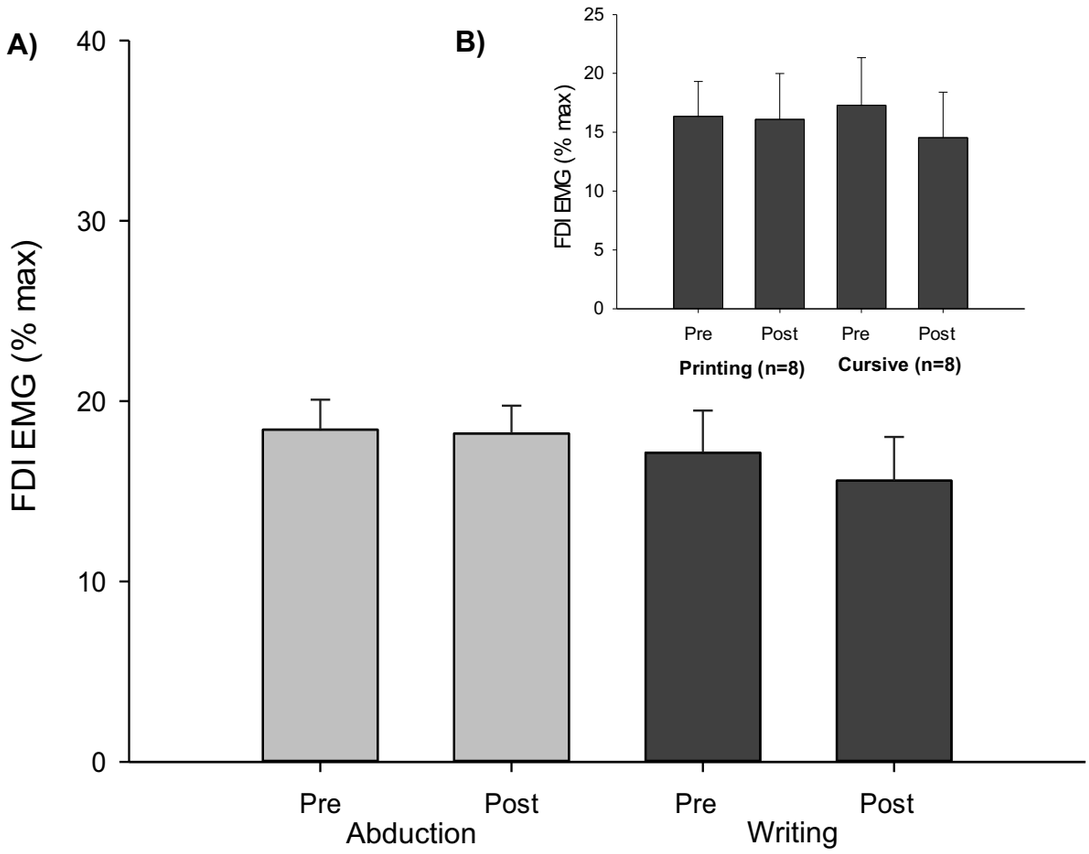


**Figure 9. Mean FDI EMG activity across tasks**
Average FDI EMG activity did not differ between tasks or pre-post fatigue (A). When printers and cursive writers were assessed separately (inset figure B), FDI EMG activity did not differ between printers and cursive writers. FDI EMG activity was normalized to MVC and is expressed as a % max (Mean±SE).

**Table 2. Total muscle activity and total time active of the FDI during each task.**
Repeated-measures ANOVA identified an interaction between task and fatigue such that both total activity and total time active were reduced following fatigue in the writing task. There was no main effect of task on either variable (Area Under Curve: $F=7.1$, $[1,18]$, $p=0.02$, $\eta_p^2=0.28$; Total Time Active: $F=21.7$, $[1,18]$, $p<0.01$, $\eta_p^2=0.55$; Mean±SD).

| | **Abduction Task** | **Writing Task** | | |
|---|---|---|---|---|
| | All (n=19) | All (n=19) | Print (n=8) | Cursive (n=8) |
| **FDI total muscle activity (area under curve, mV)** | | | | |
| **Pre** | 0.165±0.11 | 0.145±0.11 | 0.142±0.10 | 0.172±0.14 |
| **Post** | 0.163±0.11 | 0.112±0.08 | 0.101±0.08 | 0.132±0.10 |
| **Total time active (s)** | | | | |
| **Pre** | 4.26±0.13 | 3.39±0.54 | 3.32±0.48 | 3.55±0.63 |
| **Post** | 4.23±0.16 | 3.04±0.52 | 2.91±0.58 | 3.21±0.53 |

**Table 3. Average EMG Activity**
Repeated-measures ANOVA showed a significant effect of task but not fatigue on levels of ECR and FCR activity. Abduction presented with more FCR activity (F=5.5, [1,18], p=0.003**) and writing presented with more ECR activity (F=7.95, [1,18], p=0.01**). Factorial ANOVA including writing style as a categorical predictor showed a trend toward significance such that printers used more ECR than cursive writers (t=2.03, [1,14], p=0.06*)(Mean±SD)

| | **Abduction Task** | **Writing Task** | | |
|---|---|---|---|---|
| | All (n=19) | All (n=19) | Print (n=8) | Cursive (n=8) |
| **FDI EMG (%max)** | | | | |
| **Pre** | 18.4±7.25 | 17.2±10.15 | 16.3±8.40 | 17.3±11.43 |
| **Post** | 18.21±6.69 | 15.6±10.59 | 16.1±11.0 | 14.5±10.9 |
| **ECR EMG (μV)**** | | | | |
| **Pre** | 79.9±47.2 | 134.7±62.4 | 154.2±71.5 | 99.1±27.6* |
| **Post** | 83.8±44.9 | 132.7±53.1 | 147.2±61.8 | 103.8±33.6 |
| **FCR EMG (μV)**** | | | | |
| **Pre** | 81.8±51.4 | 51.8±26.5 | 61.2±30.3 | 41.9±24.7 |
| **Post** | 104.7±109.4 | 53.5±28.9 | 64.2±28.3 | 42.0±30.9 |

**Table 4. TS MEP Amplitude Coefficient of Variation**
Repeated-measures ANOVA indicated a trend toward significance for task such that the writing task had higher levels of variability (p=0.07). Independent samples t-test separating CoV by writing style indicated that printers had higher variability than cursive writers (t(30)=2.18, p=0.04*) (Mean±SD).

| | **Abduction Task** | **Writing Task** | | |
|---|---|---|---|---|
| | All (n=19) | All (n=19) | Print (n=8)* | Cursive (n=8) |
| **Pre** | 36.9±7.6 | 45.44±6.6 | 48.4±7.3 | 42.4±5.5 |
| **Post** | 38.7±9.8 | 40.05±11.9 | 45.2±14.7 | 35.9±9.7 |

## DISCUSSION

TMS has gained popularity over the past three decades as a method for measuring corticospinal excitability. However, given the highly state- and task-dependent nature of cortical and spinal excitability, it is important to consider the contexts within which these measures are attained. This study sought to measure corticospinal excitability during a relevant, daily task. As such, corticospinal excitability measured during a conventional finger abduction task was compared to measures made during handwriting. In addition, the effect of neuromuscular fatigue on these measures of corticospinal excitability were compared between the two tasks to identify if a task-dependent effect of fatigue exists. Levels of intracortical inhibition (SICI) were greater during the writing task. In addition, separating participants into those who print and those who cursive-write revealed a task-dependent effect of fatigue. This indicates that our conclusions about the effects of fatigue on corticospinal excitability depend on the task we use to measure corticospinal excitability.

