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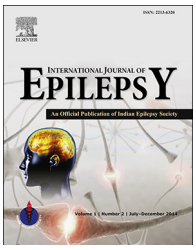

Original Article

Comparison of low frequency repetitive transcranial magnetic stimulation parameters on motor cortex excitability in normal subjects

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ABSTRACT

Background/objectives: Optimal low frequency repetitive transcranial magnetic stimulation (LF-rTMS) parameters for treating epilepsy and other brain disorders are unknown. To address this question, a systematic study of the effects of LF-rTMS frequency and intensity on cortical excitability was performed.

Methods: Using a four-period crossover design, subjects were scheduled for four LF-rTMS sessions that were at least four weeks apart. LF-rTMS was delivered as 900 pulses directed at primary motor cortex using four protocols: 0.5 Hz at 90% resting motor threshold (RMT), 0.5 Hz at 110% RMT, 1 Hz at 90% RMT, and 1 Hz at 110% RMT. Motor evoked potential (MEP) amplitude, resting motor threshold (RMT), and cortical silent period (CSP) were measured before, immediately after, and 60 min after LF-rTMS. Each of the four protocols was analyzed separately to compare baseline measurements to those after LF-rTMS.

Results: None of the four LF-rTMS protocols produced a trend or significant change in MEP amplitude, RMT, or CSP.

Conclusion: The lack of significant effect from the four LF-rTMS protocols indicates that none produced evidence for alteration of cortical excitability. The direct comparison of four LF-rTMS protocols is distinct to this investigation, as most similar studies were exploratory and studied only one or two protocols. The negative result relates only to the methods used in this investigation and does not indicate that LF-rTMS does not alter cortical excitability with other parameters. These results may be useful when designing additional investigations into the effect of LF-rTMS on epilepsy, other disorders, and cortical excitability.

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1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique for brain stimulation that can measure the state of cortical excitability and can also be used to alter the excitability. Altering cortical excitability occurs when the TMS pulses are delivered repetitively (rTMS), and the excitability is decreased in the stimulated region if the pulses rate is 1 Hz or less (low frequency). rTMS has been used as a treatment for several brain disorders, but its use in epilepsy is not well established because of mixed results.[1–6] The development of LF-rTMS for epilepsy will require additional understanding of its effects and implementation.

Optimal LF-rTMS parameters for altering cortical excitability are unknown, and this has impeded clinical research into LF-rTMS as a treatment for epilepsy, which is known to have abnormality of cortical excitability.[7] Because several studies have reported significant and discordant findings from varying LF-rTMS stimulation parameters, we sought to address this issue by systematically examining the effects of LF-rTMS frequency and intensity using a four-period crossover design.[8–12] The primary outcome measures were assessed immediately before and immediately after LF-rTMS. A secondary outcome measure was duration of effect, as assessed by measuring RMT, CSP, and MEP amplitude 60 min after LF-rTMS. The results of this investigation are intended to be useful when planning LF-rTMS treatment trials by providing a basis for selecting stimulation parameters.

2. Methods

Thirteen healthy subjects (10 women and 3 men, age 19–37 years) participated. Eleven were right-handed, and two were left-handed as assessed by the Edinburgh Handedness Inventory.[13] The University of California, Los Angeles (UCLA) Institutional Review Board approved the protocol, and informed consent was obtained from all subjects. A board-certified neurologist performed a neurological exam before and after each session. Subjects were questioned at the end of each session about adverse effects. To decrease variability, the same examiner (SS or JS) held the coil for all four sessions that each individual subject underwent.[14,15]

