THESIS

THE USE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AS AN ADJUNCT TO CONSTRAINT INDUCED THERAPY

Submitted By

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ABSTRACT

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Cerebral vascular accident (CVA) or stroke is a leading cause of disability in the United States. Hemiplegia is a common and persistent outcome of stroke and is present in 80 percent of stroke survivors. Upper extremity hemiplegia, in particular, tends to persist beyond functional recovery in other areas. Intensive training techniques, like constraint induced therapy (CIT) have been shown to significantly improve functioning of the upper extremity, months or even years post-CVA. Repetitive transcranial magnetic stimulation (rTMS) is a method of stimulating and augmenting the neurophysiology of the motor cortex in order to promote the neuroplastic changes that are associated with motor recovery. Like CIT, rTMS has demonstrated significant improvements in functional recovery of the upper extremity in stroke survivors. This study examined the potential benefits of using rTMS as an adjunctive treatment with CIT.

Methods: 16 adult stroke survivors were randomized to either a CIT plus sham rTMS group (n = 8) or a CIT plus true rTMS group (n = 7). 1 participant was lost due to attrition. This is a double blind, sham controlled study. A two-way repeated measures ANOVA was used for analysis.

Outcome Measures: TMS measures of MT, SICI, ICF, and recruitment curve. Functional measures were Wolf Motor Function Test (WMFT), Stroke Impact Scale (SIS), and Motor Activity Log- Quality of Movement (MAL-QOM).

Results: Our neurophysiologic measures did not show significant differences between groups or over time for either group. Most of our functional measures showed significant differences over time for both groups, but not between groups.

Conclusion: The small sample size, coupled with dropped data and high variability of data likely interfered with our ability to show significant differences between groups. However, 3 functional outcomes appeared to show a trend to a more sustained improvement at the 4 month follow-up assessment. These were Mal-QOM, SIS- strength and SIS- hand functioning. Further, a subset of rTMS responders may exist. These responders may have anatomical and physiological indicators that distinguish them from non-responders. We were not able to control for these difference in this study, but would recommend a deeper investigation into these potential differences for future rTMS studies.

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INTRODUCTION

Hemiplegia can persist as a significant barrier to functional gains post cerebral vascular accident (CVA). In light of this, varying treatment strategies and therapeutic techniques exist to address upper extremity impairment in stroke. Each of these techniques offers varying and inconsistent degrees of effectiveness in promoting upper extremity functioning (Barreca, et al., 2003). However, in terms of skilled training, those that employ intensive and repetitive treatment consistently demonstrate significant functional gains (Barreca, et al., 2003). These interventions utilize an active behavioral approach to maximize functioning of the affected upper extremity.

One intensive training technique, constraint induced therapy (CIT), has well established efficacy and has been shown to lead to lasting improvements in upper extremity functioning. The possibility exists, however, to maximize these benefits of CIT by combining the effects of a passive neurophysiologic treatment with the intensive behavioral training of CIT. The combination of these two treatment methods may further drive functional recovery of the hemiparetic upper extremity beyond the gains made through CIT alone. This research project examined the potential benefit of using repetitive transcranial magnetic stimulation (rTMS) as an adjunct to CIT to improve upper extremity functioning post stroke. In this study, 16 survivors of stroke received either true rTMS or sham rTMS in combination with CIT. We examined both functional as well as neurophysiologic outcome measures to determine if a potential benefit exists in combining these two treatment methods. We hypothesized that the group receiving true rTMS in combination with CIT will show greater functional and neurophysiologic changes over the group receiving sham stimulation combined with CIT.

BACKGROUND AND THEORETICAL RATIONALE

CVA or stroke is the third leading cause of death and the leading most cause of long-term disability in the United States (American Heart Association [AHA], 2010). About 795,000 Americans each year experience a new or recurrent stroke (AHA, 2010). In 2010, it was estimated that Americans would pay about $73.7 billion for stroke-related medical costs and disability (AHA, 2010). Currently, there are more than 6 million people living in the United States who have survived a stroke (National Stroke Association, 2011). Stroke survivors face many challenges. Most notably is long term impairment or disability and reduced participation in meaningful life situations. Impairment from stroke varies depending on the extent of brain damage as well as the area of the brain affected. Hemiparesis or paralysis on one side of the body is a common outcome of stroke and is a major contributor to long term disability and reduced quality of life (Nichols-Larsen, Clark, Zeringue, Greenspan, & Blanton, 2005). Hemiparesis is the dominant functional limitation in 80 percent of stroke survivors (Luft, et al., 2004). Furthermore, while most stroke survivors do regain ambulation or some level of independent mobility, many fail to experience substantial recovery of the upper extremity (Barreca, Wolf, Fasoli, & Bohannon, 2003).

Berreca et al. (2003) suggested that limited early motor recovery of the affected upper limb tends to shift the focus of therapies to general mobility and one-handed compensation strategies, rather than on remediation of the affected upper extremity. Furthermore, repeated failure in attempts to use the upper extremity in functional tasks may lead to a reduced willingness to use the affected limb all together (Van der Lee et al., 1999). This early lack of attention to the paretic upper extremity likely delays or even hinders the motor recovery of the upper extremity in survivors of stroke. With that said, motor recovery can and does occur with

appropriate demands placed on the central nervous system (CNS). The adaptive capacity of the CNS or neuroplasticity is the mechanism believed to support motor recovery after stroke. Intense and active engagement in functionally demanding tasks supports the neuroplastic changes associated with functional recovery. These tasks are repetitive in nature, and involve intense and prolonged practice (Crosbie, Lennon, Basford & McDonough, 2007; Kleim & Jones, 2008).

HUMAN MOTOR CORTEX AND NEURAL PLASTICITY

Neuroplastic changes have been associated with observable and measureable changes in the human motor cortex. The primary motor cortex (M1) is a primary brain region responsible for voluntary movement. M1 is also involved in the process of motor learning (Muellbacher, Ziemann, Boroojerdi, Cohen, Hallet, 2001; Renner, et al 2009; Kleim, Kleim, & Cramer, 2007). Cortical excitability of M1 is associated with neuroplasticity and therefore functional changes to the cortex (Kleim et al, 2007; Pascual-Leone, et al., 1998). Specific task demands and motor training offers one method to induce increases in M1 excitability (Muellbacher et al., 2001; Perez, Lungholt, Nyborg, & Neilsen, 2004).

Transcranial magnetic stimulation (TMS) offers a non-invasive method to examine the state of M1 (Pascual-Leone, et al., 1998). In this study we used TMS as a means to measure the changes in cortical excitability that have been associated with use dependent plasticity and motor learning. TMS passed a magnetic current through a magnetic coil placed above the skull at the optimal area for stimulating a specific muscle. Application of a supra-threshold stimulus to M1, via TMS, produced a motor evoked potential (MEP). The motor threshold (MT) or the lowest stimulus intensity required to elicit a MEP of >50 μV in at least 50 percent of trials, is one indicator of cortical excitability (Pascual-Leone, et al., 1998). In stroke survivors, MT is frequently higher and reflects an overall reduction in cortical excitability (Chen et al., 2008). Along with MT, the amplitude of the MEP can offer insight into the excitability of M1 (Muellbacher, et al 2001; Boyadjin & Tyc, 2010).

Paired pulse TMS is one method of studying cortical excitability. As first described by Kujirai, et al., (1993), paired pulse TMS involves the administration of a subthreshold

conditioning stimulus that is followed by a suprathreshold test stimulus. To induce intracortical inhibition (SICI), the interstimulus interval (ISI) or time between conditioning stimuli is 1-5 ms. In SICI the resultant MEP is reduced in size compared to the MEP evoked by a single test stimulus. To induce intracortical facilitation (ICF), the ISI is 8-30 ms (Chen, 2000). In ICF, the resultant MEP is larger than the MEP evoked by a single test stimulus. SICI and ICF are separate processes that originate in the motor cortex and provide information on the re-organization of the motor cortex that occurs following motor learning and skill acquisition (Chen, 2007). A reduction in SICI and an increase in ICF are indicative of enhanced cortical excitation. SICI is the lowest threshold system in the hand area and can therefore detect even minor changes in cortical excitation. Gallasch, Christova, Krenn, Kossey, and Raffolt (2008) found reduced SICI during the early phases of skill acquisition of the hand. In another study examining feedback methods and skill acquisition, Smyth, Summers, and Garry (2010) revealed a greater reduction in SICI measures in a group that demonstrated higher skill acquisition over a group which demonstrated lower skill. Increased ICF measures have also been associated with skill acquisition. Lotze, Braun, Birbaumer, Anders and Cohen (2003) noted significant increases in ICF measures following active but not passive wrist training. Further, the participants engaged in active motor training developed significantly higher skill performance. In this case, higher ICF measures occurred with higher skill attainment.

The recruitment curve, also known as the stimulus response or input-output curve, is a measure of the increase in MEP amplitude resulting from increasing TMS intensities (Chen, 2000). Figure 1 is an example of recruitment curve measures from one study participant at all test times. Recruitment curves may reflect the extent of neuronal reorganization by assessing neurons that are less excitable and further from the center of TMS activation (Chen, 2000). The

slope of the recruitment curve will be steeper in muscle groups with a lower motor threshold and with increasing cortical excitation of those muscles. Consequently, increases in slope occur with enhanced cortical excitation and recruitment of neurons adjacent to lesioned areas. Increases in cortical excitation and recruitment of adjacent neurons occur with functional neuroplastic changes to the nervous system. Recruitment curve measures have been linked to motor learning and skill acquisition. Lotze et al. (2003) and Perez, Lungholt, Nyborg, and Nielson (2004) both found significant increases in recruitment curve slopes following active skill training. These increases were present only with increased skill attainment. Therefore, recruitment curve measures reflect cortical changes associated with functional gains.