It is well established that neuromuscular fatigue effects corticospinal excitability. Neuromuscular fatigue has been studied in several muscles of the human body including the FDI. Previous studies have found a reduction in unconditioned (TS) MEP amplitudes in the target muscle following neuromuscular fatigue. (Brasil-Neto et al., 1993; Kalmar & Cafarelli, 2004). This depression has been attributed to central mechanisms of fatigue (Brasil-Neto et al., 1993; Gandevia, Petersen, Butler, & Taylor, 1999). Accordingly, paired-pulse TMS techniques have been used to identify intracortical mechanisms of fatigue (Latella, Hendy, Vanderwesthuizen, & Teo, 2018; Maruyama, Matsunaga, Tanaka, & Rothwell, 2006; Sharples, Gould, Vandenberk, & Kalmar, 2016). Following fatiguing contractions of the FDI, levels of SICI are decreased while levels of ICF are increased (Maruyama et al., 2006; Sharples et al., 2016). This decrease in

inhibition and increase in facilitation following fatigue may serve as a mechanism of compensation for optimizing motor output (Benwell et al., 2006).

The present study identified a task-dependent effect of fatigue. If conclusions were made about central fatigue within the abduction and writing tasks, we would have concluded that neuromuscular fatigue did not affect the specific intracortical pathways measured in the study. However, when breaking down the writing task into a printing task and a cursive-writing task based on participant's writing styles, the story changed. Similar to previous research (Maruyama et al., 2006; Sharples & Kalmar, 2012), increased ICF was found following fatigue. However, this was unique to printers, and was not found in cursive writers or during the conventional finger abduction task. The word 'name' was specifically selected for the writing task because the pen movements used to make the letters n, a, m, and e are similar when printed and when written in cursive. Accordingly, the word was selected knowing writing styles would differ between participants. Although the original intent of this study was to compare excitability between a natural task (writing) and a conventional laboratory task (isometric finger abduction), we found that writing presented as two different tasks that were associated with different intracortical effects of fatigue.

Because the level of EMG activity from the recorded muscle effects levels of corticospinal excitability (Darling, Wolf, & Butler, 2006), one might surmise that differences between printers and cursive writers were due to differences in muscle activation between the two writing styles. However, levels of FDI EMG activity between printers and cursive writers, and during the abduction task were not significantly different. Therefore, the differences in intracortical measures of excitability pre- and post-fatigue cannot be attributed to differing EMG activity between the

tasks. As well, though total FDI activity was different following fatigue during the writing task, pre-stimulus (500ms) EMG activity did not differ between task nor fatigue, thus, would not affect the elicited MEP. While FDI EMG activity between abduction and writing did not differ, extensor (ECR) activity was higher during the writing task in comparison to abduction. It has been suggested that activity and position of proximal muscles can have an effect on the corticospinal pathway leading to the distal muscle of interest (Devanne, Cohen, Kouchtir-Devanne, & Capaday, 2002; Dominici, Popa, Ginanneschi, Mazzocchio, & Rossi, 2005). This relationship was shown between the ECR and anterior deltoid during a pointing task, where deltoid activity resulted in facilitation of ECR MEPs. However, in the same study, cortical parameters of the FDI were not dependent on activity of the deltoid or the ECR (Devanne et al., 2002). Therefore, differences in SICI and ICF were not likely due to differences in proximal wrist muscle activity. However, it is important to note that Devanne et al. (2002) used a pointing task paradigm to study these cortical circuits, so further investigation is warranted with regard to the effect of proximal muscle activity within different tasks. Though EMG activity of wrist muscles differed between the two tasks in our study, we highlighted the important factor that the target FDI muscle activity was kept constant across all tasks.

The writing task and abduction did differ in that one task is dynamic and the other is steady. Writing often involves start-stop motions between letters within a word, with printing involving a more discontinuous pattern of activity to lift the pen between individual letters. The fact that writing involves dynamic activity might provide an explanation for the greater amounts of inhibition seen during writing. This is highlighted in the EMG recordings of those individuals who print, where distinct bursts of EMG activity are present (Figure 5D). It should be noted that while

short-interval intracortical inhibition (SICI) was lower during writing, cortical silent period (CSP) did not change. These two mechanisms act via different mechanisms, SICI via $GABA_A$ receptors, and CSP via $GABA_B$ receptors, with this being highlighted in the present study as SICI was reduced while CSP remained constant following fatigue (Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999). Printing and cursive writing can be seen as more dynamic tasks, involving concentric contractions, while abduction is an example of a steady, isometric contraction. As printing is even more discontinuous than cursive writing, this may also explain the task-dependent effect of fatigue found in printers and not cursive writers. In comparing corticospinal excitability between dynamic and steady contractions, MEPs were facilitated during dynamic abduction contractions of the deltoid muscle (Aranyi, Mathis, Hess, & Rosler, 1998). In contrast, the present study found greater levels of inhibition during the dynamic writing task compared to the steady abduction contraction task. However, Aranyi and colleagues (1998) also found that MEPs were not different between dynamic and steady contractions of the abductor digiti minimi. This finding points to the significance of excitability being muscle- and task-dependent. Previous studies which identified a task-dependent facilitation of corticospinal excitability in intrinsic muscles of the hand used a precision grip task (Flament, Goldsmith, Buckley, & Lemon, 1993; Geevasinga, Menon, Kiernan, & Vucic, 2014; Kouchtir-devanne, Capaday, Cassim, Derambure, & Devanne, 2018; Tinazzi et al., 2003). Comparing these previous study's findings with Aranyi and colleagues (1998) and the present study, the significance of task-dependency once again emerges.

