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Effects of Different Doses of Low Frequency rTMS on Motor Corticospinal Excitability

Shailesh S. Kantak[1,2]*, Beth E. Fisher[1,2], Katherine J. Sullivan[1] and Carolee J. Winstein[1,3]

[1]*Motor Behavior and Neurorehabilitation laboratory, Division of Biokinesiology and Physical Therapy, University of Southern California, 1540 E. Alcazar Street, CHP 155, Los Angeles, California 90089, USA*
[2]*Neuroplasticity and Imaging Laboratory, Division of Biokinesiology and Physical Therapy, University of Southern California, 1540 E. Alcazar Street, CHP 155, Los Angeles, California 90089, USA*
[3]*Department of Neurology, Keck School of Medicine, University of Southern California, USA*

Abstract

Low frequency (1Hz) repetitive transcranial magnetic simulation (TMS) is known to reduce motor corticospinal excitability. The purpose of this study was to systematically investigate the effects of different intensities and durations of LF-rTMS on measures of motor cortical excitability and inhibition, while trying to minimize sources of variability that affect corticospinal excitability. 9 non-disabled young adults were recruited and screened for contraindications to TMS. We employed a repeated measures design to investigate the effect of the following four intensity-duration combinations (doses) on motor corticospinal excitability: 1) subthreshold intensity (90%Resting Motor Threshold (RMT)) for 10 minutes, 2) subthreshold intensity (90%RMT) for 20 minutes, 3) suprathreshold intensity (110%RMT) for 10 minutes and 4) suprathreshold intensity (110%RMT) for 20 minutes. Each rTMS dose was administered at 4 different sessions separated by at least 7 days. Changes in the motor corticospinal excitability and inhibition were measured using 1) MEP amplitude evoked by 120% RMT at rest and during active contraction and 2) cortical silent period. 1Hz rTMS applied at suprathreshold intensity (110% RMT) reduced corticospinal excitability at rest, irrespective of the duration of stimulation. In contrast, subthresold 1Hz rTMS significantly decreased corticospinal excitability at rest only when applied for a longer duration (20 min compared to 10 min).Subthreshold rTMS when applied for 10 min induced cortical inhibition as evidenced by a significant lengthening of the silent period. Down regulation of corticospinal excitability is dose-dependent with supra-threshold 1Hz rTMS more effective, even with a shorter duration compared with a longer duration of stimulation. Further, our study while not confirmatory, suggests that different doses of 1Hz rTMS may affect excitatory and inhibitory circuits differently within the motor cortex.

Introduction

Low Frequency (1 Hz) repetitive transcranial magnetic stimulation (LFrTMS/ 1Hz rTMS) is a useful method to study brain-behavior relationships by modulating cortical excitability. In addition it is also used to influence learning [1,2] and rehabilitation in patients with neurological disorders [3,4,5,6,7,8]. 1Hz rTMS has been shown to suppress motor corticospinal excitability [9,10]. However, the suppressive effect of 1 Hz rTMS shows considerable variability across studies. Many studies have failed to show any modulation in corticospinal excitability with LFrTMS while in other studies, the reported decrease ranges in magnitude from 16% to 30% [9,11,12] and in durations from 10 minutes to 1 hour [13,14].

There are a number of factors that contribute to the observed variability in response to LFrTMS across studies. First, there are some general features of TMS methodology that result in experimental variability such as inconsistent coil position and angle. Second, inter-subject variability may arise from individual factors such as attention, age, genetics or differences in resting muscle tone [15,16,17]. Indeed, Maeda et al. [11] reported considerable inter-individual variability in the modulation of cortical responses to rTMS, [18]. Similarly, Gangitano et al. [19] identified two subpopulations of subjects who after application of rTMS exhibited different patterns of cortico-spinal modulation. One group showed a suppression of corticospinal excitability with 1Hz rTMS and an increase in corticospinal excitability after 20 Hz rTMS; while the other group showed the exact opposite pattern of modulation (increase in cortical excitability after 1Hz rTMS and decrease in cortical excitability after 20 Hz rTMS) [19].

