

THESIS

ESTABLISHING DIFFERENCES IN INTRACORTICAL INHIBITION AND EXCITATION  
BETWEEN INDIVIDUALS WITH AND WITHOUT STROKE

Submitted by

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## ABSTRACT

### ESTABLISHING DIFFERENCES IN INTRACORTICAL INHIBITION AND EXCITATION BETWEEN INDIVIDUALS WITH AND WITHOUT STROKE

**Background and purpose:** Even though there is much information and research on neuroplasticity, many questions remain unanswered about how the brain changes and recovers after a stroke. Transcranial magnetic stimulation (TMS) has been used as the primary method of direct stimulation to assess change especially in the primary motor cortex because it allows for study of the specific excitatory and inhibitory mechanisms. The purpose of this study was to investigate and identify differences in TMS-induced intracortical inhibition and facilitation when comparing survivors of stroke to individuals unaffected by stroke.

**Methods:** Fourteen subjects who had experienced a stroke and 19 non-stroke subjects were investigated using single and paired-pulse TMS. TMS was applied over the affected hemisphere for subjects with stroke and over the dominant hemisphere of the non-stroke subjects. Resting motor threshold (MT) was established. Forty motor evoked potentials (MEPs) were collected from the first dorsal interosseus muscle, using surface electrodes, for each subject. These were subdivided into 10 trials of single-pulse conditioning stimulus, 10 trials of single-pulse test stimulus (TS), 10 paired-pulse intracortical facilitation (ICF), 10 paired-pulse intracortical inhibition (ICI); the order of stimulation condition for the 40 trials was randomized.

**Results:** The stroke group exhibited significantly higher MT and significantly lower motor evoked potential amplitudes for TS, ICF, and ICI specific trials compared to the group without

stroke. Finally, the ratio of ICF to ICI was found to be significantly lower in the stroke group, indicating less facilitation.

**Conclusion:** Overall the affected hemispheres of the participants surviving stroke were found to be significantly less excitable than the dominant hemispheres of the non-stroke participants. These findings and the usefulness of TMS to directly access and assess differences in the brain's baseline excitability following stroke will hopefully add to existing knowledge that informs therapeutic interventions aimed at increasing post-stroke performance in daily activities.

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## INTRODUCTION

Cerebral vascular accidents, or strokes, occur in the United States at a rate of one every four seconds (American Heart Association (AHA), 2012), resulting in 795,000 new strokes each year. Stroke is the leading cause of long-term disability in the United States associated with approximately \$73.7 billion in 2012 in stroke-related medical costs and disability (AHA, 2012; Dafotakis et al., 2008; Edwards & Fregni, 2008).

Motor dysfunction is a common residual impairment that leads to inability to independently perform activities of daily living (Edwards & Fregni, 2008). Only 12% of survivors of stroke regain complete recovery (Dafotakis et al., 2008), and 30%-60% of hemiplegic stroke patients never regain function of the paretic arm (Kwakkel et al., 2008). Motor dysfunction can be directly related to neuronal function because it can reflect damage within the primary motor cortex as opposed to damage to the corticospinal motor pathway (Hodics et al., 2006). These researchers describe the initial recovery process following a stroke as different for each individual and as involving spontaneous recovery of function, reflecting plastic changes in the brain, from a week to a few months afterwards.

Neuroplasticity has been defined as the ability of the nervous system to reorganize structure, function, and connections; it occurs during many phases of neurological recovery following injury and developmental stages of life (Kandel, 2000). Neuroplasticity occurs in response to learning, environmental changes, disease, and as a reaction to therapy; and these changes in the brain can positively or negatively impact functioning (Cramer et al., 2011). The adult brain retains some of its ability to reorganize itself in response to a stroke that impairs motor ability (Di Lazzaro et al., 2008; Kandel, 2000). Excitability is defined as the ability of one neuron to facilitate the activity of another and inhibition is defined as a presynaptic neuron inhibiting

another neuron to fire (Saladin, 2010). Even though the excitability of the cerebral cortex may change, neuronal networks can reorganize to facilitate some recovery of motor function (Kandel, 2000). While there is much information and research on neuroplasticity, many questions remain unanswered specifically about how the brain changes and recovers after a stroke (Cramer et al., 2011; Schaechter & Perdue, 2008). By understanding these changes at a neuronal level, we can better understand what we see functionally in individuals who have had stroke.

Transcranial magnetic stimulation (TMS) is the main way researchers can assess neuron function in the primary motor cortex. TMS capabilities can be used to assess intracortical facilitation (ICF) and intracortical inhibition (ICI), but limited work exists to characterize the stroke-affected brain in contrast to the neurologically-intact brain. Such information would be useful for understanding the nature of stroke damage and the recovery process following stroke, and to both inform and impact therapeutic interventions. Practitioners could use this information to understand what is happening in the brain as reflected in what they are seeing in patients functionally. Practitioners may use this information to determine if lack of upper extremity function is due to interneuron function. This would enable practitioners to better determine therapeutic approaches for functional upper extremity gains. The more that is understood about the underlying mechanisms, the better practitioners will be able to choose a combination of intervention modalities to improve motor performance for clients who have had a stroke. The current study used TMS to look more deeply at the specific excitatory and inhibitory mechanisms in the primary motor cortex of the post-stroke brain.

## **Purpose**

The purpose of this study was to investigate and identify differences in intracortical inhibition and facilitation when comparing survivors of stroke to individuals unaffected by stroke. The following questions were investigated during this study:

1. Are there significant differences in motor threshold (MT) and amplitude of motor evoked potentials (MEPs) during supra-threshold, single-pulse transcranial magnetic stimulation (TMS) between people who have had a stroke as compared people who have not had a stroke?
2. Are there significant differences in intracortical facilitation (ICF) and intracortical inhibition (ICI) between people who have had a stroke as compared to subjects without stroke?
3. Does the ratio of ICF to ICI differ significantly between individuals with and those without stroke?