2.1. *Cortical excitability measurements using single-pulse TMS*

To minimize the chance of finding a false positive result due to multiple testing, analysis was restricted to three primary outcome measures: change in resting motor threshold (RMT), cortical silent period (CSP), and motor evoked potential (MEP) amplitude. Cortical excitability measurements were obtained using a Cadwell High Speed Magnetic Stimulator (Kennewick, WA, USA) and a 9 cm focal point coil. The stimulator produces single cosine wave pulses of approximately 200 microseconds duration. The round portion of the coil was held flush with the scalp such that the coil's tip was pointed anteriorly and elevated off the scalp. The ''hot spot'' for the dominant hemisphere was found by starting at the vertex and exploring the region just lateral and anterior to the vertex to locate the coil placement that reliably produced MEPs amplitudes of the highest amplitude. A clockwise current was used to stimulate the right hemisphere, while a counterclockwise current was used for the left. EMG signals were recorded using metal disk electrodes taped to the muscle belly and tendon of the dominant hand's first dorsal interosseous (FDI) muscle. A filter bandpass of 1–1000 Hz and sampling rate of 1000 Hz were used. The data were digitally displayed and stored in 500 millisecond samples for later analysis (Labview, National Instruments). To assess muscle activity preceding the TMS pulse, 100 milliseconds of EMG was recorded prior to the TMS pulse in addition to 400 milliseconds after each pulse. Single-pulse TMS was administered using pulses separated by 5–10 seconds.

Each session began with single-pulse TMS that was applied to the dominant hemisphere to determine the scalp location producing the most reliable and highest amplitude MEP for the FDI (also known as the ''hot spot''). This scalp location that was used for all cortical excitability measurements for the remainder of the session. The location and orientation of the coil with respect to the head when the hot spot was found were carefully marked on a tight-fitting elastic swim cap worn by the subject.

For each subject, four separate TMS sessions were scheduled at least four weeks apart. Within each session, dominant hemisphere cortical excitability was measured: (1) before LF-rTMS (Pre), (2) immediately after LF-rTMS (Post), and (3) 60 min after LF-rTMS (60 min). Cortical excitability was evaluated using RMT, MEP amplitude, and CSP, measured in fixed order.

To determine the RMT, the TMS intensity was reduced in step-wise decrements of 2% to find the intensity that produced an MEP of at least 50 μV peak-to-peak amplitude for at least 5 of 10 stimulations. If the last 2% decrement was below RMT, the stimulator output was increased by 1% to determine if the intermediate intensity was the RMT.

To determine the MEP amplitude, 20 MEPs were acquired from the FDI with the muscle at rest using an intensity of 120% RMT. The average amplitude of the 20 MEPs was calculated. If muscle activity was present during the 100 ms preceding the TMS pulse, that MEP was discarded and an additional MEP was acquired in its place.

To determine the CSP duration, ten CSPs were recorded, and the average duration of the 10 CSPs was calculated. Each CSP was obtained using an intensity of 120% RMT while the dominant hand FDI was isometrically contracting at 10% maximum voluntary contraction. Prior to administering TMS pulses for CSP acquisition, subjects pinched a partially inflated sphygmomanometer with maximal force between the index finger and thumb with the index finger abducting against the thumb to activate the FDI. The sphygmomanometer reading for maximal force was recorded. During the CSP acquisition, subjects watched the sphygmomanometer dial and held the pinch at 10% of maximal force.

The MEP and CSP data were analyzed off-line with a modular MATLAB (Mathworks, MA) software data analysis tool, dataWizard (version 0.5.1, A.D.W., UCLA) and individually verified by visual inspection by the same investigator. The MEP

amplitude for each tracing was the voltage difference between the peak and trough of each MEP. The CSP duration was measured from the MEP onset to the sustained reappearance of rectified, integrated EMG activity of at least 20 μV amplitude.

2.2. LF-rTMS

LF-rTMS was performed using a Magstim Super Rapid biphasic stimulator (current induced postero-anterior followed by antero-posterior) with a rise of time of approximately 80 μs and a total pulse duration of 250 μs via an air-cooled figure-of-8 coil with an outside diameter of 7 cm per wing (The Magstim Company Ltd, Wales, UK). The point of intersection of the figure-of-8 coil was placed against the skull, and the coil was held at a 45-degree angle to the sagittal plane with the handle oriented posterolaterally.[16]

Using a four-period crossover (Latin square) design, subjects underwent four LF-rTMS sessions at least four weeks apart. At each session, 900 pulses were directed at the dominant primary motor cortex using one of four LF-rTMS protocols: A) 0.5 Hz at 90% RMT, B) 0.5 Hz at 110% RMT, C) 1 Hz at 90% RMT, and D) 1 Hz at 110% RMT. Subjects were assigned to one of four groups. The group to which the subject was assigned determined the order in which the individual underwent the different LF-rTMS protocols, A–D:

Group 1: First A, then B, then C, then D.
Group 2: First B, then C, then D, then A.
Group 3: First C, then D, then A, then B.
Group 4: First D, then A, then B, then C.