Importantly, the specific parameters of rTMS stimulation including frequency, intensity and duration can influence the nature of its effects on corticospinal excitability. For example, 1 Hz rTMS delivered at a suprathreshold intensity (115%RMT) resulted in Motor Evoked Potential (MEP) suppression, whereas 1 Hz rTMS delivered at a subthreshold intensity (85% RMT) had no effect on MEP amplitude [20]. Other studies have reported MEP suppression following subthreshold low frequency rTMS [11,21,19,13]. Further difficulty in comparing rTMS effects across studies arises from differences in dependent measures employed to probe cortical excitability. Some studies measured MEP amplitude evoked with suprathreshold single pulse TMS, while others used input-output curves, stimulating across a range of intensity levels [11,21,19,13]. Finally, the MEPs recorded by EMG in response to the same intensity of stimulation at a particular motor cortical site can be highly variable given the fluctuations in cortical as well as spinal segmental motoneuron excitability levels [22].

The overall goal of this study was to determine an optimal intensity and duration combination (dose) of LFrTMS (1 Hz rTMS) that reliably and consistently down regulates motor cortical excitability as reflected by MEP amplitude and cortical silent period duration. It is

***Corresponding author:** Shailesh S. Kantak , University of Southern California, 1540 E. Alcazar Street, CHP 155, Los Angeles, California 90089, USA, E-mail: sskantak@gmail.com

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important that the dose-response relationship of rTMS is identified to ensure the optimal dosage for its therapeutic application. We systematically compared the effects of different 1Hz rTMS doses on motor corticospinal excitability, while minimizing the other sources of variability described. In particular, a neuronavigation system was employed to minimize the variability in coil position and angle. To minimize intersubject variability, we chose a with-in subject design to systematically compare the effects of four different LFrTMS doses on motor corticospinal excitability. Further, to reduce the variability due to diurnal factors, we standardized the time of testing. Finally, we ensured that the participants were alert during the entire testing session through frequent verbal instructions. After a small pilot study, four 1Hz rTMS doses were chosen by combining two levels of intensity (sub threshold- 90%MT and suprathreshold-110%) and two levels of duration (10 min and 20 min).

Methods

Subjects

Nine right-handed volunteers (3 men, 6 women), aged 23- 34 (mean, 26.2 ± 2.9 years) participated in the study. All participants gave written informed consent for a protocol that was approved by the Institutional Review Board of the University of Southern California. All subjects were screened for TMS safety prior to the experiment and showed no contraindication to TMS in their medical, personal or family history [23,24,25].

EMG recording

Surface EMG was recorded from the right first dorsal interosseous (FDI) muscle with disc electrodes placed in a tendon-belly arrangement over the bulk of the muscle and the metacarpo-phalangeal joint of the index finger. The EMG signal was filtered with a band pass of 1–1000 Hz, amplified and digitized at 2000 Hz. The data were graphically displayed and stored for offline analysis.

Experimental design

We employed a within-subject design in which participants underwent one of four 1Hz rTMS sessions, at least a week apart. At each session, participants received one of the following 1Hz rTMS doses (intensity-duration combinations): Sub threshold (90%MT) rTMS for 10 minutes, Sub threshold (90%MT) rTMS for 20 minutes, Suprathreshold (110%MT) rTMS for 10 minutes and Suprathreshold (110% MT) rTMS for 20 minutes. The order of the doses was counterbalanced across participants.

Measures of cortical excitability and inhibition

Motor corticospinal excitability was quantified by measuring the average peak-to-peak amplitude of motor evoked responses (MEP amplitude) to suprathreshold (120% of resting motor threshold) TMS pulses prior to and immediately after each rTMS session. MEP amplitude was measured at rest and during active contraction. Motor cortical inhibition was quantified from silent period duration.