CONSTRAINT INDUCED THERAPY

Principles of motor learning theory assert that engagement in activity and motor training evoke relatively permanent structural and physiological changes in the CNS (Kleim & Jones, 2008). These changes are associated with skill acquisition and improvement (Adkins et al., 2006; Gillen & Burkhardt, 2004). Neuroplasticity is the reorganization of neuronal pathways, as well as the synaptic and dendritic growth of CNS neurons (Adkins et al., 2006). Such plasticity is thought to represent the mechanism by which motor learning in the intact as well as damaged brain occur. Its principles form the basis for effective rehabilitative strategies in persons who have sustained CNS damage. CIT, which has its theoretical roots in motor learning concepts, employs constraint of the unaffected limb to overcome learned non-use of the affected limb (Taub et al., 1993; Wolf, Lecraw, Barton, Brigitte, 1989). The affected limb is then engaged in intense and repetitive practice. The pattern of learned non-use begins with a period of CNS shock that immediately follows damage to CNS tissue. This period of shock creates an inability to use the affected limb, which over time supports, through negative reinforcement, non-use of the extremity (Taub et al., 1993). In order to overcome this phenomenon, CIT forces use of the hemiparetic upper extremity by constraining the unaffected limb, usually with a mitt, cast or sling, and engaging the hemiparetic limb in mass repetitive practice (Wolf et al., 2006). The protocol, described by Taub et al. (1993), consists of 14 days of wearing a sling on the unaffected limb for over 90% of waking hours. During this 14 day period participants spend each weekday engaged in 6 hours of tasks using only the affected extremity. Several studies speak to the effectiveness of CIT in improving functional and motor outcomes of stroke survivors with hemi-paresis. In a large randomized controlled trial, Wolf et al. (2006) demonstrated highly significant improvements in both functional recovery of the upper extremity

as well as self-perceived recovery of hand function in participants who received CIT over standard rehabilitative care. These improvements were sustained and significant even at 12 months post intervention.

CIT has been associated with positive changes in the human motor cortex. Following a two-week course of CIT, Liepert, et al. (1998) found evidence of enhanced cortical excitability through TMS measures of MEP amplitude in six chronic stroke participants. After training, The MEP sizes in the affected hemisphere increased significantly. All six participants demonstrated increased functional abilities of the affected upper extremity. In the Wittenberg et al. (2003) study, patients who received CIT had a significantly increased size of the motor map of the affected hemisphere as compared to a control group. These patients also demonstrated greater improvement in functional recovery over the control group. Liepert, Bauder, Miltner, Taub, and Weiller (2000) compared the cortical motor area of 13 stroke survivors before, immediately following, and up to 6 months post CIT treatment. The mapped motor representations were significantly larger post CIT as compared with before CIT. Motor performance remained at a high level immediately following and 6 months post CIT treatment.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

rTMS can influence and alter the neurophysiologic functioning of the cortex. rTMS is a form of TMS that uses repetitive pulses or trains of either high or low frequencies to influence the human motor cortex (Hallet, 2007). Lower frequencies (0.1-1 Hz) produce inhibition while higher frequencies (greater than 5 Hz) will induce facilitation (Hallet, 2007; Fitzgerald, fountain & Daskalakis, 2006). With rTMS, the induced cortical changes outlast the stimulation period (Hallet, 2007). Given the potential of rTMS to induce lasting changes in cortical excitation, and because cortical excitation is associated with neuroplastic changes, rTMS may support the functional motor recovery of stroke survivors (Di Lazzaro et al., 2006).

Several studies have investigated the effects of high frequency rTMS to the lesioned motor cortex (Kim et al., 2006; Quartarone et al., 2005; Chang et al., 2010; Khedr, Etraby, Hemeda, Nasef, & Razek, 2010). Most studies show promising evidence of the utility of rTMS in enhancing cortical excitation and motor function. Kim et al. (2006) examined the effects of high frequency rTMS on MEP amplitude, movement accuracy and time on 15 stroke survivors. They found significantly increased MEP amplitude, motor accuracy and time in the rTMS group as compared to the sham group. Quartarone et al. (2005) demonstrated an increase in corticospinal excitability, as measured by unconditioned MEP amplitude and paired pulse measures, in 10 healthy participants.

To examine more long-term effects of rTMS on motor function, Chang et al. (2010) assessed the motor and functional recovery of an rTMS group and a sham group at 3 months post treatment. The results indicated a significant and sustained effect of rTMS over a three month period in regards to improved motor recovery. Similarly, Khedr, Etraby, Hemeda, Nasef, and

Razek (2010) demonstrated the long-term benefits of rTMS at 12 months post rTMS treatment. They examined motor recovery and cortical excitability measures immediately following rTMS. They examined motor recovery again at a one-year follow-up. Several motor recovery measures continued to remain significantly higher at 12 months follow-up in the rTMS group (Khedr, et al., 2010).

rTMS AS AN ADJUNCT TO CIT

CIT is a well-established behavioral and therapeutic tool to promote functional recovery in stroke. rTMS is unique in that it is a passive method of altering the excitability of the motor cortex and thereby promote functional neuroplastic changes. Combining the activity-dependent effects of CIT with the facilitating effects of rTMS may offer a more effective mechanism for driving motor recovery than either one method performed alone. Using rTMS in adjunct with other therapies, including CIT is still quite novel, with few studies that have investigated its efficacy. In a preliminary study, Malcolm et al. (2007) combined high frequency rTMS with CIT. While primary outcome measures did not demonstrate significant differences, some secondary measures, including motor threshold and one functional assessment, did demonstrate a significant improvement with rTMS combined with CIT over the sham rTMS plus CIT control group. The results of this study certainly speak to the potential for using rTMS as an adjunct to CIT in stroke rehabilitation.

METHODS

This study randomized 16 adult survivors of stroke to either a CIT plus true rTMS or a CIT plus sham rTMS. 15 of those 16 completed the study and Table 1 provides demographic information on these participants. The study participants, functional outcome evaluators, and evaluators analyzing TMS measures were blinded to condition. The study included a baseline assessment followed by a two-week period of no intervention prior to the pretest evaluation. Both groups received two weeks of the CIT training similar to the methods described by Taub et al. (1993) and Wolf et al. (2006). This included 10 consecutive weekdays each of intensive mass practice of the affected upper extremity for 5 hours per day. Actual CIT time was reduced to 5 hours because participants received rTMS during the first hour. Each task was performed for 15 to 20 minutes with grading of the task to increase task requirements. Participants were not allowed to remove the constraining mitt during the task practice. Participants wore the mitt on the affected upper extremity for 90 percent of waking hours with only agreed upon activities, like toileting, in which the mitt could be removed. Compliance with the restraint was monitored by compliance devices that monitor wearing time. In addition, participants completed an activity log each day to record activities performed and reasons for removing the mitt. In the event that a participant was not able to wear the mitt for 90% of waking hours, study personnel reviewed the participants' daily activity log and problem-solved ways to increase mitt wearing time.

Inclusion criteria included: participants had a unilateral stroke at least 9 months prior to the study. The location and extent of lesions were verified by MRI. Additional inclusion criteria followed standard CIT criteria (Taub, Uswatte, & Pidikiti, 1999). This includes active wrist extension of at least 20 degrees, metacarpophalangeal and interphangeal extension of at least 10 degrees, a score of at least 24 on the Mini Mental Status Exam (Folstein, Folstein, & McHugh,

1975), the ability to sit independently for 5 minutes, the ability to stand with the support of an assistive device for 2 minutes, the ability to actively participate for 6 hours in therapy with short rests, and passive range of motion at all upper extremity joints of at least 50 percent of normal full range. Included participants also received medical clearance from their primary care physicians as well as underwent EEG testing to rule out risk of seizures.

Exclusion criteria included: taking medications that lower seizure threshold, history of CNS disease other than CVA or present with evidence of another CNS disease other than CVA, presence of epileptiform activity as measured by EEG, history of hemorrhagic stroke, arteriovenous malformation, intracortical hemmhorage, subarachnoid hemorrhage, bilateral cerebral vascular disease, mental retardation, poorly controlled psychiatric or other medical illness, alcohol or drug abuse with in the past year, have an implanted pacemaker or medical pump, metal plate in the skull, or metal object in the eye or skull, have intracardiac lines or significant heart disease, are pregnant, or younger than 40 years of age.

Hypothesis 1: Participants who received true rTMS in conjunction with CIT will demonstrate a greater improvement on functional outcome measures over the group that received sham rTMS with CIT.

Hypothesis 2: Participants who received true rTMS in conjunction with CIT will demonstrate a greater improvement in neurophysiologic measures of cortical excitation over the group that received sham rTMS with CIT.

rTMS protocol

The participants received either rTMS or sham rTMS at the beginning of each of the 10 weekday treatment sessions. In each session, EMG electrodes were placed over the abductor

pollicis brevis (APB), first dorsal interosseous (FDI) and biceps brachii (BB). rTMS was administered via a Magstim Super-Rapid Magnetic Stimulator (Magstim Company US, Woburn, MA) with an air-cooled figure eight shaped coil placed over the optimal area for eliciting a MEP. Each daily treatment consisted of 2000 stimulations administered as 50 trains of 40 stimuli at a rate of 20 Hz. Each train was 2 seconds with a 28-second rest interval between each train. Stimulus intensity was at 90 percent of resting motor threshold. Motor threshold was defined as the lowest stimulus intensity eliciting MEPs > 50 mV in at least 5 of 10 trials. The sham rTMS was administered using the Magstim sham 70 mm figure eight coil (VIASYS Healthcare, Madison, WI) that simulated the sound and vibration of rTMS trains as well as used 20 Hz electrical impulses to simulate the scalp irritation associated with rTMS.

Blinding Procedure

Participants were blinded to group assignment throughout the study. Because the sensory experiences differ between the TMS assessments and both the true and rTMS experiences, subjects were alerted to this difference prior to the start of the study. During the baseline and pre-test assessments the principle and co-principle investigators, who administered the assessment were blinded to group assignment. For safety reasons however, the principle and co-principle investigators needed to know if real or sham stimulation was provided. Therefore, they were unblinded to group condition during the intervention stage. All trainers, evaluators, data processors, and the statistician were blinded to group assignment throughout the entire study.

Each group of participants received the intensive 5 hour session of CIT immediately following either rTMS or sham rTMS. Both groups underwent assessments at baseline, pre-intervention, post-intervention, and at 4 months follow-up. Functional outcome measures

assessed motor skill and functional use of the affected upper extremity. Neurophysiologic measures used TMS to assess the cortical changes associated with CNS functioning.

