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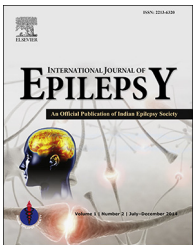

Original Article

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

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ARTICLE INFO

Article history:
Received 2 January 2015
Accepted 22 October 2015
Available online 23 April 2016

Keywords:
Low frequency repetitive transcranial magnetic stimulation
Stimulation parameters
Cortical excitability
Brain stimulation

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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http://dx.doi.org/10.1016/j.ijep.2016.02.003

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