A brain navigation system, the *Brainsight* frameless stereotaxy system, was used to precisely guide the position of the coil over the motor cortex. A sample MRI brain image was used for all participants. A three dimensional (3D) image of the cortex was reconstructed in *Brainsight* by processing a two-dimensional MR image. The neuronavigation system allowed for systematic sampling of the stimulation sites as well as accurate placement of the coil during stimulation [24]. Markers were then placed at specific anatomical landmarks on the MR image. The participant's anatomical landmarks were then coregistered with the anatomical landmarks on the MR image such that it ensured an optimal transformation between actual skin points on the participant and the skin surface of the MRI

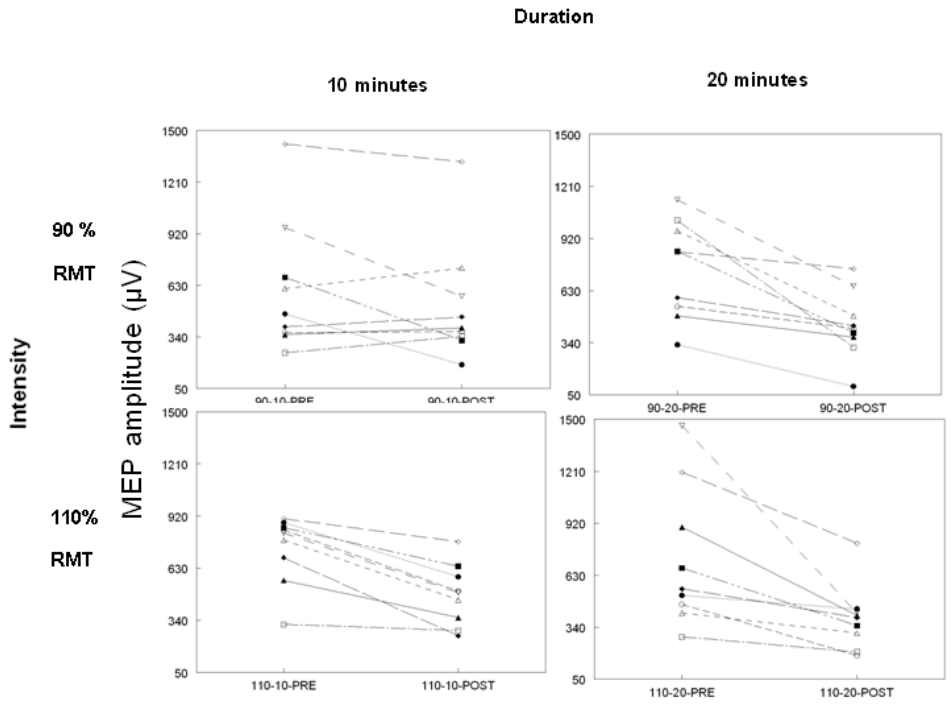

Figure 1: Individual subject data showing change in the MEP amplitude (PRE and POST) with each dose of rTMS . MEP amplitude is in μV.

reconstructed human model. After this, the TMS coil was calibrated. This allowed a real time display of the relative positions of the coil and the participant's head and brain surface, which was critical in guiding the placement of the coil over motor cortex. Of particular importance, use of the neuronavigation system helped ensure that the coil placement was maintained over the hot-spot during the entire rTMS session.

Participants were seated in a comfortable chair with the forearm supported in a prone position and hand resting on an arm support. Each session lasted approximately 2 hours. Single TMS pulses were applied over the left motor cortex with a 70mm figure of eight coil attached to Magstim Rapid Stimulator (The Magstim Company). The coil was held tangentially to the scalp with the handle pointing posteriorly away from the midline at an angle of 45°. Current induced from this position is directed approximately perpendicular to the central sulcus (Brasil-Neto, 1992; Mills, 1992). A "hot-spot" for FDI was determined as the site at which the largest MEP was obtained from FDI at lowest TMS intensity. The coil was then fixed over the hotspot for the rest of the experiment and the intensity was systematically reduced to determine the resting motor threshold (RMT). RMT is the minimum TMS intensity required to invoke MEP amplitude of at least 50μV, in 5 out of 10 consecutive trials.