We hypothesized that corticospinal excitability would be greater during writing compared to abduction given the similarities in writing and precision grip. However, it is clear that writing and precision grip tasks greatly differ. Writing is most often done in a dynamic tripod grip

involving the 3rd digit as a stabilizer, in contrast with the precision grip which exclusively involves the thumb and index finger. With the involvement of more muscles as well as the dynamic nature of writing, the precision grip task employed in previous task-dependent research is quite distinct from writing. The precision grip tasks not only exclusively involve two fingers, but are also externally cued, visually-guided precision tasks. While maintaining a specific grip between the thumb and index finger, participants are instructed to follow a force or EMG tracing, making the task visually-guided and precision-based, requiring control and external guidance. In addition, the precision tasks are steady contractions. This can be contrasted with writing, which is a dynamic, internally-generated task that is retrieved and implemented from memory (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003; Elsinger, Harrington, & Rao, 2006). Writing involves higher levels of activation in brain networks such as the dorsal premotor cortex (PMd) as well as unique brain networks in comparison to simple finger contraction tasks (Horovitz, Gallea, Najee-ullah, & Hallett, 2013). This association of writing with higher cognitive demands would suggest that writing is a more complex task in comparison to simple finger contractions. However, as writing has been learned and practiced from a young age into adulthood, an automaticity develops (Jones & Christensen, 1999). Automaticity allows one to write a word with their eyes closed for example, highlighting the internal nature of the generation of written text. These details emphasize the fact that though the precision grip is similar to writing with regard to the grip, the nature of the tasks are quite different. Most studies utilizing a precision grip use a task that is unpracticed, unnatural, and externally guided, thus presenting as a more complex and demanding task. This fact may explain why we did not find increased excitability with writing, which is contrasted with

previous research who found increased facilitation during manual tasks in comparison to isolated finger abduction.

TMS studies often use conventional laboratory tasks such as isometric abduction to reduce variability of MEPs. However, considering the dynamic nature of the writing task, our study showed that MEP variability was not that much greater during writing in comparison to abduction. Introducing writing or other functionally relevant tasks can increase our knowledge about the motor tasks and mechanisms we wish to understand. Clinical professionals such as occupational therapists can benefit from the present findings of our research. As everyday tasks do not require a force transducer and other laboratory materials and software, they are more accessible in a clinical setting. While conventional contraction tasks in a laboratory have the benefit of controlling for extraneous variables, they do not represent the changing environment within which individuals interact. The sensitive populations clinicians work with make it even more imperative that research is done in a context- and task-specific manner. For example, children with autism spectrum disorder (ASD) often present with difficulties writing in comparison to their typically-developing peers. Atypical handwriting, such as irregular letter spacing, larger letter sizing, and poorer legibility, is often cited in children with ASD (Grace et al., 2018). A possible cause for atypical writing in those with ASD is a lack of inhibition within the motor system. In a TMS study, those with ASD were found to have decreased levels of inhibition in comparison to typically developing children (Enticott, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2010). However, this study used the typical conventional contraction protocol. Those with ASD and other neurocognitive disabilities are highly sensitive to the changing environment around them. In order to better understand the neurophysiological underpinnings of ASD and disorders alike, research should aim to create

experimental paradigms that mimic our dynamic environment. The present study used writing to demonstrate the possibility for the use of relevant motor tasks to study corticospinal excitability. Levels of variability between the two tasks was comparable considering the dynamic nature of writing. Further actions can be taken to decrease this variability in the future. The task dependent nature of corticospinal excitability highlighted in previous literature as well as the current study emphasize the importance of studying corticospinal excitability in the context of specific tasks.

### *Conclusion*

This study was the first to assess corticospinal excitability and the effect of fatigue during a writing task. Though the effects of fatigue have been well documented over three decades, this study highlighted the importance of understanding fatigue in a task-specific manner. Corticospinal excitability following neuromuscular fatigue can differ depending on the task used to asses it, as we saw effects of fatigue on intracortical measures of excitability during printing but not cursive writing or isometric abduction. Additionally, the task-dependent nature of corticospinal excitability emphasizes the need for experimental paradigms that take into account the dynamic qualities of natural motor tasks and the changing environment around us. This will allow for stronger transformation of findings from the laboratory to the real world. Finally, the results of this study highlight the importance of considering how experimental tasks differ from volitional movement in a natural context. Had we used only a conventional finger abduction task, we would have concluded that there was no effect of fatigue on our measures of corticospinal excitability. With this in mind, it is essential that studies of corticospinal excitability consider the "task at hand".

# CHAPTER IV: FUTURE DIRECTIONS

As this study was the first to assess corticospinal excitability during a writing task, several questions remain. The word name for the writing task was selected to minimize variations in EMG during writing, such that the letters were of the same height within the word. As well, the word name written in printing follows similar strokes as when it is written in cursive. However, it was unexpected that different styles of writing would have a significant effect on our measures. Though 19 individuals participated in the study, the number of participants in each group of writing style (printers or cursive writers) was 8. As such, it would be interesting to continue this project and recruit more individuals to get a higher-powered result. In addition, it would be interesting to capture the effect of a mixed writing style (mix of printing and cursive) as these individuals (n=3) were excluded from the secondary analysis. Further investigation of this project should also take into account grip style during writing. Though the present study encouraged maintenance of the same grip for the duration of the protocol, the specific grip participants were using was not recorded. Controlling for grip style might help better understand the nature of the task-dependent modulation of excitability.

Due to limitations, activity from only one muscle of the hand and two accessory muscles were measured. As writing and pencil grip is a dynamic task, it would be beneficial to record activity of more intrinsic muscles of the hand to identify their use and contribution to writing. As well, as a muscle-dependent effect of excitability has been cited, it would be interesting to note differences in response to TMS of the different muscle during writing as well as following neuromuscular fatigue.

The use of TMS over the past three decades has contributed to many areas of neurophysiological research including brain mapping (Metman, Bellevich, Jones, Barber, &

Streletz, 1993), aging (Oliviero et al., 2006; Peinemann, Lehner, Conrad, & Siebner, 2001), disability (Enticott et al., 2010), and disease (Lazzaro et al., 2004). However, recognizing the sensitivity of the state- and task-dependency of TMS measures warrants attention. Current studies seek to minimize variations in experimental conditions that ultimately are deeply-rooted in the successful performance of these tasks outside the laboratory. As the present study found that changes in intracortical excitability following fatigue depend on the motor tasks used to assess excitability, future studies should create paradigms that mimic natural motor tasks. While perhaps sacrificing experimental consistencies, designing such protocols would allow questions to be answered in a context-specific manner, providing a better understanding of motor control during the tasks we ultimately wish to understand. These design protocols can be applied to disease populations such as stroke patients and Alzheimer's disease, or those with neurodevelopmental disabilities such as developmental coordination disorder or ASD. Understanding the task-specific nature of disease and disorder, whether it be through hand-writing or other manual tasks, will help uncover task-specific neural mechanisms governing different pathologies and disabilities.