## LITERATURE REVIEW

### **Neuroplasticity**

Neuroplasticity occurs during human development as well as after trauma to the nervous system. It is the ability of the nervous system to reorganize structurally, functionally, and connectively (Kandel, 2000). Plastic changes, viewed as adaptive when associated with functional gain and maladaptive when there is loss of function, occur in response to learning, environmental changes and disease, and as a reaction to therapeutic intervention (Cramer et al., 2011). In order to comprehend motor neuroplasticity, understanding the chain of events associated with motor function is necessary.

Stroke can affect many parts of the innervation chain associated with motor function, including the activity of excitatory and inhibitory interneurons residing within the primary motor cortex, and affecting the final descending motor command (Liepert et al., 2000). For example, Hebbian Theory states when one neuron repeatedly participates in firing a second neuron, either dendritic growth or metabolic change occurs so that the efficacy of the first neuron to fire the second neuron increases (Kandel, 2000; Pell et al., 2011). If the system is not functioning properly, such as with the presence of a lesion, then neuron pathway changes, or metabolic changes occur, in an attempt to make the motor chain more efficient (Kandel, 2000). Understanding synaptic efficacy has implications for stroke rehabilitation in as much as therapeutic approaches can be designed to influence the efficiency of the motor innervation system.

### **Technologies Used to Study Neuroplasticity**

Several technologies have evolved for the purpose of studying neuroplasticity (Hodics et al., 2006; Pell et al., 2011). A few include electroencephalography (EEG), functional magnetic

resonance imaging (fMRI) and non-invasive brain stimulation. The most common brain stimulation technique is transcranial magnetic stimulation (TMS). TMS has been used as the primary method to assess and effect change especially in the primary motor cortex (Chen et al., 1998; Fujiyama et al., 2011; Kujirai et al., 1993; Silvanto et al., 2008). TMS specifically allows for investigation of intracortical excitatory and inhibitory mechanisms within the primary motor cortex (Pell et al., 2011; Thickbroom, 2007).

Richards and co-workers' 2008 meta-analysis revealed a variety of technologies used to measure both somatosensory and primary motor cortical changes with post-stroke motor skill learning. They found that measureable changes occur in the sensorimotor cortex within the lesioned hemisphere when upper extremity motor gains are made during targeted intervention. In their study combining constraint-induced therapy with therapeutic brain stimulation to affect restoration of motor skill following a stroke, Schaechter and Perdue (2008) investigated brain activation using functional magnetic resonance imaging (fMRI). Their findings showed that, in subjects with and without stroke, performing motor tasks activated networks of the primary motor cortex. The fMRI images depicted areas of the brain that became activated (as demonstrated by blood oxygen level dependent changes) during synergistic, non-synergistic, and non-synergistic-synergistic motor tasks (Schaechter & Perdue, 2008). While the imaging depicted activation, it is necessary to investigate further the mechanisms that cause the activation of the primary motor cortex, for example, intracortical facilitation and inhibition. There is a crucial need to understand the mechanisms involved, so that therapeutic intervention can target improvement of those mechanisms.

## **Transcranial Magnetic Stimulation**

TMS activates neurons using a high-intensity magnetic field (Chen et al., 1998; Fujiyama et al., 2011; Pell et al., 2011). TMS specifically allows for investigation of excitatory and inhibitory mechanisms within the primary motor cortex (Kujirai et al., 1993; Pell et al., 2011; Thickbroom, 2007). An electric current is passed through a highly insulated figure-of-eight-shaped TMS coil, resulting in a perpendicular magnetic field that penetrates the scalp to reach the cortex (Kujirai et al., 1993). This magnetic field generates an electrical field in the cortex that excites the neurons (Pell et al., 2011). Changes and differences in excitability and inhibition can be measured by comparing the amplitude of motor evoked potentials (MEP) resulting from TMS (Chen et al., 1998; Kujirai et al., 1993; Woldag et al., 2008).

TMS is used to establish motor threshold (MT), the stimulus intensity necessary to produce an MEP through the influence of postsynaptic neurons and their membrane potential (Pell et al., 2011). Butefisch and colleagues (2008) defined resting motor threshold as “the minimum stimulus intensity to evoke a motor-evoked potential (MEP) of >50 microvolt in at least 5 of 10 trials” (p. 8). In this way, the MEP amplitude resulting from TMS reflects the level of global excitability of corticospinal neurons (Pell et al., 2011).

There is a breadth of research using TMS to increase understanding of the brain because TMS is used as a primary measure of cortical excitability. First, TMS has been used in combination with EEG to gain information about excitability in the brain (Kicic et al., 2008). Kicic and colleagues (2008) used a combination of TMS and EEG to discover that unilateral motor reactions involved bilateral increase in sensorimotor cortex excitability. Second, TMS has been used to measure changes in cortical excitability during lifting of objects and performance of specific movement (Alaerts et al., 2010; Izumi et al., 2008). TMS was used to measure whether

primary motor cortex excitability during observation of an action reflects the motor cortex excitability of actual performance of grasping and lifting an object (Alaerts et al., 2010). These authors found that the same corticospinal excitability modulations occur during observation of and actual performance of an action. Izumi and colleagues (2008) used TMS, along with measures of hand function, to determine that non-invasive brain stimulation combined with maximal effort at hand opening reduced spasticity or improved performance of voluntary hand movement.