Motor corticospinal excitability was assessed prior to- (pre) and immediately after (post) the rTMS protocol. Ten pulses of TMS were then applied over the hot-spot at 120%MT intensity under two conditions: resting and active, in that order. For the resting condition, the participants maintained relaxation of the FDI muscle. For the active contraction condition, the participant abducted the index finger to the transducer's force pad (Jamar hydraulic dynamometer) and pressed to a force of 10 % of the maximum voluntary force. Care was taken to avoid fatigue during the entire session. The recorded motor evoked potentials (MEPs) from FDI were amplified, digitized and stored for off-line analysis.

rTMS procedure

One Hz repetitive TMS (rTMS) was delivered to the left motor cortex with a 7 cm figure of eight coil held tangential to the scalp in a posterior-anterior direction and applied using the Magstim Rapid stimulator (The Magstim Company). At each of the four sessions separated by at least a week, every participant received one of the four doses (intensity-duration combinations) of 1Hz rTMS. The measures of corticospinal excitability and inhibition were obtained before and after each rTMS session.

Data analysis

MEPs were analyzed offline using *DataWizard*, a customized MATLAB-based program. Peak-to-peak amplitude was measured for each recorded MEP. For both resting and active conditions, mean peak-to-peak amplitude was calculated for 10 MEPs pre- and post-rTMS. Silent period (SP) was calculated beginning from the TMS pulse to the first return of EMG after the MEP [26]. Mean change from baseline (pre-rTMS) in MEP amplitude and SP was compared among the four doses using Repeated measures ANOVA. Individual paired t tests were used to compare the pre-TMS MEP amplitude and SP to post-TMS MEP amplitude and SP, respectively.

Results

Resting MEP amplitude

Figure 1 summarizes the effect of four rTMS doses on resting MEP amplitude for each participant. Out of the four 1Hz rTMS doses, three were shown to significantly downregulate resting motor cortical excitabilty (Figure 2). 1 Hz rTMS at 90%MT for 20 min ($t = 4.324$, $p = 0.003$), 110%MT for 10 ($t = 6.274$, $p < 0.001$) and 20 minutes ($t = 3.352$, $p = 0.012$) led to significant reduction in the resting MEP amplitude compared to baseline. There was no significant difference in mean MEP amplitude reduction between the three doses ($p = 0.721$). 1Hz rTMS at 90%MT applied over M1 for 10 min did not significantly affect MEP amplitude compared to baseline ($t = 1.362$, $p = 0.21$).