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# APPENDICES

**Appendix A: Data Tables**

**Table A1. Data summary**

| | | | | | *Effects* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Abduction** | | **Writing** | | **Task** | | | **Fatigue** | | | **Task x Fatigue** | | | **Task x Fatigue x Method** | | |
| ***Variable*** | Pre | Post | Pre | Post | df | F | p | df | F | p | df | F | p | df | F | p |
| **TS (mV)** | 1.6 ±1.1 | 1.5±1.1 | 1.8±1.5 | 1.6±1.7 | 1,18 | 0.09 | 0.76 | 1,18 | 10.5 | 0.005** | 1,18 | 2.2 | 0.15 | 1,14 | 0.77 | 0.40 |
| **SICI (norm)** | 0.9±0.3 | 0.93±0.3 | 0.8±0.2 | 0.9±0.2 | 1,18 | 3.2 | 0.09 | 1,18 | 1.25 | 0.28 | 1,18 | 0.25 | 0.63 | 1,14 | 1.37 | 0.26 |
| **ICF (norm)** | 1.2±0.3 | 1.2±0.3 | 1.1±0.2 | 1.3±0.3 | 1,18 | 0.09 | 0.77 | 1,18 | 0.39 | 0.54 | 1,18 | 3.6 | 0.07* | 1,14 | 9.90 | 0.007* |
| **FDI EMG (norm)** | 0.18±0.07 | 0.18±0.07 | 0.17±0.1 | 0.16±0.1 | 1,18 | 1.41 | 0.25 | 1,18 | 2.17 | 0.16 | 1,18 | 1.3 | 0.27 | 1,14 | 0.57 | 0.46 |
| **ECR EMG (mV)** | 0.02±0.01 | 0.03±0.01 | 0.04±0.02 | 0.04±0.02 | 1,18 | 7.95 | 0.01** | 1,18 | 0.08 | 0.78 | 1,18 | 0.86 | 0.37 | 1,14 | 2.82 | 0.12 |
| **FCR EMG (mV)** | 0.02±0.02 | 0.03±0.03 | 0.02±0.008 | 0.02±0.009 | 1,18 | 5.47 | 0.03** | 1,18 | 2.14 | 0.16 | 1,18 | 1.7 | 0.21 | 1,14 | 0.57 | 0.46 |
| **CSP (ms)** | 80.9±21.4 | 80.7±22.8 | 76.7±15.1 | 75.0±16.3 | 1,18 | 2.02 | 0.17 | 1,18 | 0.47 | 0.50 | 1,18 | 0.29 | 0.59 | 1,14 | 0.30 | 0.60 |
| **CoV (%)** | 36.9±7.6 | 38.7±9.8 | 45.4±6.6 | 40.0±11.9 | 1,18 | 3.65 | 0.07* | 1,18 | 1.55 | 0.23 | 1,18 | 3.59 | 0.07* | 1,14 | 0.02 | 0.89 |

**significant
*trend toward significance

**Table A2. Test stimulus (TS) MEP amplitude (mV)**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 3.1 | 3.0 | 3.9 | 3.1 |
| 2 | 1.4 | 1.2 | 1.4 | 0.9 |
| 3 | 4.1 | 2.0 | 5.3 | 5.4 |
| 4 | 0.5 | 0.4 | 1.2 | 0.8 |
| 5 | 0.7 | 0.5 | 0.8 | 0.9 |
| 6 | 0.4 | 0.8 | 0.8 | 0.3 |
| 7 | 0.5 | 0.6 | 0.9 | 0.6 |
| 8 | 0.8 | 0.6 | 0.6 | 0.5 |
| 10 | 1.3 | 1.2 | 1.3 | 0.5 |
| 11 | 3.5 | 2.5 | 4.8 | 3.9 |
| 13 | 2.4 | 0.8 | 0.9 | 0.8 |
| 14 | 2.4 | 3.9 | 4.6 | 5.1 |
| 15 | 1.5 | 1.5 | 1.5 | 3.6 |
| 16 | 1.2 | 1.4 | 1.4 | 0.9 |
| 17 | 1.2 | 1.2 | 1.4 | 0.8 |
| 18 | 0.8 | 1.1 | 1.5 | 0.7 |
| 19 | 3.0 | 4.3 | 0.8 | 0.6 |
| 20 | 1.2 | 0.9 | 1.1 | 0.8 |
| 21 | 1.0 | 1.4 | 0.8 | 1.0 |
| **Average** | **1.6** | **1.5** | **1.8** | **1.6** |
| **SD** | 1.1 | 1.1 | 1.5 | 1.7 |

**Table A3. TS MEP amplitude % change following fatigue**

| Participant | Abduction | Writing |
|---|---|---|
| 1 | -2.0 | -20.8 |
| 2 | -17.9 | -35.7 |
| 3 | -50.9 | 1.3 |
| 4 | -25.5 | -34.3 |
| 5 | -25.8 | 5.5 |
| 6 | 89.6 | -66.4 |
| 7 | 18.0 | -35.0 |
| 8 | -27.1 | -4.9 |
| 10 | -7.0 | -61.4 |
| 11 | -29.3 | -18.1 |
| 13 | -67.6 | -10.0 |
| 14 | 60.0 | 11.0 |
| 15 | 4.6 | 135.6 |
| 16 | 18.1 | -30.9 |
| 17 | -3.0 | -45.3 |
| 18 | 27.0 | -54.1 |
| 19 | 44.3 | -20.5 |
| 20 | -27.6 | -31.2 |
| 21 | 48.9 | 25.7 |
| **Average** | **1.4** | **-15.2** |
| **SD** | 39.8 | 44.0 |

**Table A4. Normalized SICI**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 1.0 | 1.2 | 0.7 | 1.0 |
| 2 | 0.7 | 0.7 | 0.6 | 0.5 |
| 3 | 0.9 | 0.5 | 0.9 | 1.0 |
| 4 | 0.8 | 1.0 | 1.0 | 1.1 |
| 5 | 1.1 | 1.4 | 1.3 | 1.1 |
| 6 | 0.6 | 0.7 | 0.5 | 1.2 |
| 7 | 1.1 | 1.1 | 0.7 | 1.0 |
| 8 | 1.1 | 1.2 | 1.1 | 0.8 |
| 10 | 0.9 | 0.9 | 1.1 | 1.0 |
| 11 | 0.5 | 0.6 | 0.5 | 0.7 |
| 13 | 0.4 | 1.0 | 0.8 | 0.7 |
| 14 | 0.6 | 0.3 | 0.6 | 0.5 |
| 15 | 1.4 | 1.0 | 0.8 | 0.6 |
| 16 | 1.1 | 1.4 | 0.8 | 1.0 |
| 17 | 1.0 | 1.1 | 0.8 | 0.9 |
| 18 | 0.8 | 1.0 | 0.8 | 0.9 |
| 19 | 1.0 | 0.7 | 0.8 | 0.6 |
| 20 | 0.9 | 0.9 | 0.8 | 1.0 |
| 21 | 1.3 | 0.9 | 0.7 | 0.9 |
| **Average** | **0.9** | **0.9** | **0.8** | **0.9** |
| **SD** | 0.3 | 0.3 | 0.2 | 0.2 |