Researchers have also utilized TMS to measure the activation of specific muscles as well as to assess the effects of specific interventions (Gerachshenko et al., 2008; Lee et al., 2008; Renner et al., 2005; Woldag et al., 2004). TMS was used to assess pre-contraction changes in MEP amplitude of the biceps brachii following stroke as compared to subjects without stroke; these researchers determined that corticomotor excitability of the antagonist biceps brachii was increased post stroke (Gerachshenko et al., 2008). Lee and colleagues (2008) concluded that TMS is a valid and reliable method to assess voluntary activation of the wrist extensors as well as the effects of interventions targeting cortical activation in upper extremity muscle groups. In another study, healthy subjects were found to have no change in motor cortex excitability when both hands were simultaneously activated in the non-dominant hemisphere when compared to voluntary activation of the ipsilateral hand alone; stroke patients were found to have additional facilitation in the affected hemisphere with simultaneous hand activation as compared to activation of the affected hand alone (Renner et al., 2005). Woldag and colleagues (2004) concluded that excitability of the ipsilateral hemisphere was not inhibited during voluntary activation of the non-dominant hand for healthy individuals or the affected hand of patients with stroke.

## **Intracortical Facilitation and Intracortical Inhibition**

TMS has been used to measure both facilitatory and inhibitive neuronal systems.

Intracortical facilitation (ICF) is a process in which the activity of one neuron will facilitate the activity of another neuron, whereas intracortical inhibition (ICI) involves a presynaptic neuron inhibiting the firing of another neuron (Saladin, 2010). ICF is understood to reflect activity in the glutamatergic system (Chen et al., 1998); and ICI, the GABA<sub>A</sub> system (Chen et al., 1998; Kujirai et al., 1993; Ziemann et al., 1996). TMS initiates action potentials by depolarizing cell membranes, leading to the opening of voltage-sensitive ion channels (Ilmoniemi & Kicic, 2010). TMS activates both excitatory and inhibitory intracortical interneurons simultaneously. However, through different protocols of stimulation, intracortical facilitation (ICF), intracortical inhibition (ICI), and motor threshold can be assessed individually (Chen et al., 1998; Fujiyama et al., 2011; Pell et al., 2011; Sanger et al., 2001).

In ICF and ICI paired-pulse TMS protocols, a suprathreshold test stimulus is delivered to the primary motor cortex, preceded by a subthreshold conditioning stimulus (Chen & Garg, 2000). The length of the inter-stimulus interval determines whether intracortical facilitatory or inhibitive circuits are activated and measured (Kujirai et al., 1993). When a suprathreshold test stimulus is applied 2ms after a subthreshold conditioning stimulus, the MEP is partially inhibited, i.e. intracortical inhibition (Butefisch et al., 2008; Kujirai et al., 1993). Alternatively, the MEP is facilitated (ICF) when the test-stimulus is delivered 15ms after the conditioning stimulus (Chen et al., 1998; Kujirai et al., 1993).

## **Individuals with Stroke as Compared to those Without**

Using TMS, researchers have measured mechanisms, such as ICI and ICF, within the primary motor cortex to understand differences between people who have had a stroke as

compared to those who have not, however more information is needed and the current study also compared the ratio of ICF to ICI (Liepert et al., 2000; Waller et al., 2008). Researchers have also used TMS to measure differences between the lesioned and non-lesioned hemisphere in subjects who have had a stroke. To understand disordered motor function and the lesioned brain, it is necessary to understand the brains of individuals without stroke. Waller and colleagues (2008) examined ICI and ICF with different types of movement using paired-pulse TMS in relation to handedness of the individual; they concluded that the dominant motor hemisphere exerts a strong inhibitory influence over the non-dominant hemisphere. Bilateral muscle activation was found to disinhibit both the dominant and non-dominant hemispheres (Waller et al., 2008). Studying the difference between the hemispheres allows researchers to gain insight into the changes that can occur post stroke.

In individuals who have had stroke, researchers have conducted studies comparing the lesioned hemisphere to the non-lesioned hemisphere (Butefisch, 2004; Cramer et al., 2011; Di Lazzaro et al., 2008; Liepert et al., 2004). Other studies have compared individuals with stroke to individuals without stroke (Butefisch et al., 2008; Liepert et al., 2000). Di Lazzaro and colleagues (2008) reported that stroke survivors tend to have a higher resting motor threshold and decreased motor evoked potential amplitude in the affected hemisphere as compared to the unaffected hemisphere, indicating that there is decreased overall motor cortex excitability in the affected hemisphere. Cramer and colleagues (2011) also reported decreased cortical excitability following a stroke in the lesioned hemisphere as compared to the non-lesioned hemisphere. Reporting more work on inhibition, a systematic review by Butefisch (2004) reported decreased ICI in the perilesional motor cortex when compared to the non-lesioned hemisphere, and Liepert et al., (2004) found that regardless of lesion location, patients who had a stroke had decreased ICI in the primary motor

cortex of the affected hemisphere. While Liepert et al. (2000) did not find a significant difference in ICF between subjects with stroke versus subjects without stroke, their stroke survivors were found to have significantly reduced ICI when compared to age matched healthy subjects (Liepert et al., 2000). Finally, in the consideration of both excitation and inhibition, Butefisch and colleagues (2008) were able to show, with functional imaging and TMS as dependent measures, that post-stroke participants demonstrated decreased short interval cortical inhibition as compared to subjects without stroke.

### **Summary**

Stroke is a substantial problem in the United States because it is the leading cause of disability and affects hundreds of thousands of people per year (AHA, 2012). Much remains unknown about how the brain changes and recovers following a stroke. With further research on neuroplasticity, specifically measured by TMS, current knowledge can be enhanced concerning intracortical excitability and intracortical inhibition following the occurrence of stroke. This knowledge will ideally support the development of effective therapeutic interventions that specifically impact underlying neural mechanisms, hopefully leading to effective rehabilitation and recovery following stroke.

## HYPOTHESES

Compared to individuals who have not experienced a stroke, stroke survivors will demonstrate:

1. Significantly higher motor thresholds (MT).
2. Significantly lower motor evoked potential (MEP) amplitudes during test stimulus specific trials.
3. Significantly decreased intracortical facilitation (ICF), as indicated by lower MEP amplitudes.
4. Significantly decreased intracortical inhibition (ICI) as indicated by higher MEP amplitudes.
5. A significantly different ICF to ICI ratio.