Functional Outcome Measures

Our primary functional outcome measures were the Wolf Motor Function Test (WMFT) (Wolf, et al., 2005), The Motor Activity Log (MAL) (Quality of Movement) (Uawatte, Taub, Morris, Light, & Thompson, 2006) and the Stoke Impact Scale (SIS) (Duncan et al., 2002). Each of these assessments is commonly used in CIT research to assess upper extremity as well as overall recovery from stroke. The WMFT is a standardized laboratory based assessment that uses timed as well as function-based assessments to evaluate motor skills (Wolf, et al., 2005). In this study mean performance time (in seconds), strength, grip strength, and functional ability scores were used for analysis. Morris, Uswatte, Crago, Cook, and Taub (2001) examined the reliability of the WMFT on 24 participants with chronic hemiparesis. They found a high test-retest reliability ($r = .95$) for the functional assessment as well as for the performance time ($r = .90$). Additionally, they found high reliability for the functional assessment (ICC= .93) as well as for performance time (ICC = .99). Whitall, Savin, Harris-Love, and Waller (2006) established concurrent validity of the WMFT with the upper extremity portion of the Fugl-Meyer Assessment on 66 stroke survivors. Concurrent validity was excellent at $r = .88$. Wolf et al. (2001) examined construct validity by use of known groups validity.

The MAL (Quality of Movement [QOM]) is a questionnaire scale that asks participants to rate how well they feel they are able to use the affected upper extremity on a variety of functional tasks. The MAL uses a 6-point scale from zero to five, with .5 increments between whole numbers on the scale. Participants are asked to rank themselves with 0 indicating that the

affected arm is not used at all for a specific task and with 5 indicating that the affected arm is able to perform the task as well as before the stroke. The score is based on an average of the number of items scored. This accounts for the items that receive an "NA" rating because they do not apply to the individual. Lower scores on the MAL QOM scale are indicative of lower functioning. Uswatte et al. (2006) investigated the psychometric properties of the MAL from 220 participants who had participated in a large multi-site clinical trial. Convergent validity was established at r = .72. Test re-test reliability was high at r-.80.

The SIS is a self-reporting stroke specific questionnaire that asks for participants to rate multiple areas of functioning. These include: strength, hand function, activities of daily living (ADLs and IADLs), mobility, communication, emotion, memory, thinking and participation (Duncan et al., 2002). Each item is rated on a 5 point scale based on the difficulty the person has with performing each item. The scores range from 1 to 5 with 1 indicating an inability to perform the task and a 5 indicating that there is no problem with performance of the task. One item in the scale assesses the participant's perception of recovery and uses a visual scale from 0 to 100, where 0 indicates no recovery and 100 indicates full recovery. This study used only those subscale items most pertinent to upper extremity functioning in the analysis. These are hand functioning, strength, ADL performance, and perceived percent recovery. The overall SIS recovery scores were also included in the analysis. The scores from each of the subscales (strength, hand function, ADL performance, and perceived amount of recovery) were added up separately. Duncan et al. (1999) evaluated the test-retest reliability of the SIS version 2.0 in 25 participants. They found test retest reliability ranged from ICC – 0.7 to 0.92. The emotion domain had a weaker correlation (ICC = 0.57). Duncan et al. (2002) examined the concurrent

validity of the SIS version 3.0. Pearson correlations ranged from adequate to excellent (r = 0.42 to r = .77) on the various assessments.

Neurophysiologic Outcome Measures

At each baseline, pre-test, post-test and 4-month follow-up, TMS measures, which included SICI and ICF measures, recruitment curve and motor threshold, were conducted. Magnetic stimulation was delivered through a 7 cm Magstim figure eight coil. The coil was placed over the optimal area for eliciting MEPs and determining rMT. A fitted cloth cap was used to create a grid to determine this optimal location for coil placement. Each participant was seated in a dentist style chair with Electromyography (EMG) electrodes placed over the abductor pollicis brevis (APB), first dorsal interosseous (FDI), extensor digitorum communins (EDC), and biceps brachii (BB) muscles to monitor individual muscle activity for response to stimuli and any background muscle activity.

To assess intra-cortical excitability, paired pulse methods were used to induce SICI and ICF conditions in the motor cortex of the affected side. This method involved first administering a conditioning stimulus (CS) at a subthreshold intensity of 90 percent of rMT. Then, following either a 2 ms interval or a 15 ms interval, a second test stimulus (TS) was administered at 116 percent of rMT. A 2ms interval between stimuli induces the intracoritcal inhibitory response or SICI. A 15 ms interval between stimuli induces the intracortical facilitation response or ICF. Ten trials each of SICI, ICF, and TS measures were carried out in pseudorandom order with a 6-second inter-trial interval. Measures of ICF and SICI were assessed by comparing the MEP responses from these conditions with the TS responses. Each SICI and ICF MEP response was expressed as a ratio of the amplitude of their MEPs over the amplitude of the TS responses.

MEPs were measured using peek amplitude. Measures of MT followed the guidelines described above that have been established by Pascual-Leone et al. (1998). For recruitment curve measures in this study, stimuli from the Magstim 7 cm figure eight coil were administered at intensities increased in 5 percent intervals ranging from 30 to 100 percent of the maximum stimulator output. Five stimuli were delivered at each intensity at a rate of 0.2 to 0.3 Hz. These data were plotted as a function of the stimulus intensity. This created the depicted recruitment curves and subsequent slopes of one study participant shown in figure 1. The slopes were calculated in Excel (2007) using all data points from first stimulation to last.

Statistical Analysis

We chose to use a two-way repeated measures design in order to capture the differences between our two groups across the four measurement times. A two-way repeated measures ANOVA was conducted for each variable with the within-subjects factor being time (baseline, pre-test, post-test, and follow-up). The between subjects factor was group condition (sham or rTMS). The dependent variables were the results of each of the functional and neurophysiologic outcome measures. We conducted three additional paired t-tests to identify a potential trend in response differences at follow-up for three functional measures. It is important to make note here that there were multiple statistical tests conducted and we did not adjust for multiple tests.

RESULTS

We have categorized the results of this study as either neurophysiologic or functional outcome measures. Table 2 summarizes the mean results from all neurophysiologic measures. Table 3 summarizes the mean results from all functional outcome measures.

Neurophysiologic Outcome Measures

SICI/ICF

This study examined the responses from the APB and FDI muscles of the affected upper extremity to SICI and ICF conditions. The results for each of these conditions were highly variable within each group and across all testing times. Table 3 shows the means and standard deviations at each test time for SICI and ICF conditions. Table 4 shows the individual responses to SICI/ICF conditions on FDI, while Figure 2 illustrates these responses. Of the 15 participants, four participants could not be included in this analysis because they had either a TS response of zero or only one data point across the four points. For the APB muscle 13 participants' data could be included in the analysis. The results of the ANOVA did not show significant differences between groups on either muscle (FDI $F_{(1,7)} = 1.89$, $p = 0.18$, APB $F_{(1, 9)} = .63$, $p = .43$) for the SICI condition. There were no significant differences detected between groups for either muscle (FDI $F_{(1, 7)} = .60$, $p = 0.44$, APB $F_{(1, 9)} = .00$, $p = .97$) for the ICF condition. No significant differences were detected over time for either muscle (FDI $F_{(1, 7)} = .75$, $p = 0.53$, APB $F_{(1, 9)} = .85$, $p = 0 .48$) for the SICI condition. Similarly, no significant differences were detected over time for either muscle (FDI $F_{(1, 7)} = .57$, $p = 0.64$, APB $F_{(1, 9)} = 1.20$, $p = 0.32$) for the ICF conditions.

Recruitment curve

Recruitment curve slopes were calculated using the line of best fit for all recorded MEPs plotted as a function of stimulator intensity. No significant differences found between groups at baseline for either FDI ($t_{(12)} = 0.958$, $p = 0.357$), or APB ($t_{(12)} = .393$, $p = .700$). No significant differences were found for the main effect of time (FDI $F_{(1,10)} = .95$, $p = 0.35$, APB $F_{(1,10)} = .95$, $p = 0.35$). There was no significant difference found for the main effect of group condition (FDI $F_{(1,10)} = .26$, $p = .619$, APB $F_{(1,10)} = .50$, $p = .491$). While there was no significant main effects, there was a significant interaction for FDI ($F_{(1,10)} = 6.31$, $p = 0.027$) between group condition and time. Figure 3 illustrates the change in mean slopes for FDI across testing times for the sham and rTMS groups. The rTMS group had higher slopes at baseline then the sham group. However, between pre-test and post-test the rTMS group had a decline in slope while the sham group increased some. This is counter to what we had expected. We anticipated that the rTMS group would demonstrate a greater increase in slope over time than the sham group.

Motor threshold

There were no significant differences in MT between the rTMS group and the sham group at baseline. There were also no significant changes in MT over time for either group ($F_{(1,7)} = 3.45$, $p = .096$). There were no significant differences between groups ($F_{(1,7)} = .04$, $p = 0.85$). There were no significant interaction effects ($F_{(1,7)} = .99$, $p = 0.35$). Pairwise comparisons did reveal a significant increase in MT from baseline to pre-test for the rTMS group. Figure 4 shows average MTs for each group over all testing times.

Functional Outcome Measures

Wolf motor function test

The WMFT subtests of functional ability and affected upper extremity time were found to have significant changes over time. For functional ability, the main effect of time was significant ($F_{(1,11)} = 11.86$, p=0.004), indicating that both groups had a significant improvement in functional ability over time. Neither group condition nor interaction were significant with $F_{(1,11)} = .79$, p= 0.39 and $F_{(1,11)} = 2.80$, p=0.12 respectively. Figure 5 illustrates the change in functional ability across test times for both groups. There was a significant ($F_{(1,11)} = 4.81$, p=0.047) decrease in the mean amount of time for the affected upper extremity to complete the timed tasks of the WMFT for both groups (see Figure 6). Neither group condition ($F_{(1,11)} = .628$, p=0.44) nor interaction effect ($F_{(1,11)} = .93$, p=0.35) were significant. There was a trend toward significance in the main effect of time for mean grip strength ($F_{(1,11)} = 4.02$, p=0.066) and time difference between unaffected and affected upper extremities ($F_{(1,11)} = 4.00$, p=0.067). Pairwise comparisons of grip strength revealed a trend toward significance from baseline to post-test (p=0.057) and from baseline to follow-up (p=0.068). Pairwise comparisons for mean difference between affected and unaffected times revealed a significant difference from pre-test to follow-up (p= 0.045). The comparisons also revealed a trend toward significance from baseline to follow-up (p= 0.077) and from pre-test to post test (p= 0.062).