**Table A5. SICI % change following fatigue**

| Participant | Abduction | Writing |
|---|---|---|
| 1 | -20.3 | -44.5 |
| 2 | -4.6 | 16.6 |
| 3 | 45.4 | -4.1 |
| 4 | -17.1 | -13.6 |
| 5 | -28.2 | 17.1 |
| 6 | -15.0 | -166.8 |
| 7 | -7.7 | -36.8 |
| 8 | -9.3 | 25.7 |
| 10 | -4.4 | 5.8 |
| 11 | -14.6 | -40.2 |
| 13 | -128.5 | 7.4 |
| 14 | 40.8 | 15.6 |
| 15 | 25.3 | 21.0 |
| 16 | -25.1 | -26.9 |
| 17 | -15.5 | -17.0 |
| 18 | -25.5 | -2.2 |
| 19 | 26.5 | 22.1 |
| 20 | 9.1 | -25.7 |
| 21 | 31.7 | -29.5 |
| **Average** | **-7.2** | **-14.5** |
| **SD** | 37.5 | 43.5 |

**Table A6. Normalized ICF**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 1.5 | 1.8 | 0.8 | 1.2 |
| 2 | 1.5 | 1.2 | 1.8 | 1.7 |
| 3 | 1.1 | 1.0 | 1.0 | 0.9 |
| 4 | 1.2 | 1.5 | 1.1 | 1.2 |
| 5 | 1.0 | 1.6 | 0.8 | 0.9 |
| 6 | 1.3 | 1.3 | 1.0 | 1.8 |
| 7 | 1.0 | 1.0 | 0.7 | 1.4 |
| 8 | 1.3 | 1.1 | 1.2 | 1.2 |
| 10 | 0.6 | 0.9 | 1.1 | 1.1 |
| 11 | 1.1 | 0.9 | 1.6 | 1.6 |
| 13 | 1.0 | 1.3 | 1.0 | 1.3 |
| 14 | 1.5 | 1.3 | 1.5 | 1.4 |
| 15 | 1.2 | 1.1 | 1.2 | 1.0 |
| 16 | 2.1 | 1.9 | 1.0 | 1.1 |
| 17 | 1.0 | 1.2 | 0.9 | 0.9 |
| 18 | 1.3 | 0.9 | 1.1 | 2.0 |
| 19 | 1.5 | 1.0 | 1.3 | 0.9 |
| 20 | 0.9 | 1.0 | 1.2 | 1.3 |
| 21 | 1.4 | 0.8 | 1.3 | 1.2 |
| **Average** | **1.2** | **1.2** | **1.1** | **1.3** |
| **SD** | 0.3 | 0.3 | 0.3 | 0.3 |

**Table A7. ICF % change following fatigue**

| *ICF % change following fatigue* | | |
|---|---|---|
| **Participant** | **Abduction** | **Writing** |
| 1 | 17.2 | 50.8 |
| 2 | -21.3 | -5.0 |
| 3 | -5.4 | -8.7 |
| 4 | 27.0 | 13.3 |
| 5 | 49.9 | 8.3 |
| 6 | -3.3 | 77.5 |
| 7 | 3.2 | 98.2 |
| 8 | -18.9 | -1.3 |
| 10 | 52.4 | -6.0 |
| 11 | -16.1 | -3.2 |
| 13 | 31.2 | 32.0 |
| 14 | -12.9 | -6.4 |
| 15 | -13.8 | -16.4 |
| 16 | -11.7 | 6.6 |
| 17 | 10.7 | 2.1 |
| 18 | -26.4 | 78.8 |
| 19 | -32.0 | -31.2 |
| 20 | 7.1 | 9.1 |
| 21 | -44.9 | -8.4 |
| **Average** | **-0.4** | **15.3** |
| **SD** | 26.6 | 35.7 |

**Table A8. Cortical silent period (ms)**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 65.6 | 63.8 | 74.4 | 82.4 |
| 2 | 88.7 | 83.6 | 98.8 | 94.1 |
| 3 | 88.2 | 76.1 | 68.6 | 71.6 |
| 4 | 56.9 | 53.8 | 53.8 | 48.6 |
| 5 | 61.4 | 62.2 | 67.0 | 70.5 |
| 6 | 59.0 | 74.6 | 65.8 | 64.2 |
| 7 | 73.6 | 69.4 | 70.1 | 58.7 |
| 8 | 65.9 | 62.2 | 70.4 | 66.4 |
| 10 | 126.4 | 125.2 | 87.6 | 83.7 |
| 13 | 115.5 | 90.1 | 68.5 | 72.1 |
| 14 | 116.0 | 135.7 | 100.1 | 99.4 |
| 15 | 66.9 | 68.2 | 71.5 | 75.5 |
| 16 | 88.9 | 99.1 | 100.9 | 93.2 |
| 17 | 58.3 | 59.9 | 64.3 | 57.4 |
| 18 | 66.7 | 64.7 | 60.0 | 57.4 |
| 19 | 91.3 | 93.8 | 86.8 | 88.8 |
| 20 | 75.4 | 69.8 | 71.2 | 61.5 |
| 21 | 91.4 | 101.1 | 100.8 | 105.3 |
| **Average** | **80.9** | **80.7** | **76.7** | **75.0** |
| **SD** | 21.4 | 22.8 | 15.1 | 16.3 |

**Table A9. CSP % change following fatigue**

| Participant | Abduction | Writing |
|---|---|---|
| 1 | -2.7 | 10.7 |
| 2 | -5.8 | -4.8 |
| 3 | -13.7 | 4.4 |
| 4 | -5.4 | -9.5 |
| 5 | 1.3 | 5.1 |
| 6 | 26.6 | -2.4 |
| 7 | -5.8 | -16.3 |
| 8 | -5.7 | -5.6 |
| 10 | -1.0 | -4.4 |
| 13 | -22.0 | 5.3 |
| 14 | 17.0 | -0.7 |
| 15 | 1.9 | 5.5 |
| 16 | 11.5 | -7.6 |
| 17 | 2.8 | -10.7 |
| 18 | -3.0 | -4.4 |
| 19 | 2.7 | 2.3 |
| 20 | -7.4 | -13.6 |
| 21 | 10.6 | 4.4 |
| **Average** | **0.1** | **-2.4** |
| **SD** | 11.2 | 7.5 |

**Table A10. FDI EMG as a percentage of max (maximal EMG) – average activity during 90 trials pre ad post**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 29.47 | 29.53 | 34.13 | 37.51 |
| 2 | 12.30 | 13.09 | 8.39 | 5.75 |
| 3 | 30.54 | 25.22 | 20.61 | 18.18 |
| 4 | 11.33 | 11.68 | 11.86 | 10.36 |
| 5 | 8.79 | 9.16 | 8.97 | 8.85 |
| 6 | 13.47 | 13.88 | 10.97 | 9.19 |
| 7 | 3.17 | 3.29 | 6.84 | 5.78 |
| 8 | 15.44 | 15.99 | 9.02 | 9.07 |
| 10 | 18.90 | 19.26 | 15.24 | 7.72 |
| 11 | 15.16 | 14.54 | 12.67 | 9.22 |
| 13 | 19.67 | 18.59 | 35.75 | 31.68 |
| 14 | 29.04 | 29.16 | 38.28 | 33.48 |
| 15 | 15.08 | 15.62 | 18.26 | 16.06 |
| 16 | 23.55 | 22.96 | 21.15 | 10.62 |
| 17 | 16.57 | 17.18 | 9.61 | 8.74 |
| 18 | 19.25 | 18.73 | 12.79 | 28.04 |
| 19 | 22.13 | 22.17 | 7.50 | 5.36 |
| 20 | 24.98 | 24.72 | 29.76 | 28.26 |
| 21 | 21.08 | 21.19 | 13.97 | 12.33 |
| **Average** | **18.42** | **18.21** | **17.15** | **15.59** |
| **SD** | 7.25 | 6.69 | 10.15 | 10.59 |