Active MEP amplitude

There was no significant effect of any of the rTMS doses on active

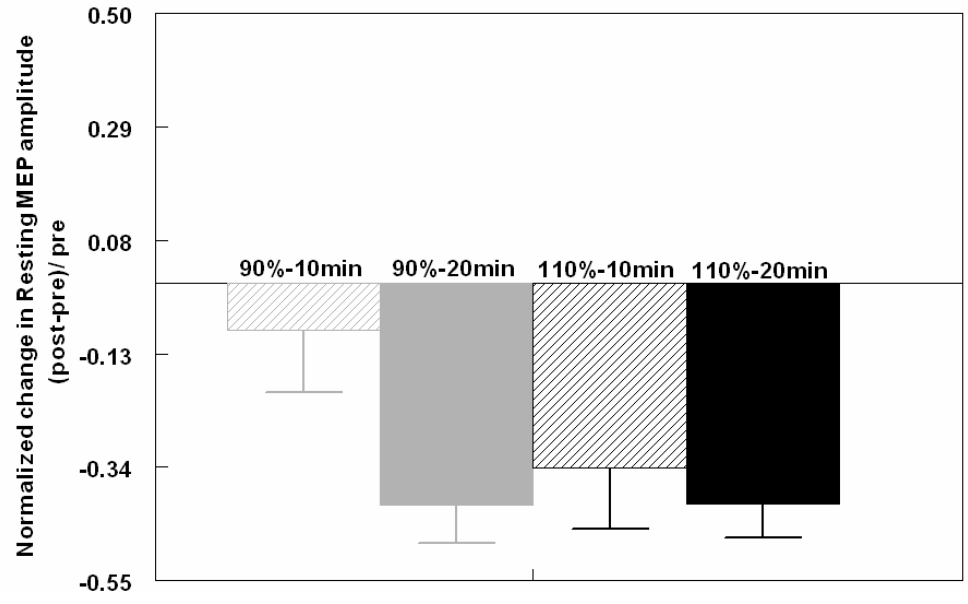

Figure 2: Mean normalized change in the peak-to-peak resting MEP amplitude following each of the 1Hz rTMS doses. The error bars represent the Standar Error of the Mean (SEM).

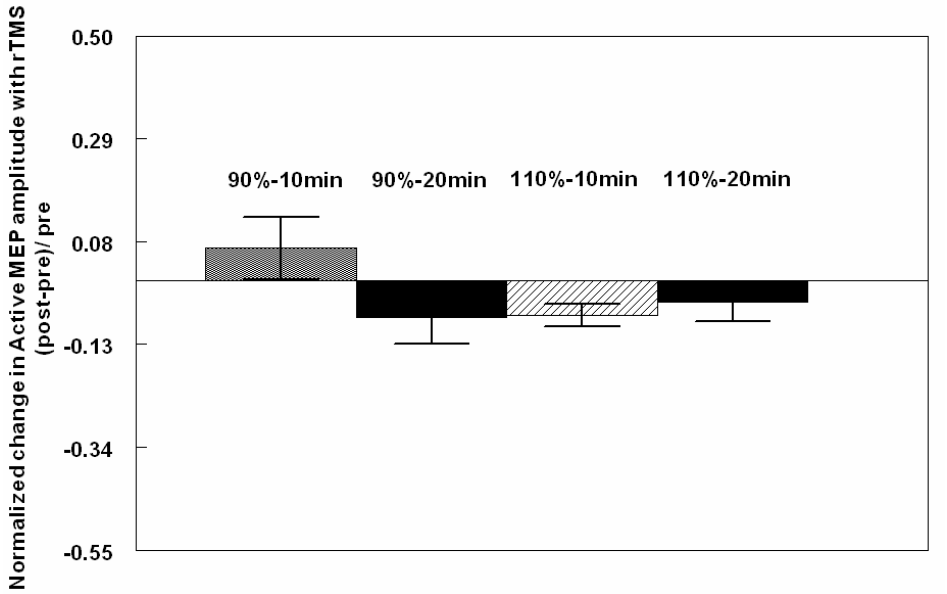

Figure 3: Mean normalized change in the peak-to-peak Active MEP amplitude following each dose of 1Hz rTMS. The error bars represent the SEM.

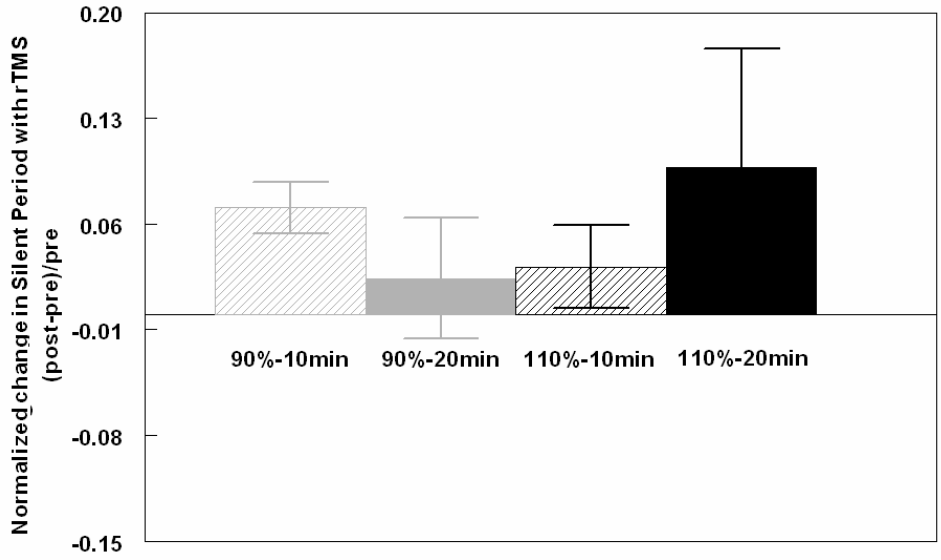

Figure 4: Mean normalized change in the Silent period (SP) duration following each dose of 1Hz rTMS. The error bars represent SEM.