Stroke impact scale

On the SIS, participants reported a significant improvement in three of the five subtests we choose to analyze. These demonstrated a significant main effect of time. These were percent recovery ($F_{(1,11)} = 10.25$, p= 0.007), overall SIS score ($F_{(1,11)} = 8.69$, p=0.011),and hand

functioning ($F_{(1,11)}$ = 16.76, p= 0.001). Strength ($F_{(1,11)}$ = 4.58, p= .052) and ADLs ($F_{(1,11)}$= 2.40, p= 0.146) did not reach significance for change over time. Strength, however, does trend toward significance with a p value of 0.052. Pairwise comparisons revealed a significant improvement in strength between baseline and post-test and from pre-test to post test. However, because of a decline in score after post-test, strength over time, did not reach significance. This declined appears somewhat more apparent in the sham group. There was no significant difference found between groups. There was a significant interaction effect ($F_{(1,11)}$ = 4.81, p=.047) for perceived percent of overall recovery between groups that occurred as a result of the sham group reporting a decrease in overall recovery between baseline to pretest, while the rTMS group did not. Figure 7 shows this interaction. A t-test revealed no significant difference between the groups at baseline (p= 0.56). Pairwise comparisons of percent recovery show a significant increase in perceived percent recovery from baseline to post-test (p= 0.030), baseline to follow-up (p= 0.020), pre-test to post test (p= 0.001). This improvement levels off some at follow-up with a non-significant increase from post-test to follow-up (p=0.98). Pairwise comparisons of overall SIS scores reveal significant increases from baseline to post-test (p= 0.007) and from pre-test to post test (p= 0.007). This improvement is not fully sustained from baseline to follow-up (p= .055). Pairwise comparisons of SIS hand functioning show significant improvements for both groups through all test times except baseline to pre-test. This improvement was not sustained at a significant level at follow-up for the sham group. The rTMS group reported continued improvement in hand function at follow-up while the sham group reported a small decline in hand functioning from post-test to follow-up. A paired samples t-test of mean SIS hand functioning scores between baseline and follow-up revealed a significant improvement in the rTMS group ($t_{(6)}$ = 3.48, p = 0.013). This difference was not fully sustained at follow-up for the

sham group ($t_{(6)}$ =2.35, p=0.051). The graph in figure 8 depicts the change in perceived hand functioning overtime for the two groups.

Motor activity log- quality of movement

The repeated measures ANOVA for MAL scores revealed a significant increase in scores across time for both groups ($F_{(1,11)}$ = 23.11, p< 0.001). The improvement occurs across all test times except baseline to pre-test. The between group comparisons did not reveal significant difference ($F_{(1,14)}$=.007; p=.937). Pairwise comparisons show the most significant change from pre-test to post test (p< 0.001). There is a trend toward a significant interaction effect ($F_{(1,11)}$ = 3.50, p= .084). This is likely because the sham group reports a decline between post-test and follow-up with a mean of 3.25 at post-test to 2.85 at follow-up. Results of a paired sample t-test showed this decline to be significant ($t_{(7)}$ = 2.48, p= .042). The rTMS group maintained improved MAL scores between post-test and follow-up with a mean score at post-test of 3.18 and a mean score of 3.30 at follow-up. Figure 9 illustrates the change in MAL scores for each group over time.

DISCUSSION

This study was designed to investigate the possible adjunctive benefits of rTMS to CIT in the treatment of hemiparesis resulting from stroke. Several results revealed what we had expected while others conflicted with our anticipated results. A high level of variability in neurophysiologic responses may have contributed to these differences. However, these variations may also reflect important differences in treatment responses not accounted for in this study and may speak to a need to tailor or individualize rTMS treatments to maximize the benefits of CIT. Additionally, the results of several interaction effects as well as differing changes between groups overtime may suggest other effects of rTMS not explored in this study.

Our neurophysiologic measures did not demonstrate significant differences between groups in the main effect of group condition. This may be the result of high variability in responses between and within individual subjects. SICI and ICF, in particular, demonstrated a high level of inter- as well as intra-subject variability. A possible reason for this is that neurophysiologic responses to CIT are highly variable. This may be particularly true of measures of cortical excitation. Liepert (2006) investigated inhibitory as well as facilitative responses to CIT in patients with either cortical or subcortical lesions. He found that all patients improved to the same degree on functional measures, however, half of the patients had increases in SICI, while the other half had decreases. Patients with cortical lesions tended to have a greater change in SICI in either direction. In addition, spasticity appeared to be a factor in that patients with higher levels of spasticity demonstrated a greater decrease in SICI after CIT. In our study, we did not specifically control for spasticity. However, if spasticity limited a participant's ROM so that they were not able to meet the minimum ROM requirements, then they were not included in the study. Liepert's study suggests that both increases as well as decreases in SICI

may be associated with functional gains following CIT. Furthermore, injury location, as well as spasticity, may influence the brain's response to CIT. All participants in our study, received CIT, however, in this highly heterogeneous population it appears that responses will inevitably vary on a neurophysiologic level, even with similar functional gains. Variations in CIT responses of our participants may have made interpretation of cortical excitation measures more difficult, in particular, the direction of SICI. If this were the case, then any additional impact of rTMS would also be difficult to identify using cortical excitation measures.

It is also possible that physiological differences exist in the way people respond to rTMS. In a study by Ameli et al. (2009), the authors had actually categorized participants as "rTMS responders" and "rTMS non-responders" based on kinematic movement performance changes following rTMS. The majority of participants with only a subcortical stroke responded well to rTMS, while none of the participants who had additional cortical involvement responded favorably to rTMS. Furthermore, they found differences in neuronal activity between responders and non-responders. Through fMRI, they found that movements of the affected hand resulted in widespread activation in the ipsilesional hemisphere for rTMS responders, while non-responders had generally weaker activation of the ipsilesional hemisphere. In response to rTMS, responders had significantly reduced over activity of the contralesional hemisphere, while non-responders had the opposite effect of increased activity over the contralesional hemisphere (Ameli et al., 2009). Further, they found that rTMS actually induced a maladaptive pattern of bilateral neuronal activation in persons with ischemic strokes involving cortical areas. While further study is warranted, these data speak to the potential for a negative response to rTMS in some stroke survivors. At the very least, as the authors suggest, a "one size fits all" approach to rTMS may not be the most beneficial approach (Ameli et al., 2009). In our current study, physiological

variations in the way participants responded to rTMS may account for the variability in responses. It may be that the specific type and location of rTMS stimulation used in this study was not appropriate for all participants. Of the seven participants in our study who received rTMS, three of them demonstrated greater than average improvement on at least two neurophysiologic and three functional measures. Two of the three had a subcortical stroke, while the other, a cortical stroke. These three participants may be rTMS "responders" as described by Ameli et al. (2009). However, within the context of receiving concurrent CIT treatment, where variations in CIT responses are also likely present, it is difficult to say for sure. Ameli et al.'s 2009 study does draw attention to the fact that rTMS treatments and research may benefit from a more in-depth consideration of stroke region and neuronal activity in both the contra- and ipsilesional hemispheres prior to treatment.

One of our neurophysiologic measures, recruitment curve, showed a significant interaction effect. As figure 2 illustrates, this interaction occurs at two different measurement intervals, between pre-test and post-test and then again between post-test and follow-up. Between pre-test and post-test, the mean slope for the rTMS group declined significantly, while the mean slope increased slightly during this time for the sham group. This is contrary to our expected results during these two test times. We expected both groups would have steeper recruitment curves from the effects of CIT. We also hypothesized that the rTMS group would have steeper curves than the sham group. The second interaction occurs following the post-test period when the rTMS group experiences an increase in mean slope, while the sham group experienced a small decline. Neither of these changes was significant. One possible explanation for these results may be transient cortical excitability responses to rTMS. Khedr, Rothwell, Ahmed, Shawky, and Farouk (2006) found that increases in recruitment curve slopes returned to

pre-rTMS levels after just two hours post rTMS treatment. In our study, it may be that by the time of the post test-period, recruitment slopes had returned to pre-rTMS levels. However, the benefits of the initial impact on recruitment curves may not have been realized until the follow-up period. If this were the case, then the immediate effects of rTMS on recruitment curve measures would be too transient to be present at post-test, however, by the follow-up period, sufficient time has allowed for the neuroplastic changes to occur that would create steeper recruitment curves. Another possible explanation for these results is the test-re-test reliability for recruitment curve measures. On healthy volunteers, test-re-test reliability, for APB and FDI have been found to be acceptable at ICC = .78 and ICC = .82 respectively (Malcolm, et al., 2006). However, Koski, Lin, Wu, and Winstein (2007), who examined recruitment curves in 9 stroke survivors, found a significant increase in slopes measured on the lesioned side across two test sessions. The authors of this study ultimately conclude that measures of cortical excitability, in particular recruitment curves, on the lesioned hemisphere of stroke survivors is generally less reliable than on the unlesioned hemisphere. Limited reliability of the recruitment curve measure could explain why results seemed to go up and down for both groups between testing sessions.

A transient impact of rTMS that later supports sustained recovery following CIT may also explain why several functional outcome measures related to hand functioning showed significant differences between groups when comparing post-test to follow-up periods only. These measures were participants' reports of hand functioning and strength on the SIS scale and participants' report of quality of movement (MAL- QOM). While both groups demonstrated and reported significant improvements in upper extremity functioning at post-test and follow-up, on these three reported measures, the true rTMS group tended to report a more lasting impact at 4-months post treatment. Of note, we did not find significant long lasting changes on TMS

measures and can therefore speak only to a potential toward a sustained impact of rTMS. Further, the neurological mechanism for these changes is unclear. Chang et al (2010), similarly, found that a true rTMS group had sustained improvements at 3-months post rTMS treatment combined with motor practice. In this study, improvements were more pronounced for the true rTMS group after the first post-test period. Therefore, the beneficial effects of rTMS as an adjunctive treatment may become more apparent as time passes beyond the treatment sessions. Again, this may be because adequate time has passed to allow for neuroplastic changes. It may also be that the initial effect of CIT had masked the effect of rTMS and by four months post treatment, the initial impact of CIT had leveled off and the effects of rTMS became more apparent.