## METHODS

Data for this study were collected during two previous stand-alone studies. These data are the basis for the comparison of participants who had survived a stroke to those who had not had a stroke. Informed consent was obtained for each subject and both studies were approved by the Colorado State University Institutional Review Board.

### **Sample**

The stroke group was a convenience sample consisting of people recruited through stroke support groups, neurologist contacts, and therapist contacts. The inclusion criteria for the group with stroke included being 40 years or older and having had a stroke at least 9 months prior that affected the person's ability to use an arm or hand. Subjects were excluded if they had a history of seizures, epilepsy, head trauma leading to loss of consciousness, mental retardation, poorly-controlled psychiatric or mental illness, bipolar disorder, increased intracranial pressure, alcohol or drug abuse within the past year, implanted pace maker or medication pump, metal plate or metal objects in the eye or the skull, aneurism clips, cochlear implant, intracardiac lines, or significant history of heart disease. Subjects were excluded if pregnant. Fourteen stroke survivors between the ages of 40 and 82 years old (mean:  $62.2 \pm 11.8$  years) (nine female, five male) were included in the study. Eight of the 14 subjects survived a stroke in the right hemisphere, five subjects' strokes were left hemispheric, and one subject's stroke affected the left pons and cerebellum.

The non-stroke group was also a convenience sample comprised of 19 participants who all were right-handed and between the ages of 21-35 years old (mean:  $25.7 \pm 3.4$  years) (ten female, nine male). In addition to the exclusion criteria included in the aforementioned study, subjects were excluded if they had evidence of mass brain lesions, hemorrhagic stroke,

arteriovenous malformation, intracortical hemorrhage, subarachnoid hemorrhage, or bilateral cerebrovascular disease. Subjects were also excluded if pregnant or were left-handed.

## **Procedure**

### **Set-Up**

Each subject was seated in a semi-reclined dental chair with a pillow behind the neck and a pillow beneath the forearm and hand. The support pillow was placed under the affected forearm and hand for subjects who had had a stroke and underneath the right forearm and hand of participants who had not had a stroke. A cloth cap was placed on each participant's head.

### **EMG**

Surface EMG electrodes were applied to the first dorsal interosseus (FDI). MEPs were observed and recorded using surface electromyographic electrodes over the FDI muscle of the stroke affected hand for the subjects with stroke and over the FDI of the right hand for subjects without stroke. Surface electrodes were connected to and activity was recorded by a Nicolet Viking Select (Nicolet Biomedical, USA) Electromyograph. EMG silence was monitored. Trials contaminated by voluntary muscle activity were rejected.

### **TMS**

Excitability and inhibition of the primary motor cortex were investigated using neuronal activation through single and paired-pulse transcranial magnetic stimulation (TMS) using a Magstim 200(2) brain stimulation module (Magstim Ltd, UK). The magnetic stimulation was delivered through a 7cm figure-of-eight shaped coil centered over the area of the primary motor cortex controlling the hand. Optimal stimulation area was determined as the location that consistently elicited the largest amplitude motor evoked potentials (MEPs). The vertex was marked at the intersection of the nasion-inion and interaural lines. Positioning of the coil was

established at an angle of 45 degrees from the midsagittal line (Pell et al., 2011). A TMS protocol was administered to each subject in the left motor cortex in the non-stroke group, and the lesioned hemisphere in the stroke-affected group. The TMS consisted of a total of 40 pseudorandom-ordered stimulation trials with a 6-second inter-trial interval, consisting of 10 trials of single-pulse TS, 10 trials of single-pulse CS, 10 trials of paired-pulse ICF, and 10 trials of paired-pulse ICI. MEP wave forms were analyzed for peak-to-peak amplitude for each trial using Lab Chart 7 Pro (ADInstruments Ltd., USA). The beginning and end points for each MEP were determined; then peak amplitude was determined as the greatest mV between the MEP positive and negative peaks.

### **Dependent Measures**

Dependent measures included motor threshold (MT), amplitude of motor evoked potentials (MEPs) during supra-threshold, single-pulse transcranial magnetic stimulation (TMS), intracortical facilitation (ICF), intracortical inhibition (ICI), and the ratio of ICF to ICI. MT has previously been defined as the lowest stimulus intensity resulting in MEPs greater than 50 microvolts in 5 out of 10 consecutive stimulations and was established at the optimal stimulation area (Chen et al., 1998). MT was established first, and was determined as the minimum output of the Magstim 200(2) necessary to elicit an MEP in the relaxed FDI in 5 out of 10 trials (Chen et al., 1998; Kujirai et al., 1993). Stimuli were applied at 5% steps between 30 and 100% of stimulator output to find MT. Once the MT was found, the test stimulus (TS) was determined by calculating 116% of the MT (Chen et al., 1998). The CS was calculated as 90% of the MT.

Paired-pulse TMS protocols were used to assess ICI and ICF. The intensity of the first stimulus, or CS, was subthreshold; it was not enough to generate an MEP but did activate intracortical neurons (Chen et al., 1998; Kujirai et al., 1993). The second stimulus, or TS, was a

suprathreshold stimulus that produced an MEP. By manipulating the interstimulus interval (ISI), ICI and ICF was assessed (Chen et al., 1998; Huntsman et al., 1995; Kujirai et al., 1993). A 2ms ISI was used to induce ICI and a 15ms ISI was used to induce ICF (Chen et al., 1998; Kujirai et al., 1993).

Because CS trials did not result in MEPs, no values were reported in this study. The ratio of ICF to ICI had not been used previously to report excitability in the primary motor cortex. It was utilized in this study as a means to understand the difference between the excitability and inhibition of adults who have had a stroke as compared to adults without stroke in yet another way (Massie et al., 2013). A higher ratio indicates more facilitation. A ratio closer to one would indicate less facilitation and possibly less inhibition.