The first subject was assigned to Group 1, the second to Group 2, and so on. Because of dropouts, some subjects were assigned to a group out of order in attempt to balance the number of subjects in each group.

2.3. Statistical analysis

Values for RMT, MEP amplitude, and CSP were obtained at baseline (Pre), immediately after LF-rTMS (Post) and 60 min after LF-rTMS (60 min). For analysis of data from all four periods, each of the four LF-rTMS protocols was analyzed separately using paired *t*-tests to determine whether a significant change in RMT, CSP, and MEP amplitude occurred immediately after (Pre compared to Post) or 60 min after (Pre compared to 60 min) LF-rTMS. Due to a high drop out rate, analyses comparing four different LF-rTMS protocols were not done to avoid unknown biases from missing data.

3. Results

3.1. Effect of LF-rTMS on RMT, MEP amplitude, and CSP

Of 13 subjects, seven completed all four sessions, one completed three, one completed two, and four completed one. Nine underwent protocol A, ten underwent B, nine underwent C, and nine underwent D, so each protocol had results for at least 9 subjects. No LF-rTMS protocol produced a significant change in RMT, CSP, or MEP amplitude immediately after or 60 min after LF-rTMS. In addition, no LF-rTMS protocol produced an obvious trend.

3.2. Dropouts and adverse effects

All subjects had a normal neurological exam before and after TMS. Six subjects dropped out over the course of the study. Two subjects were lost to follow-up over the course of the several-month study duration. Four subjects experienced intolerant adverse effects that caused them to drop out of the study. In two of these subjects, the adverse effects were reported at the TMS session. One subject was at the beginning of his second TMS session when he reported nausea during the single-pulse TMS testing that preceded LF-rTMS. The other subject reported discomfort from stimulations after completing the single-pulse TMS testing immediately after LF-rTMS. In two subjects, adverse effect reporting was delayed by days to weeks. Two days after the first TMS session with protocol A, one subject reported difficulty concentrating and feeling dizzy for 24 h. The other subject was contacted two weeks after her third TMS session (protocol B) and reported headaches ever since that session ended.

The two common adverse effects did not cause subjects to exit the study. The most frequent complaint was discomfort from the tight-fitting swimming cap. The second most common complaint was transient neck stiffness due to muscle strain from holding their heads still throughout TMS testing.

4. Discussion

Numerous investigators have explored the therapeutic potential of LF-rTMS in epilepsy and other brain disorders, yet the optimal LF-rTMS parameters for reducing cortical excitability remain unknown. Published studies have assessed the effects of LF-rTMS on cortical excitability and inhibition. Most directed LF-rTMS at primary motor cortex and measured effects on ipsilateral motor cortex excitatory and inhibitory tone by assessing RMT, CSP, MEP amplitude, intracortical inhibition (ICI), and/or intracortical facilitation (ICF). Each of these measurements has been reported to be affected by LF-rTMS in some studies and *un*affected by LF-rTMS in other studies.[1] Even studies with strikingly similar LF-rTMS protocols have had different outcomes.[7,17–19] Therefore, our findings of no LF-rTMS-induced change in MEP amplitude, RMT, or CSP align with findings in many other reports and supplement the understanding of the effect by assessing for changes in one systematic approach.

The LF-rTMS-induced change in cortical excitability that has been most likely to be reported is reduction in MEP amplitude, and this was not found in our study. In the review by Fitzgerald and colleagues, five of six studies reported no effect of subthreshold LF-rTMS on MEP amplitude, suggesting that LF-rTMS intensity may be important.[1] However, in our study, there was no significant effect or trend from subthreshold or suprathreshold LF-rTMS on MEP amplitude.