LIMITATIONS

The small sample size and subsequent low power is a significant limitation to this study. The sample size is of particular importance, given the high variability of responses, especially neurophysiologic, in this study. Compounding this limitation were problems with attrition as well as low to no TMS responses, leading to dropped data. Several participants in this study had very low to no MEP responses for many neurophysiologic measures. Five of the sixteen participants had low to no responses for either APB, FDI or both muscles. Four of those five had no responses to TS. One person attended only the baseline session and was therefore dropped from analysis. In another participant, MT was unattainable so this person's neurophysiologic data was not included in the analyses. One participant missed the baseline assessment, while another missed the four-month follow-up session. The data for these participants were still included in the analysis.

Another potential limitation to this study is the inevitable heterogeneity of the sample population of stroke survivors. The participants in this study did vary in age, gender, side and location of stroke. The groups in this study were balanced based on gender, severity of impairment, side and location of stoke (cortical vs. subcortical). However, dropped data and attrition likely altered this balance.

CONCLUSION

The results of this study revealed highly variable responses to both neurophysiologic and functional outcome measures. This high variability, coupled with a small sample size may have contributed to our inability to demonstrate significant differences in the main effect of group condition. The variation in responses may be the result of a natural variation in the way people respond to either rTMS or CIT. There may be a subgroup of stroke survivors who respond more favorably to rTMS than others. This variation may be related to location of lesion and other neurophysiologic differences. At the very least, this study gave us a first look at the potential anatomical and neurophysiologic characteristics that future studies may screen for in determining that group of stroke survivors that is more likely to respond favorably to rTMS. Future studies may, perhaps, develop a list of characteristics that indicate a more favorable response to rTMS. Additionally, stroke survivors may have varying responses to rTMS. the TMS measures of some participants who receive CIT training and demonstrate subsequent increases in skill acquisition may differ from what would normally be expected. Skill acquisition may not necessarily result in typical TMS measures of cortical excitation. While we did not find significant differences between groups, some trends in the data may speak to a potential sustaining effect of rTMS when coupled with CIT that may not become apparent until several weeks to months following treatment. A possible explanation for this may be that the initial impact of rTMS on the motor cortex may not support further functional changes until adequate neuroplastic changes have had time to occur. Another explanation may also be that the effect of rTMS may have been masked by the initial impact of CIT, making its benefits less apparent until the follow-up period. We recommend a larger study that is better able to manage low or no TMS responses and outliers

within the data. Further studies should also examine potential long term-benefits of rTMS as and adjunct to CIT and perhaps include several follow-up periods that extend 6 months or more.

Table 1. Demographic information of the15 participants who completed the study

Participant #	Gender	Age (years)	Stroke onset	Time Since Stroke at enter (months)	Stroke Hemisphere	Lesion Location	Ethnicity/Racial
1	Female	56	2-Jul	65	right	subcortical	White
2	Female	51	7-Mar	12	left	subcortical	White
3	Female	66	1-Jul	80	left	subcortical	White
4	Male	70	7-Mar	12	left	subcortical	White
5	Male	82	5-Jun	22	right	subcortical	White
6	Female	71	5-Jun	38	right	subcortical	White
7	Female	40	7-Sep	12	left	cortical	White
8	Male	57	7-Jan	20	left	cortical	White
9	Male	72	6-Oct	24	left	brainstem	White
10	Female	61	8-Jan	12	left	subcortical	White
11	Female	47	7-Dec	16	left	cortical	White
12	Female	61	8-Aug	8.5	right	subcortical	White
13	Male	80	2-Feb	87	right	cortical +sub-cortical	White
14	Female	77	4-Jul	59	right	subcortical	White
15	Male	53	8-Jul	12	left	subcortical	White

Table 2. Neurophysiologic Outcome Results

Measure	N	Baseline Mean (SD)	Pre-test mean (SD)	Post-test Mean (SD)	Follow-up Mean (SD)
FDI SICI					
rTMS	5	.86 (.63)	.72 (.81)	.56 (.25)	1.12 (1.62)
sham	6	.77 (.55)	.47 (.35)	.57 (.14)	76 (.72)
APB SICI					
rTMS	6	.90 (.68)	.88 (.41)	.54 (.40)	1.18 (.44)
sham	7	.94 (.47)	.92 (.97)	1.01 (.85)	1.55 (2.20)
FDI ICF					
rTMS	5	2.83 (3.36)	2.13 (1.48)	2.13 (1.48)	1.63 (1.23)
sham	6	2.85 (3.08)	1.97 (1.50)	1.51 (.69)	1.40 (.91)
APB ICF					
rTMS	6	1.30 (.98)	6.87 (11.14)	1.52 (2.06)	2.71 (1.96)
sham	7	4.08 (5.32)	3.49 (2.34)	2.60 (2.28)	1.99 (1.44)
Recruitment Curve					
FDI					
rTMS	7	.017 (.024)	.034 (.032)	.015 (.020)	.037 (.041)
sham	8	.008 (.009)	.015 (.026)	.029 (.063)	.020 (.040)
APB					
rTMS	7	.018 (.031)	.019 (.030)	.019 (.026)	.025 (.042)
sham	8	.013 (.015)	.009 (.014)	.010 (.017)	.010 (.017)
MT					
rTMS	6	62.50 (18.80)	67.83(21.52)	67.83 (17.98)	64.83 (18.35)
sham	5	63.40(19.55)	65.80 (17.54)	63.20 (17.81)	61.80 (18.57)

Table 3. Functional Outcome Results

Measure	N	Baseline Mean (SD)	Pre-test mean (SD)	Post-test Mean (SD)	Follow-up Mean (SD)
WMFT					
Strength					
rTMS	7	9.71 (9.43)	9.29 (9.01)	9.86 (9.14)	10.43 (9.90)
sham	8	5.00 (7.95)	4.38 (7.56)	6.25 (8.22)	6.63 (7.63)
Grip Strength					
rTMS	7	7.57 (8.99)	8.57 (10.28)	9.14 (10.73)	9.40 (10.23)
sham	8	3.54 (5.25)	2.88 (3.60)	3.79 (5.76)	4.25 (5.47)
Functional Ability					
rTMS	7	2.63 (.66)	2.44 (.77)	2.76 (.90)	2.86 (.96)
sham	8	2.14 (1.09)	2.13 (1.09)	2.31 (1.08)	2.34 (1.10)
Mean difference (sec.)					
rTMS	7	34.22 (30.76)	37.10 (29.02)	31.73 (29.70)	29.15 (27.79)
sham	8	51.38 (37.16)	50.85 (34.33)	40.80 (34.66)	41.96 (39.20)
Mean affected (sec)					
rTMS	7	39.54 (34.21)	41.40 (32.28)	36.09 (32.75)	33.30 (31.11)
sham	8	57.74 (40.30)	57.90 (38.94)	45.83 (37.80)	47.10 (40.46)
SIS					
Percent					
rTMS	7	35.00 (29.30)	37.86 (21.57)	49.29 (29.50)	52.86 (30.53)
sham	8	48.13 (25.06)	38.75 (22.16)	51.88 (26.44)	58.13 (21.70)
ADLs					
rTMS	7	4.14 (.74)	3.97 (.65)	4.24 (.65)	4.19 (.65)
sham	8	3.99 (.49)	3.94 (.53)	4.03 (.90)	4.05 (.74)
Strength					
rTMS	7	3.07 (.99)	2.93 (1.00)	3.29 (1.08)	3.39 (.94)
sham	8	3.09 (.80)	3.03 (.49)	3.56 (.82)	3.21 (.77)
Overall					
rTMS	7	4.10 (.45)	4.13 (.48)	4.35 (.57)	4.21 (.60)
sham	8	3.91 (.23)	3.92 (.25)	4.14 (.38)	4.08 (.40)
Hand Functioning					
rTMS	7	2.81 (.70)	2.91 (.38)	3.23 (1.02)	3.64 (.92)
sham	8	2.28 (.89)	2.33 (.90)	3.06 (.93)	2.94 (1.25)
MAL					
rTMS	7	2.58 (.58)	2.35 (.55)	3.18 (.78)	3.30 (1.16)
sham	8	2.79 (1.03)	2.66 (1.06)	3.25 (.92)	2.85 (1.22)

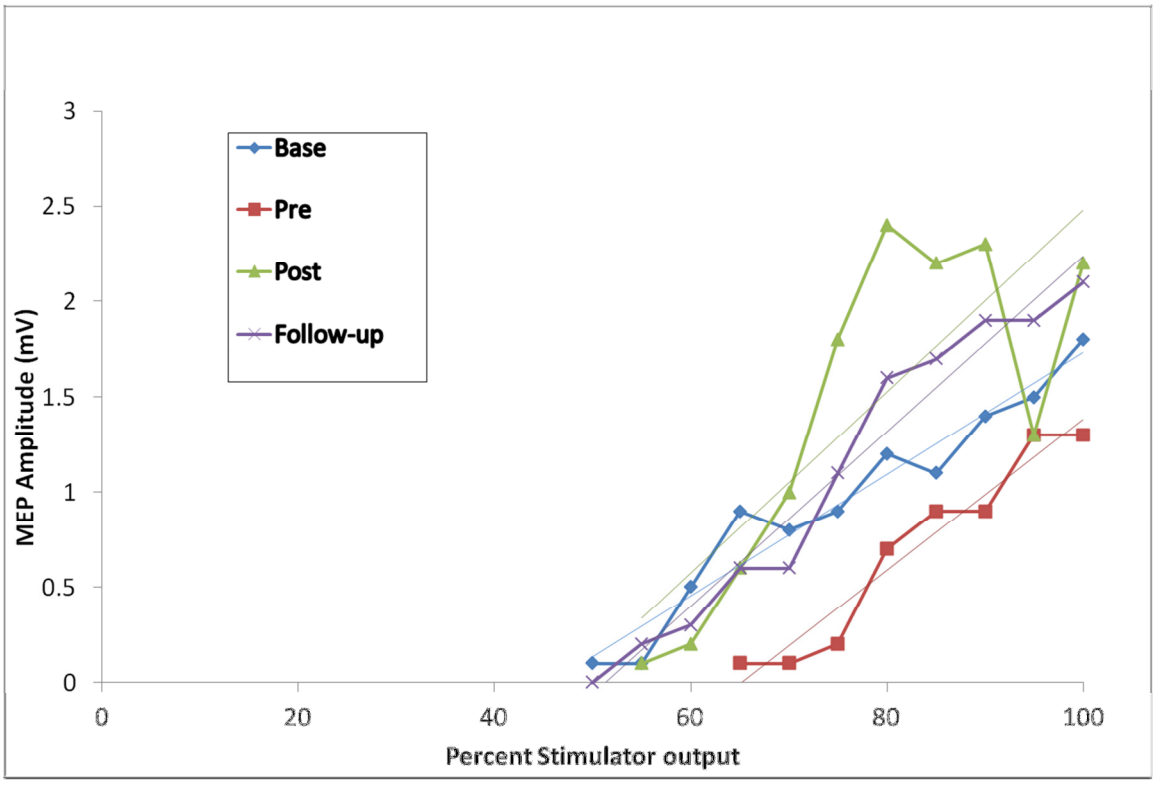

Figure 1. Representative recruitment curves (subject 11): recruitment curves for subject 11 at baseline (blue with squares), pre-test(red with squares), post-test (green with triangles) and follow-up (purple with X's) times.