### **Data Analysis and Statistical Methods**

This was a non-randomized, group-comparison study based on the attribute variable stroke versus non-stroke. For each subject, values for the 10 trials of TS were averaged. The ICF MEPs for each trial were divided by the average TS MEPs in order to normalize the data (Massie et al., 2013). Normalization of these data allowed for comparison of variables as well as comparison of groups. ICI trials were averaged and normalized using the same method. The ICF-to-ICI ratio is the ratio of normalized ICF to normalized ICI. IBM SPSS Statistics version 20 was utilized to run statistics. Descriptive statistics were run for each group individually and Box and Whisker plots were created to determine outliers for each group. Outliers were removed for each variable. Based on comparing the two groups on multiple dependent measures, a one-way ANOVA was used instead of multiple *t*-tests. The ANOVA determines significant differences between groups considering all comparisons (all dependent measures) in the multivariate analysis so that the alpha level does not need to be adjusted for each comparison to avoid a Type

I error. In order to fulfill the assumption of homogeneity of variance in the two groups for each dependent measure, the Levene's test was used. In dependent measures where the two groups varied differently, a Kruskal-Wallis one-way ANOVA was used for between-groups comparisons.

## RESULTS

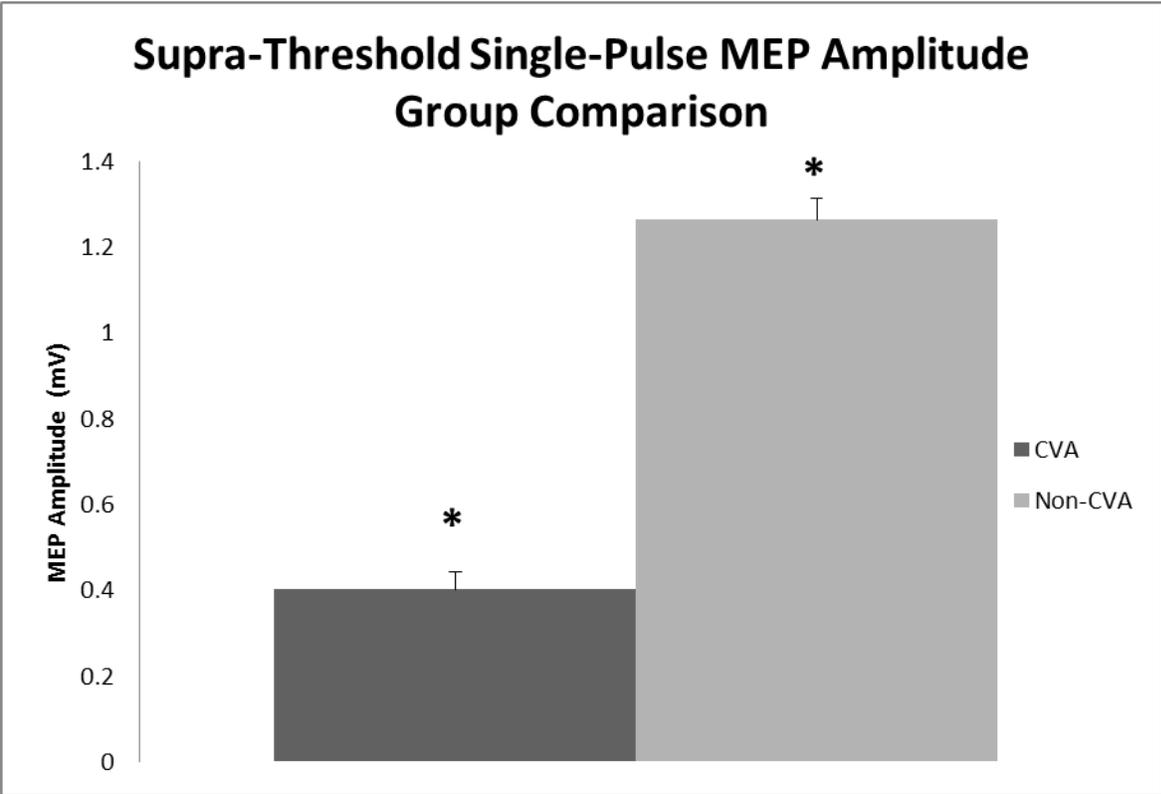
There were no adverse events or effects of the TMS, nor did any subject report discomfort with the procedures. While gender distribution was similar across groups, the mean age varied significantly ( $p < 0.001$ ) between the two groups (Table 1).