MEP amplitude (90% RMT for 10 min: t= 1.003, p= 0.349; 90% RMT for 20 min: t= 1.287, p= 0.234; 110% RMT for 10 min: t= .207, p= 0.842; 110% RMT for 20 min: t= 0.54, p= 0.604; Figure 3).

Silent period

Of the four 1Hz doses, only subthreshold (90% RMT) rTMS applied for 10 min significantly lengthened the silent period (t= 3.669, p= 0.008; Figure 4). The other three doses had no significant effect on the silent period duration (90% RMT for 20 min: t=0.51, p= 0.624; 110% RMT for 10 min: t= 0.958, p= 0.37; 110% RMT for 20 min: t= 1.08, p= 0.308).

Discussion

The present study revealed three main findings. First, 1Hz rTMS applied at suprathreshold intensity (110% RMT) for 10 min or 20 min reduced corticospinal excitability at rest. Second, subthresold 1Hz rTMS decreased corticospinal excitability at rest only when applied for a longer duration (20 min compared to 10 min). Third, interestingly, subthreshold rTMS when applied for 10 min was able to induce cortical inhibition as evidenced by lengthening of the silent period.

Multiple studies have investigated the effects of intensity and

duration of 1 Hz rTMS on measures of motor cortical excitability, facilitation and inhibition [9,11,27,28,20,29,30]. The results of these are highly variable, and there is little consensus about the optimal dose to effectively downregulate cortico-spinal excitability. In this study, we systematically manipulated intensity and duration of 1 Hz rTMS to yield four doses of rTMS, and compared the response to these doses in the same individuals. In good accordance with previous studie [27,31,32], suprathreshold rTMS at 1Hz applied for 10 min or 20 min was able to reduce the resting MEP amplitude. However, there was no significant difference in the magnitude of downregulation between these two doses of suprathreshold 1Hz rTMS. In contrast, subthreshold (90% RMT) rTMS at 1 Hz was able to reduce the resting MEP amplitude only when applied for longer duration, but not when applied for shorter duration. This is consistent with some of the previous findings which indicate that it may be necessary to apply longer trains of sub threshold, 1 Hz rTMS for consistent and significant downregulation of motor corticospinal excitability [16].

Consistent with the previous literature, suprathreshold 1Hz rTMS led to significant downregulation of corticospinal excitability compared to subthreshold 1Hz rTMS, specifically for a shorter duration of stimulation. Multiple mechanisms may underlie the increased efficacy of suprathreshold rTMS effects. Suprathreshold rTMS may influence a larger pool of motor cortical neurons compared to subthreshold rTMS, thereby inducing a larger effect in the global excitability measure (MEP amplitude). Functional imaging studies have demonstrated that 1Hz suprathreshold, but not subthreshold rTMS may, through neuronal connections, influence other non-primary motor areas such as the dorsal premotor cortex thus yielding a stronger suppression of motor cortical excitability [33]. Finally, afferent feedback generated by suprathreshold stimulation-evoked muscle twitches may also suppress the motor cortical excitability and enhance the downregulating effects of suprathreshold rTMS at 1 Hz on corticospinal excitability [32].