**Table A11. ECR EMG activity (μV)**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 18.6 | 20.3 | 290.7 | 273.6 |
| 2 | 125.9 | 160.2 | 115.1 | 116.6 |
| 3 | 141.4 | 100.8 | 103.0 | 98.2 |
| 4 | 31.4 | 45.3 | 147.9 | 163.9 |
| 5 | 49.4 | 54.7 | 85.3 | 130.8 |
| 6 | 64.4 | 58.7 | 210.3 | 183.9 |
| 7 | 38.0 | 70.0 | 73.2 | 88.4 |
| 8 | 155.7 | 188.5 | 126.1 | 132.8 |
| 10 | 91.1 | 96.3 | 42.3 | 36.1 |
| 11 | 72.5 | 60.8 | 137.3 | 128.9 |
| 13 | 24.5 | 52.5 | 258.9 | 215.8 |
| 14 | 44.2 | 48.0 | 85.3 | 75.5 |
| 15 | 23.4 | 39.1 | 73.7 | 79.1 |
| 16 | 70.2 | 66.0 | 129.0 | 117.7 |
| 17 | 51.3 | 65.6 | 121.2 | 114.0 |
| 18 | 120.1 | 129.5 | 159.3 | 153.6 |
| 19 | 131.7 | 93.7 | 114.0 | 121.1 |
| 20 | 107.6 | 93.0 | 126.5 | 138.3 |
| 21 | 155.7 | 148.7 | 160.3 | 152.2 |
| **Average** | **79.9** | **83.8** | **134.7** | **132.7** |
| **SD** | 47.2 | 44.9 | 62.4 | 53.1 |

**Table A12. FCR EMG activity (μV)**

| | Abduction | | Writing | |
|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Pre** | **Post** |
| 1 | 35.6 | 35.8 | 63.0 | 69.1 |
| 2 | 95.4 | 67.8 | 31.5 | 36.6 |
| 3 | 126.7 | 83.0 | 34.8 | 27.9 |
| 4 | 35.2 | 44.1 | 53.5 | 60.6 |
| 5 | 48.1 | 55.7 | 26.6 | 40.8 |
| 6 | 30.3 | 44.0 | 72.3 | 76.4 |
| 7 | 49.6 | 53.8 | 41.8 | 56.1 |
| 8 | 130.4 | 260.1 | 67.7 | 71.9 |
| 10 | 73.4 | 75.4 | 9.4 | 5.6 |
| 11 | 30.8 | 74.6 | 14.0 | 16.6 |
| 13 | 36.6 | 38.0 | 38.8 | 34.3 |
| 14 | 61.4 | 86.4 | 44.4 | 15.4 |
| 15 | 68.9 | 76.7 | 32.0 | 33.8 |
| 16 | 83.0 | 104.1 | 74.8 | 72.5 |
| 17 | 64.6 | 65.4 | 39.0 | 42.3 |
| 18 | 154.7 | 113.0 | 107.7 | 106.4 |
| 19 | 230.8 | 508.7 | 56.7 | 62.5 |
| 20 | 94.0 | 98.3 | 93.0 | 105.2 |
| 21 | 105.0 | 104.2 | 83.8 | 82.8 |
| **Average** | **81.8** | **104.7** | **51.8** | **53.5** |
| **SD** | 51.4 | 109.4 | 26.5 | 28.9 |

**Table A13. MVC Force (N)**

| | Day One | | | Day Two | | |
|---|---|---|---|---|---|---|
| **Participant** | **Pre** | **Post** | **Recovery** | **Pre** | **Post** | **Recovery** |
| 1 | 0.39 | 0.30 | 0.38 | 0.29 | 0.27 | 0.28 |
| 2 | 0.32 | 0.30 | 0.29 | 0.47 | 0.40 | 0.40 |
| 3 | 0.35 | 0.30 | 0.31 | 0.34 | 0.29 | 0.31 |
| 4 | 0.41 | 0.34 | 0.34 | 0.31 | 0.29 | 0.29 |
| 5 | 0.36 | 0.34 | 0.33 | 0.30 | 0.28 | 0.30 |
| 6 | 0.32 | 0.28 | 0.27 | 0.30 | 0.28 | 0.28 |
| 7 | 0.28 | 0.27 | 0.28 | 0.28 | 0.27 | 0.27 |
| 8 | 0.30 | 0.29 | 0.29 | 0.29 | 0.27 | 0.26 |
| 10 | 0.27 | 0.29 | 0.28 | 0.31 | 0.28 | 0.31 |
| 11 | 0.30 | 0.27 | 0.27 | 0.29 | 0.27 | 0.27 |
| 13 | 0.28 | 0.26 | 0.26 | 0.29 | 0.28 | 0.29 |
| 14 | 0.28 | 0.27 | 0.29 | 0.29 | 0.28 | 0.28 |
| 15 | 0.32 | 0.30 | 0.30 | 0.31 | 0.29 | 0.29 |
| 16 | 0.31 | 0.29 | 0.29 | 0.31 | 0.28 | 0.30 |
| 17 | 0.31 | 0.30 | 0.29 | 0.30 | 0.28 | 0.29 |
| 18 | 0.27 | 0.25 | 0.26 | 0.28 | 0.26 | 0.27 |
| 19 | 0.28 | 0.27 | 0.27 | 0.27 | 0.27 | 0.27 |
| 20 | 0.26 | 0.24 | 0.25 | 0.27 | 0.25 | 0.25 |
| 21 | 0.31 | 0.31 | 0.31 | 0.32 | 0.30 | 0.31 |
| **Average** | **0.31** | **0.29** | **0.29** | **0.31** | **0.28** | **0.29** |
| **SD** | 0.04 | 0.03 | 0.03 | 0.04 | 0.03 | 0.03 |