**Table 1. Demographic information**

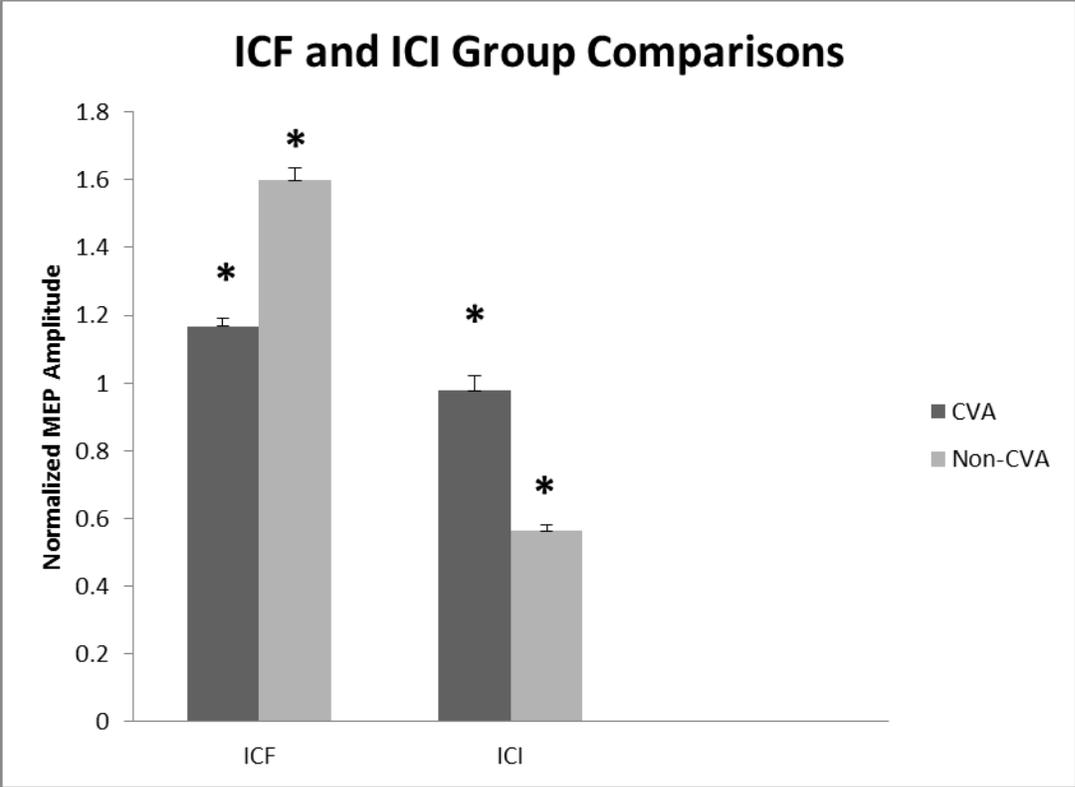
	Stroke Group	Non-Stroke Group
Gender	9 females; 5 males	10 females; 9 males
Age* Mean $\pm$ SD	62.2 $\pm$ 11.7	25.7 $\pm$ 3.4

\*stroke group subjects significantly older than non-stroke subjects,  $p < 0.001$

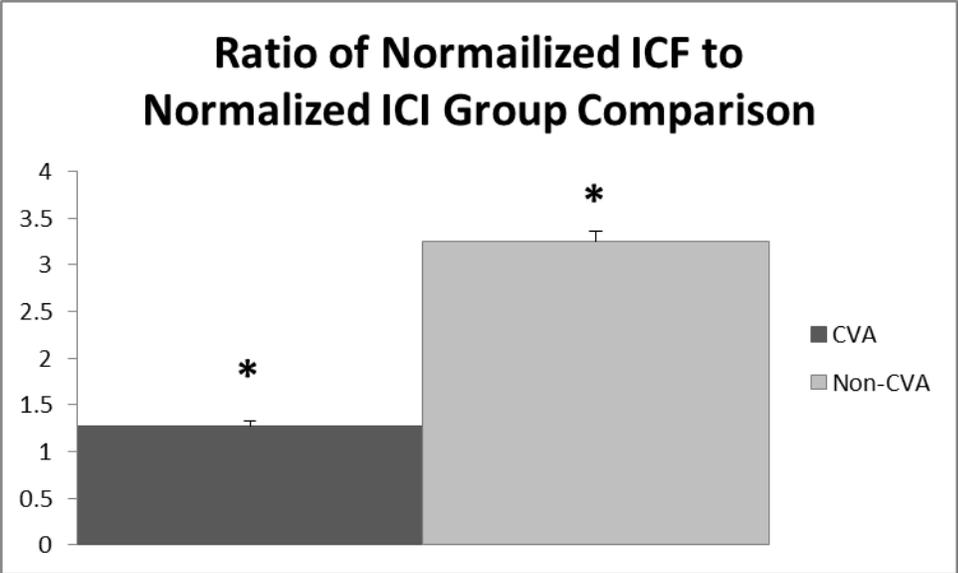
All between-groups comparisons are summarized in Figures 1 and 2; and specific mean values per variable are listed in Table 2. For comparisons where the Levene's statistic was significant, a Kruskal-Wallis one way ANOVA was run. The values of the Kruskal-Wallis were found to be identical to the values of the ANOVA; therefore the values in table include the mean, standard deviation, and F values from the ANOVA in order to compare means. Motor threshold (MT) was significantly higher ( $p = 0.001$ ) in subjects who had had a stroke. The stroke-affected group had a lower mean MEP amplitude for test stimulus (TS) than the non-stroke group ( $p = 0.001$ ). As compared to adults without stroke, survivors of stroke exhibited significantly lower normalized MEP amplitude for intracortical facilitation (ICF) ( $p = 0.040$ ), and higher normalized MEP amplitudes during the intracortical inhibition (ICI) protocol indicating significantly decreased inhibition ( $p = 0.008$ ). MEPs were absent in four subjects with stroke for ICI. Survivors of stroke had a significantly lower normalized ICF to ICI ratio ( $p = 0.003$ ) than the group without stroke. This ratio indicated that the survivors of stroke had significantly less facilitation as well as less inhibition than subjects without stroke.



**Figure 1.** Group comparisons of motor evoked potentials (MEP) obtained during supra-threshold, single-pulse TMS. \* indicates significant difference between groups.



**Figure 2.** Chart depicting group comparisons of normalized motor evoked potential (MEP) amplitudes for intracortical facilitation (ICF) and intracortical inhibition (ICI) between a group with CVA and a group without CVA. Note that a higher MEP for ICI indicates decreased intracortical inhibition. \* indicates significant difference between groups.



**Figure 3.** Chart depicting group comparison of normalized intracortical facilitation (ICF) to normalized intracortical inhibition (ICI). \* indicates significant difference between groups.