In addition to LF-rTMS frequency and intensity, there are many other factors that can influence the modulation of cortical excitability by LF-rTMS, and these factors may explain why many LF-rTMS reports appear to disagree.[20] These other

factors include: train duration, pulse configuration, pulse duration, TMS coil shape/size, device and coil manufacturer, direction of induced current, and method for stabilizing the coil placement.[21–26] Fixed factors within individual subjects also can influence the effect of LF-rTMS, and these include: skull-cortex distance, genetic factors, gender, and age. Finally, factors that fluctuate within individuals also can impact the modulatory effect of LF-rTMS, and these include: cognitive state, alertness, attention, hormones, circadian rhythms, and medications that act on the nervous system. Our systematic design was intended to minimize the impact of all of these factors and circumvent the debate raised by the discordant results in the published literature.

The lack of a significant change in our results does not necessarily indicate no effect of LF-rTMS on cortical excitability because a truly negative result requires sufficient statistical power to detect a small and relevant change. Chen and colleagues have proposed 0.38 mV as the significant effect size for mean MEP amplitude with LF-rTMS using baseline MEP amplitude 1.95 ± 1.63 mV (mean $\pm$ standard deviation) compared to 1.57 ± 1.55 mV after 0.9 Hz stimulation for 15 min.[9] Using this result, a sample size of 140 subjects would be needed for 80% power. The MEP amplitude standard deviation in our results was 0.83 mV, which is less than the result found by Chen and colleagues, and 40 subjects would be needed for 80% power to affirm that the null hypothesis is true. Prior LF-rTMS studies have included 8–20 subjects, so our study contributes to the general understanding of LF-rTMS effect size and does not necessarily suggest an absence of effect. However, it may be useful when planning additional LF-rTMS studies because it demonstrates that the effect of the parameters we choose are not sufficient to produce a significant effect.

High intrinsic variability of cortical excitability measurements within individuals and multiple statistical testing each likely contributes to the positive outcomes identified in some publications.[27,28] We found that no subject in this present study had a change in RMT or CSP with LF-rTMS that was outside of our previously published range of normal within-individual variability.[20] While cortical excitability variability can make it challenging to detect a statistically significant change, we did not appreciate a trend to suggest that a higher sample size might have brought statistical significance in this present report.

An interesting aspect of this study is a substantial dropout rate. One reason for dropouts is the long duration of this study, with some subjects lost to follow-up. Another significant issue was intolerable adverse effects, with nausea and discomfort causing two subjects to drop out during the middle of a TMS session. However, a sham stimulation exposure was not part of the protocol, so the adverse effects cannot be reliably attributed to the TMS. Similarly, the adverse effects that were present for an extended period as the participants were followed over months, including persisting headache and dizziness with difficulty concentrating, also cannot be reliably attributed to the TMS. Because of the possibility that the TMS produced these adverse effects and that the adverse effects impacted retention, future investigations comparing parameters would be best designed to include a sham stimulation group.

5. Conclusion

No LF-rTMS protocol produced a trend or significant change in MEP amplitude, RMT, or CSP. These findings are consistent with some of the other reports, while others have found LF-rTMS-induced changes in these measures. The apparent discordance in the literature is likely due to the many factors that can affect the degree of excitability modulation induced by LF-rTMS, and the use of multiple statistical testing in much of the published TMS literature may have contributed to false positive findings. This study of four LF-rTMS protocols has employed a cross-over design and more limited variables and statistical analyses to avoid the limitations of prior investigations. Over the four-week duration, this study identified LF-rTMS adverse effects that were not present immediately after stimulation, including headache, dizziness, and difficulty in concentrating, and this also adds to the understanding of LF-rTMS and its potential as a therapeutic modality.

These results do not contradict results that LF-rTMS may reduce epileptic seizure frequency, as several groups have reported.[7,29] The reported efficacy may be dependent on either a mechanism that the cortical excitability measurements do not detect or a change to cortical excitability that was not detected in our group. Furthermore, these results pertain to motor cortex only and LF-rTMS at the investigated settings may alter cortical excitability in other regions. An investigation that uses TMS with simultaneous EEG would be needed to determine this.[30] However, the results of this investigation may be useful when designing future LF-rTMS experiments and treatment trials for epilepsy. Cortical excitability has been considered as a possible biomarker for epilepsy, so consideration of the impact of LF-rTMS on motor cortex excitability may still be worthwhile when choosing stimulation parameters in future studies.[31] Investigations of LF-rTMS's effect on cortical excitability with a larger number of subjects and a control group are needed.

Conflicts of interest

All authors have none to declare.

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