**Table A14. Pre-Fatigue MVC FDI RMS amplitude (mV)**

| Participant | Day One | Day Two | Abduction Day | Writing Day |
|---|---|---|---|---|
| 1 | 0.7 | 1.3 | 1.3 | 0.7 |
| 2 | 1.1 | 1.1 | 1.1 | 1.1 |
| 3 | 1.0 | 1.4 | 1.0 | 1.4 |
| 4 | 0.9 | 0.7 | 0.7 | 0.9 |
| 5 | 0.9 | 1.0 | 0.9 | 1.0 |
| 6 | 0.9 | 0.7 | 0.7 | 0.9 |
| 7 | 1.9 | 1.8 | 1.9 | 1.8 |
| 8 | 0.9 | 0.8 | 0.8 | 0.9 |
| 10 | 0.5 | 0.8 | 0.5 | 0.8 |
| 11 | 1.2 | 1.0 | 1.0 | 1.2 |
| 13 | 0.3 | 0.7 | 0.7 | 0.3 |
| 14 | 0.7 | 1.1 | 0.7 | 1.1 |
| 15 | 1.4 | 1.4 | 1.4 | 1.4 |
| 16 | 0.6 | 0.5 | 0.6 | 0.5 |
| 17 | 0.7 | 0.8 | 0.8 | 0.7 |
| 18 | 0.6 | 1.1 | 0.6 | 1.1 |
| 19 | 1.3 | 1.5 | 1.5 | 1.3 |
| 20 | 0.4 | 0.4 | 0.4 | 0.4 |
| 21 | 0.3 | 0.7 | 0.7 | 0.3 |
| **Average** | **0.9** | **1.0** | **0.9** | **0.9** |
| **SD** | 0.4 | 0.4 | 0.4 | 0.4 |

**Table A15. Writing as a percentage of max (%) – from the 20 familiarization trials (level set from famil)**

| Participant | Day One | Day Two | Abduction Day | Writing Day |
|---|---|---|---|---|
| 1 | 40 | 30 | 30 | 40 |
| 2 | 13 | 11 | 13 | 11 |
| 3 | 24.8 | 23.6 | 24.8 | 23.6 |
| 4 | 11 | 11.5 | 11.5 | 11 |
| 5 | 8.6 | 12.2 | 8.6 | 12.2 |
| 6 | 13.3 | 15.2 | 15.2 | 13.3 |
| 7 | 3.9 | 7 | 3.9 | 7 |
| 8 | 12.8 | 16.5 | 16.5 | 12.8 |
| 10 | 20 | 16 | 20 | 16 |
| 11 | 16.0 | 15.5 | 15.5 | 16.0 |
| 13 | 37.1 | 18.4 | 18.4 | 37.1 |
| 14 | 30 | 30 | 30 | 30 |
| 15 | 21 | 15.7 | 15.7 | 21 |
| 16 | 23.5 | 30 | 23.5 | 30 |
| 17 | 24.8 | 17.6 | 17.6 | 24.8 |
| 18 | 20 | 23.5 | 20 | 23.5 |
| 19 | 10.5 | 23 | 23 | 10.5 |
| 20 | 26.6 | 30.8 | 26.6 | 30.8 |
| 21 | 18.4 | 22 | 22 | 18.4 |
| **Average** | **19.7** | **19.4** | **18.7** | **20.5** |
| **SD** | 9.5 | 7.2 | 6.9 | 9.6 |

**Table A16. Number of fatiguing sets**

| Participant | Day One | Day Two | Abduction Day | Writing Day |
|---|---|---|---|---|
| 1 | 2.7 | 2.6 | 2.6 | 2.7 |
| 2 | 5.3 | 4.4 | 5.3 | 4.4 |
| 3 | 6.5 | 6.6 | 6.5 | 6.6 |
| 4 | 5.5 | 2.8 | 2.8 | 5.5 |
| 5 | 2.8 | 4.2 | 2.8 | 4.2 |
| 6 | 4 | 4.7 | 4.7 | 4 |
| 7 | 5.9 | 5.6 | 5.9 | 5.6 |
| 8 | 6 | 3.9 | 3.9 | 6 |
| 10 | 5.8 | 1.6 | 5.8 | 1.6 |
| 11 | 3.9 | 2.4 | 2.4 | 3.9 |
| 13 | 2.9 | 2.9 | 2.9 | 2.9 |
| 14 | 13.4 | 22 | 13.4 | 22 |
| 15 | 2.8 | 3.3 | 3.3 | 2.8 |
| 16 | 2.8 | 3.8 | 2.8 | 3.8 |
| 17 | 2.8 | 2.7 | 2.7 | 2.8 |
| 18 | 2.5 | 3.3 | 2.5 | 3.3 |
| 19 | 2.5 | 4.4 | 4.4 | 2.5 |
| 20 | 3.8 | 3.3 | 3.8 | 3.3 |
| 21 | 3.5 | 3.5 | 3.5 | 3.5 |
| **Average** | **4.5** | **4.6** | **4.3** | **4.8** |
| **SD** | 2.6 | 4.4 | 2.5 | 4.4 |

**Table A17. Active motor threshold as a percentage of maximal stimulator output**

| Participant | Day One | Day Two | Abduction Day | Writing Day |
|---|---|---|---|---|
| 1 | 45 | 28 | 28 | 45 |
| 2 | 45 | 44 | 45 | 44 |
| 3 | 48 | 45 | 48 | 45 |
| 4 | 45 | 33 | 33 | 45 |
| 5 | 27 | 31 | 27 | 31 |
| 6 | 45 | 40 | 40 | 45 |
| 7 | 39 | 40 | 39 | 40 |
| 8 | 36 | 33 | 33 | 36 |
| 10 | 37 | 34 | 37 | 34 |
| 11 | 39 | 38 | 38 | 39 |
| 13 | 42 | 47 | 47 | 42 |
| 14 | 49 | 47 | 49 | 47 |
| 15 | 44 | 40 | 40 | 44 |
| 16 | 29 | 31 | 29 | 31 |
| 17 | 28 | 27 | 27 | 28 |
| 18 | 36 | 31 | 36 | 31 |
| 19 | 48 | 48 | 48 | 48 |
| 20 | 54 | 51 | 54 | 51 |
| 21 | 53 | 44 | 44 | 53 |
| **Average** | **42** | **39** | **39** | **41** |
| **SD** | 7.9 | 7.4 | 8.2 | 7.3 |

**Table A18. Handedness scores from Annett Handedness Questionnaire**

| Participant | Handedness |
|---|---|
| 1 | 6 |
| 2 | 12 |
| 3 | 12 |
| 4 | 5 |
| 5 | 9 |
| 6 | 11 |
| 7 | 9 |
| 8 | 4 |
| 10 | 10 |
| 11 | 11 |
| 13 | 9 |
| 14 | 10 |
| 15 | 4 |
| 16 | 11 |
| 17 | 11 |
| 18 | 12 |
| 19 | 11 |
| 20 | 12 |
| 21 | 12 |
| **Average** | **10** |
| **SD** | 3 |

# Appendix B: Informed Consent

**WILFRID LAURIER UNIVERSITY**
**INFORMED CONSENT STATEMENT**

You are invited to participate in a research study at Wilfrid Laurier University. The purpose of this study is to explore levels of corticospinal excitability of the primary motor cortex during a writing task before and after fatigue.