**Table 2. Between-groups comparisons and variable means.**

<b>Variable</b>	<b>Stroke group (n = 14) Mean ± SD</b>	<b>Non-stroke (n = 19) Mean ± SD</b>	<b>Test Statistic (deg. freedom)</b>	<b>Significance</b>
MT	66.2857 ± 17.0178 (n=14)	46.1053 ± 7.8379 (n=19)	F=20.893 (df=1,31)	p=0.001
TS	0.4018 ± 0.4878 (n=12)	1.2624 ± 0.8489 (n=17)	F=9.941 (df=1, 27)	p=0.001
ICF	1.1680 ± 0.2893 (n=12)	1.5987 ± 0.6915 (n=19)	F=4.152 (df=1, 29)	p=0.040
ICI	0.9777 ± 0.4278 (n=10)	0.5631 ± 0.3252 (n=18)	F=8.340 (df=1, 26)	p=0.008
ICF/ICI	1.2677 ± 0.5096 (n=9)	3.2444 ± 1.9504 (n=17)	F=8.768 (df=1,24)	p=0.003

## DISCUSSION

This study examined the effects of stroke by comparing, among other measures, intracortical inhibition (ICI), intracortical facilitation (ICF), and the ratio of ICF to ICI between individuals with stroke and those without stroke. As anticipated, the group that had stroke exhibited significantly higher motor threshold (MT), and significantly lower amplitude of motor evoked potentials (MEPs) during supra-threshold, single pulse TMS, less ICF, and less ICI. Overall the affected hemispheres of the subjects with stroke were found to be less excitable than the dominant hemispheres in the group without stroke, given that these individuals had significantly less ICF and smaller amplitude MEPs to single-pulse TMS. The difference in the ratio of ICF to ICI relates to both lower motor evoked potentials for ICF and higher motor evoked potentials for ICI in the stroke group. This ratio, specifically, suggests a difference in motor cortex excitability that has not been reported before. The findings of this study may identify specific interneuron-related changes associated with stroke that may impact the final output of the motor chain.

These findings indicate that a stroke affected primary motor cortex behaves differently at a neurological level than the dominant motor cortex of an adult without stroke. The findings regarding motor threshold indicate that it takes more stimulus to engage the neurons of the stroke affected primary motor cortex than the dominant primary motor cortex of adults without stroke. These findings are consistent with Di Lazzaro and colleagues (2008) who demonstrated that people who have had a stroke tend to have a higher resting motor threshold in the stroke-affected hemisphere as measured by decreased motor evoked potential amplitude, indicating decreased overall motor cortex excitability. These findings are also consistent with the review of Cramer and colleagues (2011), who found decreased cortical excitability in the stroke-affected hemisphere.

Overall, the findings of the current study indicate that the neurons of the primary motor cortex are less excitable in general; these findings also indicate that the pools of specialized neurons, intracortical facilitatory interneurons and intracortical inhibitory interneurons, are less excitable.

The current finding of stroke-associated higher motor evoked potentials/decreased inhibition when stimulating with the ICI protocol compares less clearly to a number of other studies. Liepert et al., 1998 found that less inhibition is an indicator of intracortical plastic changes. Consistent with the current study, several studies have reported decreased ICI in the primary motor cortex of the stroke-affected hemisphere irrespective of lesion location (Cicinelli et al., 2003; Liepert et al., 2000; Liepert et al., 2004; Manganotti et al., 2002). In a systematic review, Butefisch (2004) found evidence that ICI was decreased specifically in the perilesional region of the stroke-affected motor cortex. However, in contrast to findings of the current study, Liepert and colleagues (2004) found that subjects with a lesion in the central somatosensory cortex demonstrated mixed results, some demonstrating an increase, others a reduction in ICI.

The current study implies the glutamatergic system and GABAergic system are impacted by stroke by demonstrating a significantly decreased ICF and ICI in the stroke-affected hemisphere. This difference greatly impacted the ratio of ICF to ICI. Liepert and colleagues (2000) speculated that loss of inhibition is due to impairment of GABAergic inhibitory interneurons within the primary motor cortex. Prior research verifies the results of the current study; there is substantial evidence indicating differences in excitation and inhibition when comparing adults who have had a stroke to those without stroke. Grefkes and Fink (2011) explain that lesions may cause metabolic changes as well as changes in neurotransmitter layout of cortical areas; these changes can cause interferences with cortical network dynamics and behavior. Decreases in ICF and ICI could be an indication of these changes (Hamzei et al.,

2006). Damage to the brain caused by stroke can reduce primary motor cortex excitability, resulting in a loss of descending excitatory input to the corticospinal motor neurons (Di Lazzaro et al., 2008; Massie et al., 2013).

## **Implications**

Following stroke there may be neuronal death followed by reorganization of surviving brain elements (Hodics et al., 2006); these researchers state that despite this reorganization, patients were left with substantial disability or reduced ability to do activities of daily living. The findings of this study indicate the possible benefit of decreased MT and TS and increased ICF and ICI in the affected hemisphere of adults with stroke as compared to adults without stroke. A change in both ICF and ICI has effects upon the motor system. The summation of ICI and ICF effects has been shown to alter the input to corticospinal cells (Fitzgerald et al., 2006). This damage is also known to be a primary source of muscle weakness leading to upper extremity impairment (Gemperline et al., 1995; Gracies, 2005; Kamper et al., 2006; Massie et al., 2013).

Researchers attempt to find ways to help stroke patients improve motor system functioning through brain stimulation because time dependent plastic changes may take more time to occur. Understanding the underlying mechanisms of the lesioned primary motor cortex may lead to different approaches to rehabilitation. As information becomes available about how the underlying mechanisms of the brain change after stroke, and the response of those impaired mechanisms to interventions, rehabilitation professionals can gain insight into the effects of a combination of traditional and new therapeutic interventions that increase functional performance and enable people to fully participate in life post stroke. Based on combined information from multiple studies, such as the current study and the work of Izumi and colleagues (2008), questions can be answered regarding the benefit of combined and multilevel interventions. For example, the

benefit of interventions such as constraint-induced movement therapy (CIMT) combined with transcranial magnetic stimulation (TMS), impacting the sensorimotor system both directly through stimulation and indirectly through forced use, can begin to be understood through both improved ICF to ICI ratio measured internally and enhanced motor performance measured externally.