Table 4. Individual SICI Ratios for FDI

	Subject													
	1-Sham	2-Sham	3-rTMS	4-rTMS	5-Sham	6-rTMS	7-rTMS	8-rTMS	9-Sham	10-rTMS	11-Sham	12-Sham	14-Sham	16-rTMS
Test														
Baseline	1.50	.36	.07	1.13	.78	1.28				2.00	1.35	.43	.17	.42
Pre	.88	.00	.64		.61	1.61	3.00	.33	.00	.00	.74	.65	.38	.49
Post	.55	.71	.15			1.00	.71				.45	.72	.42	.37
Follow		.11	5.44	.45	.38	.70			2.00		1.19	.26	.59	.07

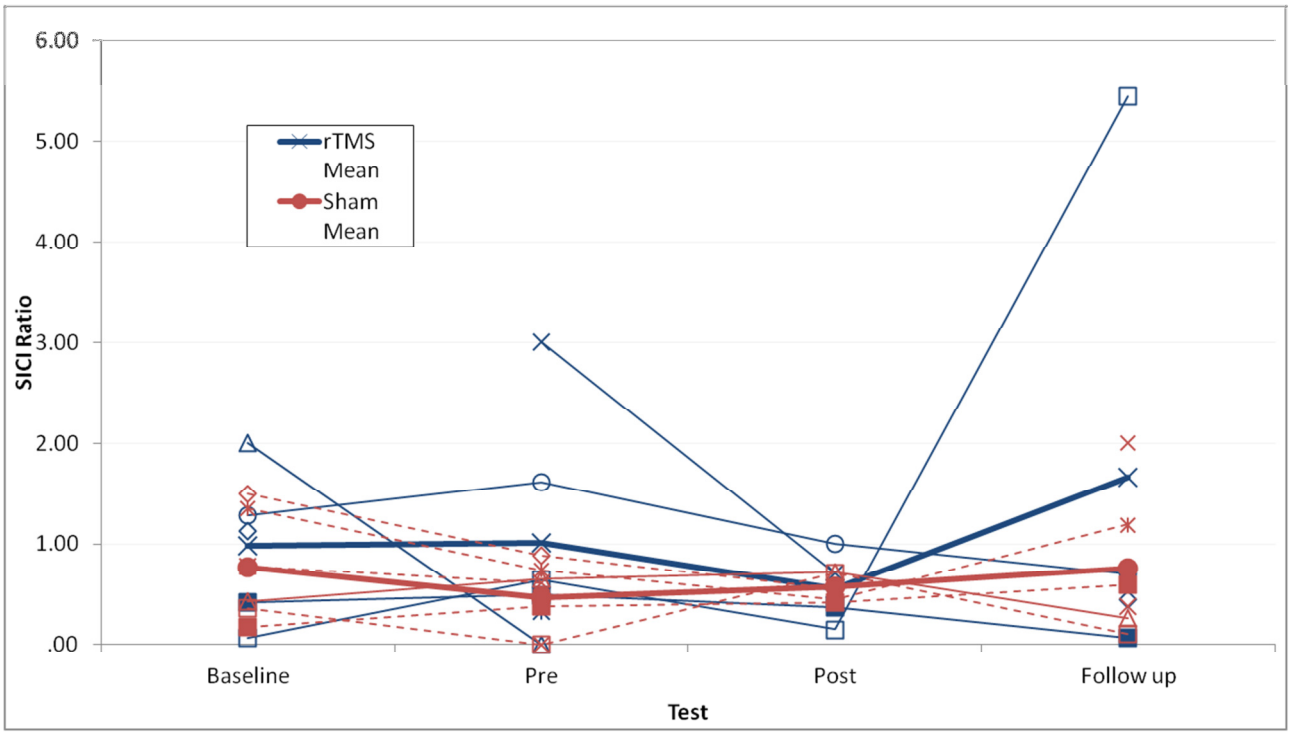

Figure 2. Short interval cortical inhibition ratios: SICI ratios for the FDI muscle of each rTMS participant (thin blue line) and each sham participant (dotted red line). The thick blue line is mean SICI ratio for the rTMS group and thick red line is mean SICI ratio for sham group. 4 of the 15 participants had no response to TS and were therefore not included in analysis.

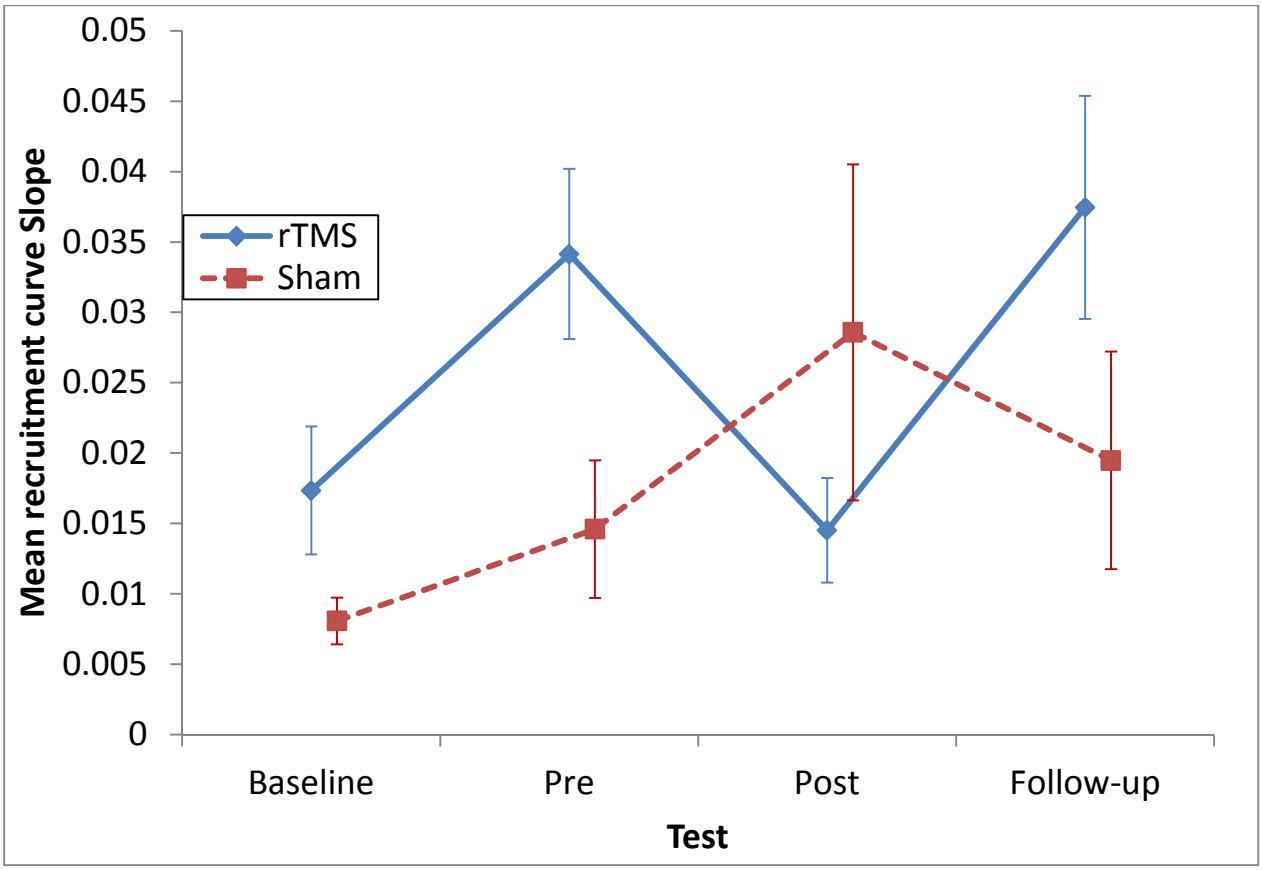

Figure 3. Mean recruitment curves for FDI muscle: Change in mean recruitment curve slopes for rTMS (thin blue line) and sham (dotted red line) at baseline, pre-test, post-test and follow-up sessions.