**Student Investigator:**
Name: Kezia Cinelli
Institution: Wilfrid Laurier University
Phone: (519.884.0710 ext. 3334)
Email: cine2150@mylaurier.ca

**Supervisor:**
Name: Jayne Kalmar, PhD
Institution: Wilfrid Laurier University
Phone: 519.884.0710 ext. 2033
Email: jkalmar@wlu.ca

**INFORMATION**

You are invited to participate in a brain stimulation study to investigate the excitability of the primary motor cortex during a simple finger contraction task (pushing the index finger against a sensor) and during a more complex hand-writing task, before and after a fatiguing series of finger muscle contractions.

If you choose to participate, you will be attending two testing sessions and performing two tasks, one on each day. One day will consist of a series of index finger abduction contractions. The other day will consist of you writing the word, "name", on an electronic tablet. On each day, you will be seated in a comfortable position at a table, with your head resting on a cushioned support placed in front of you. Throughout the experimental tasks, magnetic pulses will be delivered over the part of your brain that controls the muscles of your hand. These pulses will be delivered via a transcranial magnetic stimulation (TMS) coil placed over the scalp. There will be two types of TMS used in this study, including single-pulse TMS and paired-pulse TMS. Single-pulse TMS will be used to assess the excitability of the pathways between the brain and the recording site located on the muscle. Paired-pulse TMS will be used to assess the activity of two different brain circuits, one that inhibits muscle activity and one that facilitates muscle activity. In addition to the experimental tasks, a fatiguing task will also be completed in order to assess changes to the excitability of the motor cortex before and after muscular fatigue.

A total of 180 stimuli will be delivered in three time blocks separated by a 5-min rest period to allow you to move around and take a short break from the task. The entire experiment will take 90 to 120 minutes. Most of this time is spent setting up the coil and recording electrodes and preparing to begin the experiment. Upon completion of the study, you will be unhooked from all equipment and allowed to go home.

_____
participant's initials

**RISKS**

The risks of this study are minimal. Transcranial magnetic stimulation is a safe and well-documented procedure for people who do not have the following medical conditions or devices: epilepsy, aneurism clips, seizures, cardiac pacemakers, cochlear implants, or other implanted metal/electronic devices. Before attending your first session you will complete an "Exclusion and Contraindication Checklist" to ensure that you do not have any of the contraindications listed above. Transcranial magnetic stimulation will be used to elicit a muscle contraction and will be accompanied by a loud click that you may find unpleasant. You will be offered ear plugs if you find the noise uncomfortable, but it will not cause hearing damage. You may find the procedure and set-up time boring and grow tired of sitting at the desk and completing the repetitive task.

**BENEFITS**

This study will not benefit you directly, although you may find it interesting to see how we measure the excitability of the pathway between your brain and muscles. The study will help us understand the neural control of movement and provide insight into the task-dependent nature of corticospinal excitability during a very common task (handwriting) compared to a very simple laboratory task.

**CONFIDENTIALITY**

Confidentiality and anonymity of participants will be ensured by using a coding process to store the data that is collected. Only Kezia Cinelli and Dr. Jayne Kalmar will have access to the data. Data will be written up in a thesis document and be presented during a thesis defense. It is intended that the study also be published in a scientific journal.

**COMPENSATION**

You will not be compensated for your participation in this study.

**CONTACT**

If you have questions at any time about the study or the procedures, (or you experience adverse effects as a result of participating in this study,) you may contact the researcher, Kezia Cinelli, at (519) 884-0710, x3334. This project has been reviewed and approved by the University Research Ethics Board. If you feel you have not been treated according to the descriptions in this form, or your rights as a participant in research have been violated during the course of this project, you may contact Dr. Robert Basso or Dr. Rosemary McGowan, Vice-Chairs of the University Research Ethics Board, Wilfrid Laurier University, (519) 884-1970, extension 3131 or REBChair@wlu.ca.

**PARTICIPATION**

Your participation in this study is voluntary; you may decline to participate without penalty. If you decide to participate, you may withdraw from the study at any time without penalty and without loss of benefits to which you are otherwise entitled. If you withdraw from the study, every attempt will be made to remove your data from the study, and have it destroyed.

_____
participant's initials

**FEEDBACK AND PUBLICATION**

Results of this study will be presented in the format of a Master's thesis defense to a thesis advisory committee and fellow student peers. Results will also be submitted for publication in a scientific journal and may be presented at a scientific meeting. If you wish to receive feedback upon the completion of this study in July 2019, please email Kezia Cinelli at cine2150@mylaurier.ca.

Do you agree to allow your data from this study to be retained for future analysis of signal processing methods?

*Yes, my data may be retained indefinitely for future analysis.* ☐

*No, I do not wish for my data to be used for future analysis.* ☐

(Note: data will be retained in case of future external publication review, but will not be re-analyzed in the future).

**CONSENT**

I have read and understand the above information. I have received a copy of this form. I agree to participate in this study.

Participant's signature_____ Date_____

Investigator's signature_____ Date _____

_____
participant's initials

## Appendix C: TMS Contraindications Questionnaire

Participant Screening Questionnaire – TMS Contraindications

Participant Code:_____
Height:_____ Date of Birth:_____Sex:_____

Please circle if you have been diagnosed with or have one or more of the following (Yes=Y, No=N)

| | | | |
|---|---|---|---|
| Epilepsy | Y | N | |
| Seizures | Y | N | |
| Pacemaker | Y | N | |
| Cochlear Implant | Y | N | |
| Metal Implants (head only) | Y | N | (e.g. titanium plates, aneurysm clips) |
| Diabetes | Y | N | |
| Neurological Injury | Y | N | (e.g. Spinal cord injury, migraines, pain, tingling or numbness in distal limbs) |
| Smoker | Y | N | |
| Concussion | Y | N | |

If **yes**, when was your last concussion?

If **yes**, how long ago were you symptom free?

Medications Y N
If yes, list:

Ergogenic Aids Y N
If yes, list:

## Appendix D: Annett Handedness Questionnaire

**ANNETT HANDEDNESS QUESTIONNAIRE**

Age:_____

Sex:_____

Please indicate which hand you habitually use for each of the following activities by writing R (for right), L (for left), or E (for either)

Which hand do you use:

1. To write a letter legibly _____
2. To throw a ball to hit a target? _____
3. To hold a racket in tennis, squash, or badminton? _____
4. To hold a match while striking it? _____
5. To cut with scissors? _____
6. To guide a thread through the eye of a needle? _____
7. At the top of a broom while sweeping? _____
8. At the top of a shovel when moving sand? _____
9. To deal playing cards? _____
10. To hammer a nail into wood? _____
11. To hold a toothbrush while cleaning your teeth? _____
12. To unscrew a jar lid? _____

If you use your RIGHT HAND FOR ALL OF THESE ACTIONS are there any one-handed actions for which you use the left hand? Please record them here

_____

If you use your LEFT HAND FOR ALL OF THESE ACTIONS are there any one-handed actions for which you use the right hand? Please record them here

_____