Researchers might use this ratio to examine the relationship between the dominant and non-dominant hemispheres in adults without stroke. Studies could then use the ratio to compare the affected hemisphere to the unaffected hemisphere in adults with stroke, and whether hand dominance is a factor. Finally the ratio could be used to better understand the relationship between the unaffected and affected hemispheres following stroke as compared to individuals without stroke.

Furthermore, the ICF-to-ICI ratio could be used to determine effectiveness of interventions used post stroke. This would be clinically useful in assessing therapeutic gains. Research studies could use this ratio as an outcome measure pre and post intervention to determine change. CIMT by itself has been found to increase intracortical excitability in some patients with stroke and not in others (Hamzei et al., 2006). Bolognini and colleagues (2011) found that CIMT alone served to modulate local excitability but not in removing excess transcallosal inhibition; the combination of CIMT and bihemispheric transcranial direct current stimulation (tDCS) was found to lead to greater functional recovery. Another study found that using Hebbian-type brain stimulation in combination with robot-assisted training was found to decrease ICI (Butefisch et al., 2011). If ICF-to-ICI ratio standardization studies were completed, researchers and later practitioners could compare pre and post intervention ratios of adults with stroke to ratios of individuals without stroke. Correlations of this ratio to functional measures might yield clinically useful functional correlates to more basic neurophysiological function, and provide a

measurement of neuroplasticity that occurs following stroke. Intervention studies using CIMT, robot assisted therapy, and brain stimulation techniques could use the ratio to better understand clinically relevant changes. Practitioners could then use the information gleaned from those intervention studies to determine the most beneficial intervention necessary for a given client.

The ratio of ICF-to-ICI could be utilized to understand more about the effects of non-invasive brain stimulation. Suzuki and colleagues (2012) found that tDCS increases motor cortex excitability in subjects with stroke. In their review article investigating the effects of TMS, Hemond and Fregni (2007) found that repetitive transcranial magnetic stimulation (rTMS) has therapeutic efficacy in motor neurorehabilitation in stroke patients, and Emara and colleagues (2010) demonstrated the benefits of inhibitory and stimulatory rTMS by stimulating the ipsi-lesional and contra-lesional hemispheres at different stimulation frequencies. Takeuchi and colleagues (2008) also used rTMS to stimulate the unaffected hemisphere and found increased excitability in the affected motor cortex in subjects with stroke.

Some studies have found significant results using non-invasive brain stimulation for rehabilitation post stroke, but much research is needed. In a review, Johansson (2011) described how high frequency rTMS and anodal tDCS are used to enhance activity in the affected hemisphere; findings varied indicating the need for further study of optimal stimulation protocol. Hiscock and Miller (2008) also describe the need for further studies describing dosage of rTMS to be used. The ratio of ICF-to-ICI could be used understand if the brain stimulation dosage has been effective in eliciting positive and lasting changes in the motor cortex.

### **Limitations**

Several limitations exist for this study. Since there is a loss of neurons with age, and the stroke group was significantly older, it is possible that there are fewer interneurons responsible

for ICF in older people resulting in smaller MEPs. That is, are the smaller MEPs in the stroke group ICF trials due to old age or neuronal death due to stroke? Also interneurons responsible for ICI exist in fewer numbers in older people resulting in larger MEPs. Are these larger MEPs for the ICI trails in the stroke group due to old age or neuronal death due to stroke? There was a problem with homogeneity of variance for two variables indicating the need for a larger sample size in the stroke-affected group. Also excitability and inhibition were not compared with respect to lesion location; lesion location may impact the amount of excitability and/or inhibition present in the primary motor cortex. Finally, the non-stroke group was stimulated on the dominant side of the brain whereas the subjects with stroke were stimulated on the stroke affected side, regardless of dominance. Therefore it is unclear if the difference between the groups was due to stroke or dominance.

### **Future Research**

Studies with greater sample sizes and subjects more similar in age are needed to verify the findings of this study. A greater understanding of the importance of the ratio of ICF to ICI, the ideal ratio in the stroke-affected hemisphere, would be beneficial to the field of stroke rehabilitation, including how to improve the ratio and what combination of interventions most effectively impacts that ratio. But studies like Kicic and colleagues (2008) serve as reminders that a one-hemisphere focus after stroke is limited because optimal performance of unilateral movement requires inter-hemispheric balance between excitation and inhibition. In their review, Cramer and colleagues (2011) described cortical excitability being decreased after stroke in the affected hemisphere as a result of increased transcallosal inhibition from the contralesional hemisphere but that excitability is increased in the contralesional hemisphere. Butefisch (2004) mentions a consideration for future research indicating that changes post unilateral lesion to the

motor output system are different for the affected and non-affected hemispheres. Thus, studies comparing the underlying mechanisms of both hemispheres, of subjects with as compared to subjects without stroke, are necessary.

## **Conclusion**

This study aimed to investigate and identify differences in intracortical inhibition and facilitation comparing survivors of stroke to individuals unaffected by stroke. Overall, based on peripheral recordings of MEPs, the affected hemispheres in the group with stroke were found to be less excitable than the dominant hemispheres in the group without stroke. The more that is understood about the mechanisms, such as excitatory interneurons and inhibitory interneurons of the primary motor cortex, the better we can develop rehabilitation protocols that increase motor function. The more that is understood about the effect of and the underlying mechanisms of the primary motor cortex, using transcranial magnetic stimulation, the more will be known about the potential benefit of combining therapeutic interventions to impact those mechanisms and increase performance in daily activities. Furthermore, the findings reported in this study have not previously been reported and have value even with the aforementioned limitations.

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