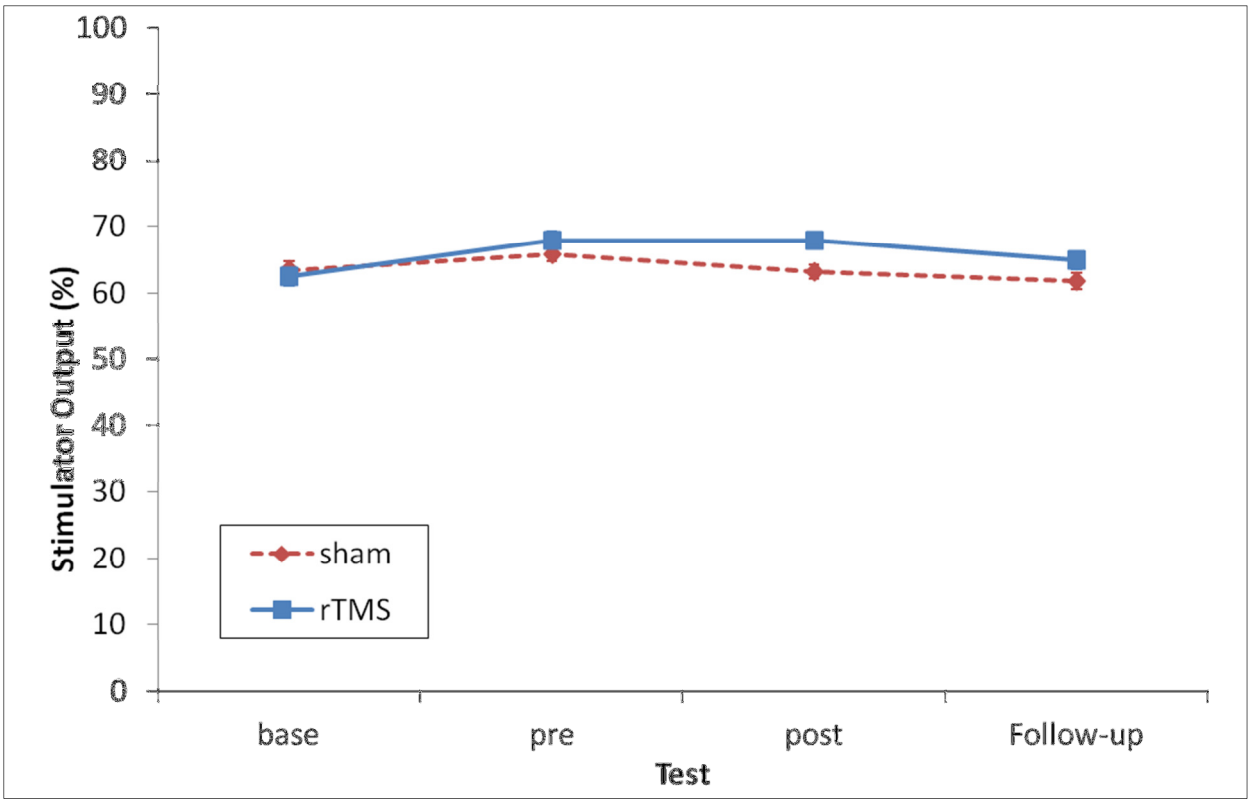

Figure 4: Motor threshold**:** mean motor thresholds for sham group (red dotted line) and rTMS group (solid blue line) at baseline, pre-test post-test and follow-up times.

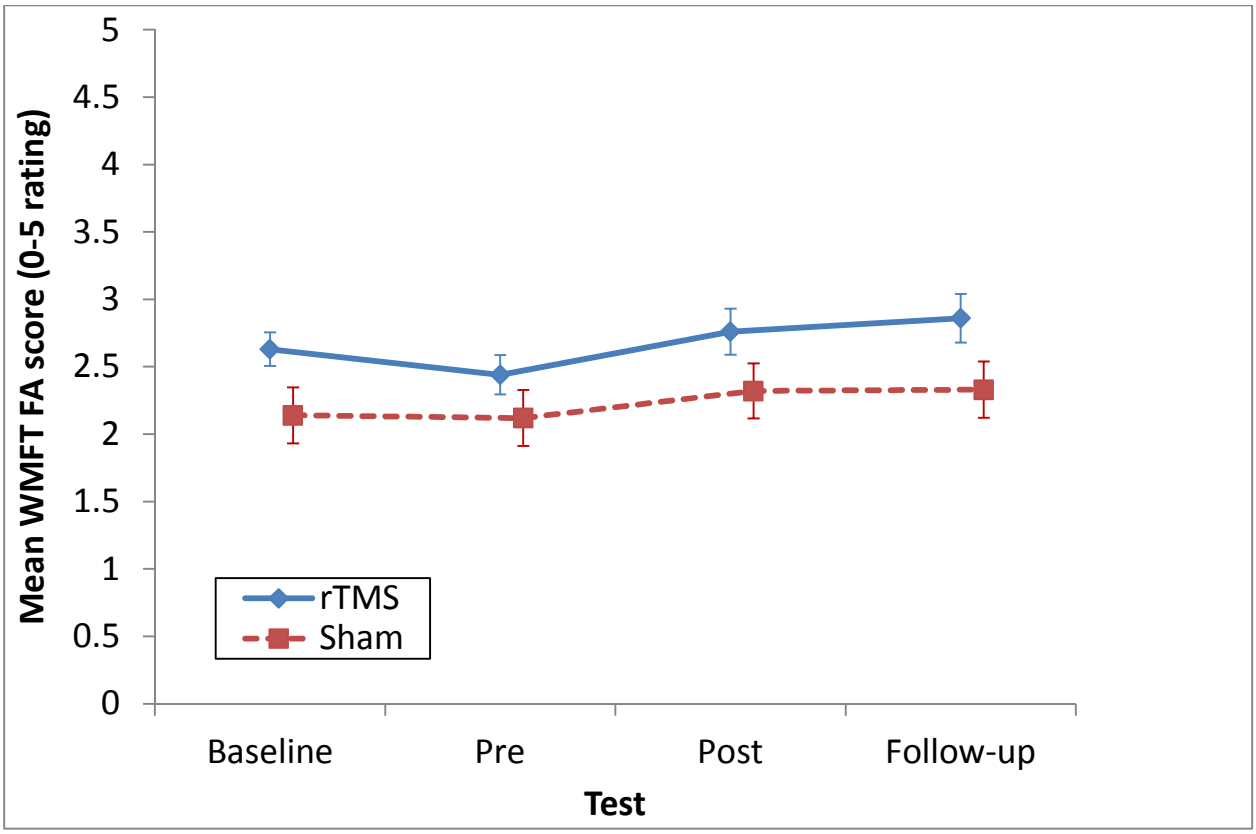

Figure 5. WMFT mean FA ratings: WMFT mean functional ability scores for rTMS and sham across each test time. (fixed n=7)

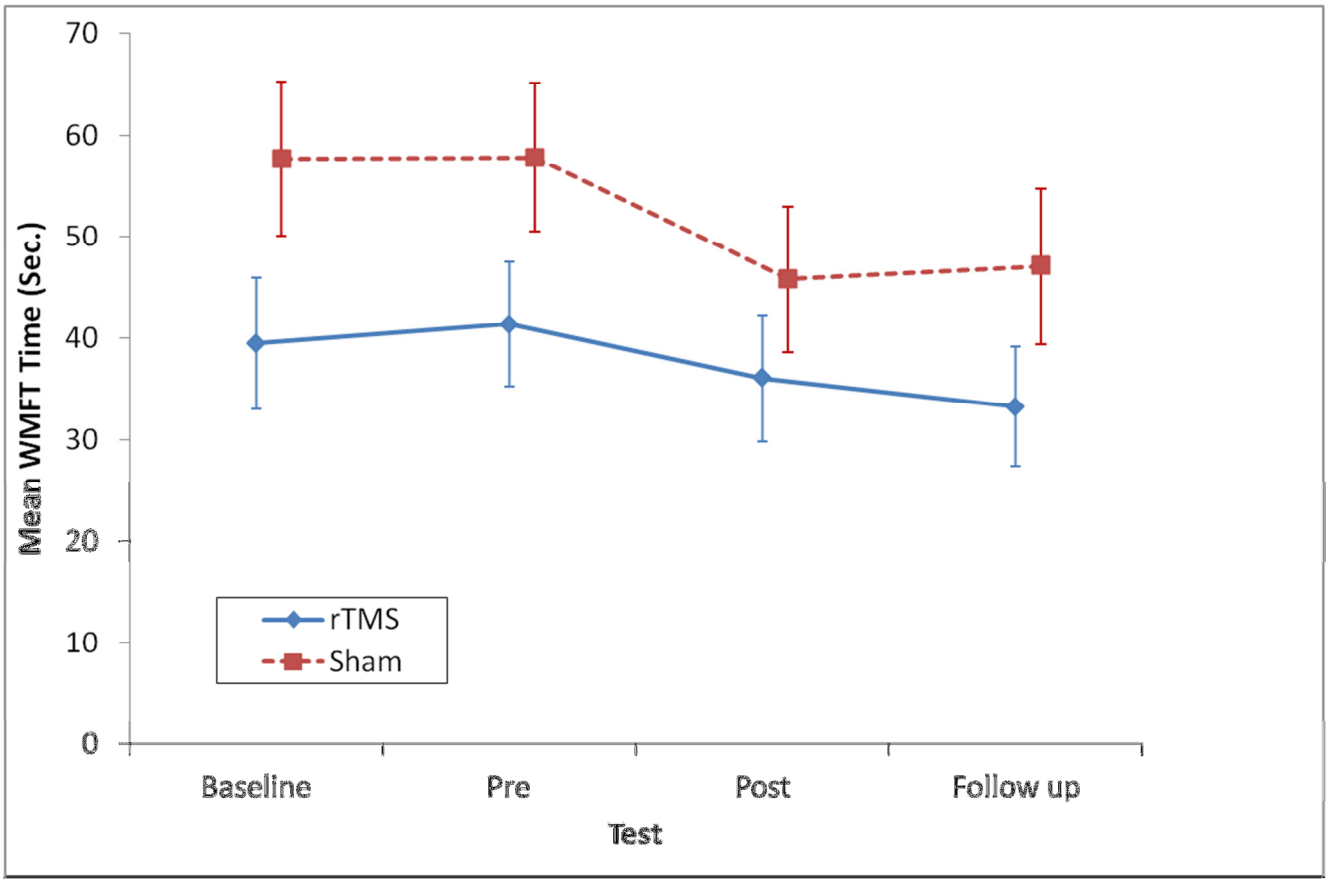

Figure 6. WMFT mean affected time: WMFT mean time of the affected upper extremity for rTMS group (solid blue line) and sham group (dotted red line) at baseline, pre-test, post-test and follow-up times.