None of the four 1Hz rTMS doses had a significant effect on MEP amplitude under the active condition (Active MEP). This finding is consistent with previous reports that did not demonstrate any change in active MEP with subthreshold [21] or suprathreshold 1Hz rTMS [28]. It is likely that tonic voluntary contraction increases the overall excitability of the corticospinal system and may mask the effects of LFrTMS on the corticospinal excitability. Therefore, it is likely that in our study, the downregulation effect of rTMS on MEP amplitude may not be detected. These findings however differ from those of [20] who demonstrated a significant decrease in active MEP following supra, but not sub-threshold 1Hz rTMS [20]. In the Fitzgerald study [20] active MEPs were recorded with TMS pulses at an intensity of 125% of Active Motor Threshold (AMT) which was the lowest intensity required to produce at least 1 MEP of 100microV in 5 trials as the subjects sustained a low intensity contaction (5-10% of MVC). Further, if AMT changed in individual subjects following rTMS, post rTMS measures were acquired with this new AMT. In contrast, in our study, stimulation intensity for the active condition was unvarying at 120% of the pre-rTMS *resting* motor threshold (RMT) both before and after rTMS. This may have resulted in relatively higher stimulation intensities for MEP recording compared to those used in the Fitzgerald study [20] since RMT is typically higher that AMT. It is likely that relatively higher intensity of stimulation in our study may have masked the reduced corticospinal excitability in active contraction condition. These differences in methods between Fitzgerald [20] and our study may likely contribute to the differences in the findings between the two studies. Measurement of motor corticospinal excitability at a single intensity (120% MT) may limit the generalization of these findings. It is likely that the differences between the effects of the four doses may emerge when tested at other intensities e.g using an input-output curve. Nevertheless, the current findings highlight a dose-dependent response of motor corticopsinal excitability to 1 Hz rTMS.

A rather surprising finding of our study was that only subthreshold 1Hz rTMS applied for shorter duration(10 min) lengthened silent period (SP). There was no significant change in SP duration with remaining rTMS doses. Daskalakis et al 2006 demonstrated an increase in SP duration with subthreshold (90%RMT) for 15 min [34]. In contrast, several others did not show an effect of subthreshold 1 Hz rTMS on SP duration [28,20,35]. Of interest is the finding that the change in SP duration was the largest following 20 min application of suprathreshold 1 Hz rTMS. However, given the smaller sample size in our study, it is likely that this biological effect may reach statistical significance with a larger sample. One of our most intriuging findings was that a 10 min dose of subthreshold 1 Hz rTMS did not significantly affect the resting MEP amplitude, but significantly lengthened SP. This finding supports previous observations that imply that rTMS may produce different effects on MEPs and SPs. MEP amplitude is a global measure of motor corticospinal excitability, while SP is predominantly mediated by GABA-B mediated inhibitory mechanisms. Our current findings, together with previous literature suggest that different doses of 1 Hz rTMS (intensity and duration) may distinctly affect activity within multiple excitatory and inhibitory circuits of the motor cortex. Suprathreshold 1 Hz rTMS and subthreshold 1 Hz rTMS for longer durations (20 min) may lead to reduction in the global excitability without significantly affecting the GABA-B mediated inhibition. In contrast, it is likely that subthreshold 1Hz rTMS for 10 min increase GABA-B mediated inhibition, but may fail to modulate the global corticospinal excitability. Further research is warranted to precisely investigate the nature of the change within specific excitatory and inhibitory circuits (e.g. Short interval cortical inhibition, Intracortical facilitation) with rTMS at different doses.

In summary, the current pilot work aimed to identify an optimal 1 Hz dose (intensity-duration combination) to down regulate motor cortical excitability. We demonstrated that the transient down regulation of corticospinal excitability with 1Hz rTMS is dose-dependent with supra-threshold rTMS being more effective, even with a shorter duration to achieve the same effect as with a longer duration of stimulation. Further, our study also suggests that different doses of 1Hz rTMS may differentially affect the excitatory and inhibitory circuits within the motor cortex. This information has significant implications for the potential use of 1Hz rTMS in research and therapy. These pilot findings may form the basis of future work to investigate the effects of different rTMS doses on specific excitatory and inhibitory neural circuits within the motor cortex. Information obtained from these studies will be critical for effective use of rTMS in research and clinical application.

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