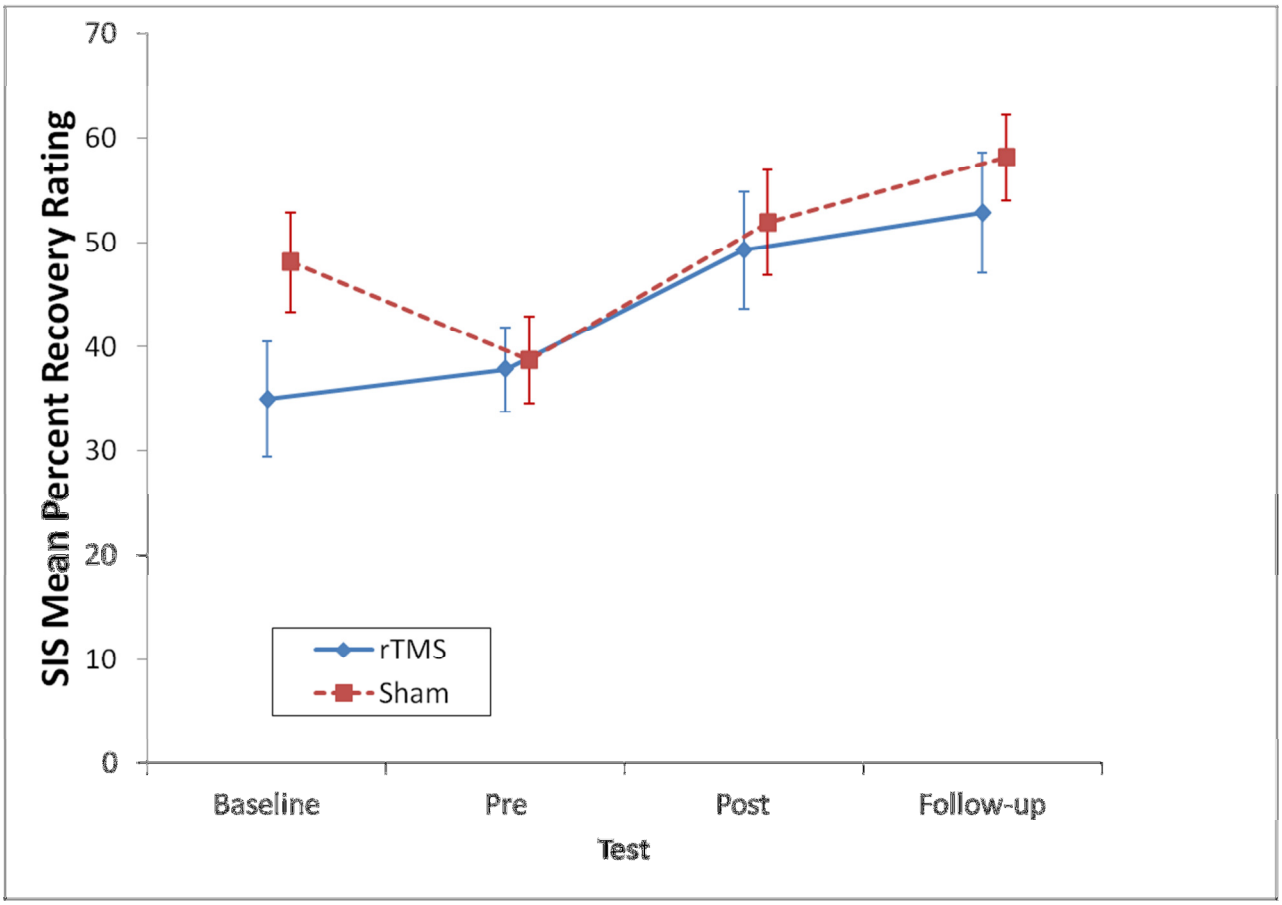

Figure 7. SIS mean percent recovery: SIS mean percent recovery scores for rTMS (solid blue line) and sham (dotted red line) at baseline, pre-test, post-test, and follow-up times.

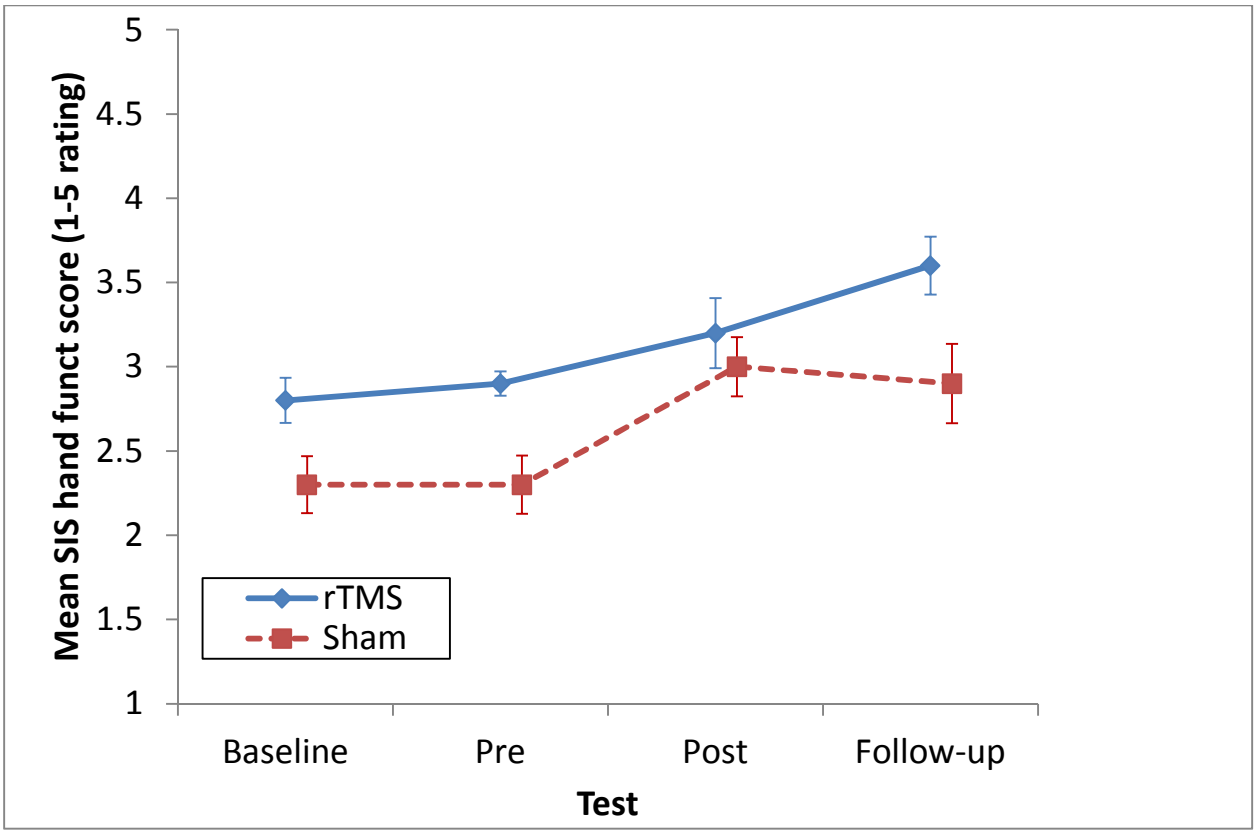

Figure 8. Mean SIS hand functioning: Mean SIS hand functioning scores for rTMS (solid blue line) and sham (dotted red line) groups at baseline, pre-test, post-test, and follow-up times.

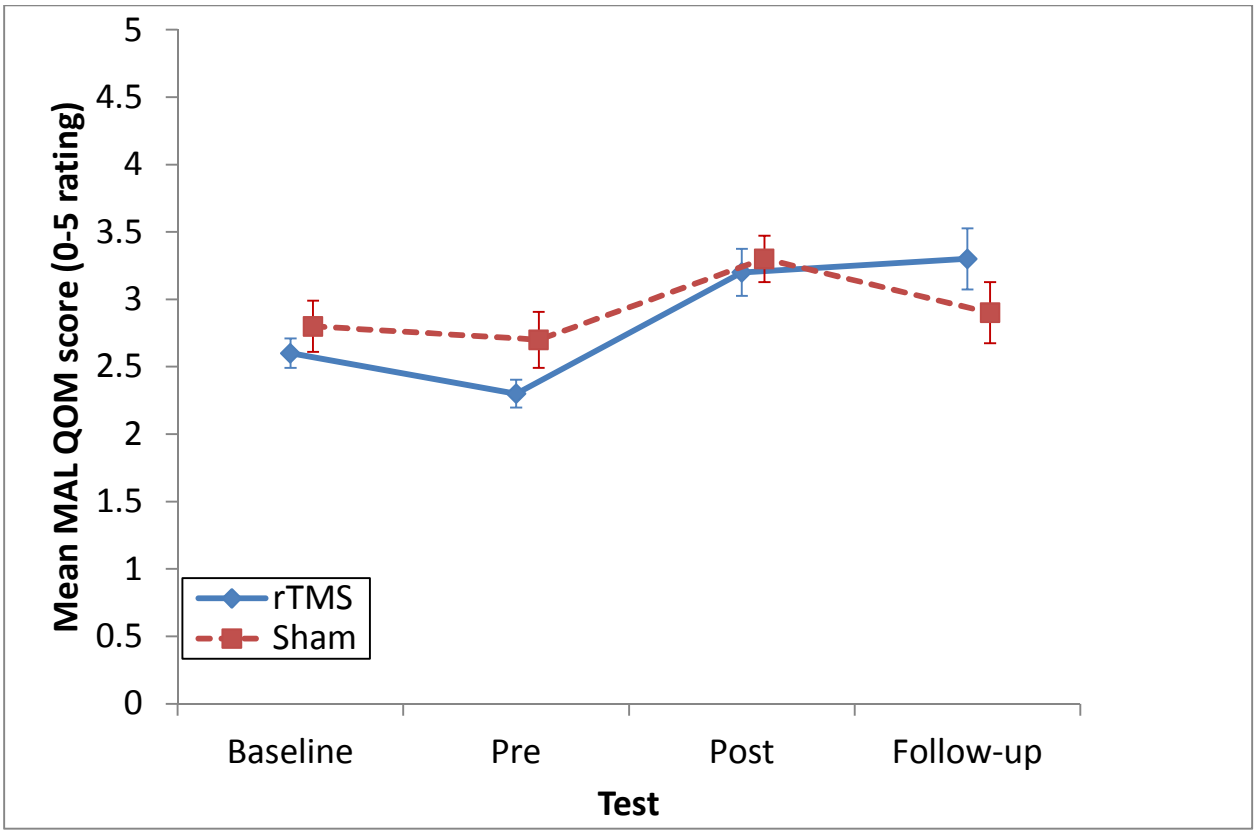

Figure 9. Mean MAL-QOM: Mean MAL- quality of movement scores for rTMS (solid blue line) and sham (dotted red line) at baseline, pre-test, post-test, and follow-up time.

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