Neuroscience Letters 457 (2009) 71–74

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Influence of 5 Hz repetitive transcranial magnetic stimulation on motor learning

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ARTICLE INFO

Article history:
Received 31 January 2009
Received in revised form 23 March 2009
Accepted 7 April 2009

Keywords:
Repetitive transcranial magnetic stimulation
Primary motor cortex
Motor training
Human

ABSTRACT

The aim of our study was to assess a possible improvement in motor learning induced by 5 Hz repetitive transcranial magnetic stimulation (rTMS) of human motor cortex. The same stimulation protocol previously enhanced perceptual learning as assessed by tactile discrimination performance when applied to the human primary somatosensory cortex. We applied 1250 pulses of 5 Hz "real" rTMS at 90% of resting motor threshold to the motor hotspot of the abductor pollicis brevis (APB) muscle in 15 healthy subjects before 1 h of motor training. Furthermore, 15 subjects received 5 Hz "sham" rTMS and served as control group. The motor task consisted of a synchronized co-contraction of the right APB and deltoid muscle. The latency between the onsets of muscle contractions was measured during training and served as a parameter for motor learning. MEP amplitudes were assessed in a subgroup of 10 subjects before and after rTMS as a parameter of corticospinal excitability. We found a significant learning effect in both groups as indicated by a reduction of latencies between the onsets of muscle contractions in the course of the training. Corticospinal excitability increased after "real", but not after "sham" rTMS. However, "real" rTMS did not significantly influence motor learning as compared to "sham" rTMS. We conclude that 5 Hz rTMS of human primary motor cortex is not able to improve motor learning in healthy subjects, which might be due to the higher complexity of motor learning as compared to perceptual learning in the tactile domain.

Transcranial magnetic stimulation (TMS) is a non-invasive tool that has been widely used to study human motor physiology during the last two decades [4]. Whereas single pulse TMS can lead to acute stimulation effects (online effects), repetitive TMS (rTMS) and theta-burst-stimulation (TBS) induce effects that outlast the duration of the stimulation (offline effects) [8,18]. Generally, these outlasting rTMS effects depend on stimulation intensity and frequency, with high frequency rTMS (≥5 Hz) leading to an increased cortical excitability [17].

It still is a matter of debate if such an increase of cortical excitability by rTMS alone is sufficient to induce an improvement in modal function. If this was the case, rTMS would offer new therapeutic options e.g. in the neurorehabilitation of patients with central nervous system lesions who often have limited cooperative abilities. In the somatosensory system, such a link between increased cortical excitability and improved function was already established: it was shown that 5 Hz rTMS applied to the primary somatosensory cortex (S1) in healthy subjects leads to improvement in tactile discrimination performance, which is accompanied by an enlargement of cortical finger representation as demonstrated by fMRI [28].

In the motor system, studies applying excitatory high frequency rTMS to the motor cortex to assess its effects on motor learning in healthy subjects yielded contradictory results [1,9], whereas in stroke patients, there is some evidence that inhibitory low frequency rTMS applied to the contralesional motor cortex or excitatory high frequency rTMS applied to the lesioned motor cortex might be able to improve motor abilities of the affected limb [6,13,14,24,25].

Therefore, the aim of the present study was to further examine the effect of high frequency rTMS on subsequent motor learning in healthy volunteers, using an established 5 Hz rTMS protocol and an established motor learning paradigm.

We tested 30 healthy subjects between 20 and 35 years of age (mean age = 26.8 years, standard deviation (S.D.): ±3.37 years). They were randomly divided into two groups, each of 15 subjects. The groups were balanced with respect to their sex and age: the "real" rTMS group consisted of 7 male and 8 female subjects, with a mean age of 27.0 years (S.D.: ±2.5 years), while the "sham" stimulation group included 9 female and 6 male subjects, with a mean age of 26.6 years (S.D.: ±4.15 years). They all gave their written informed consent. The protocol was approved by the local ethical committee of the Ruhr-University of Bochum and was performed in accordance with the Declaration of Helsinki (2008).

In the experimental session, one group received "real" rTMS and one group "sham" rTMS prior to motor learning. All participating subjects were blinded to the experimental condition. For

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[1] http://www.bergmannsheil.de/31.0.html.

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doi:10.1016/j.neulet.2009.04.015

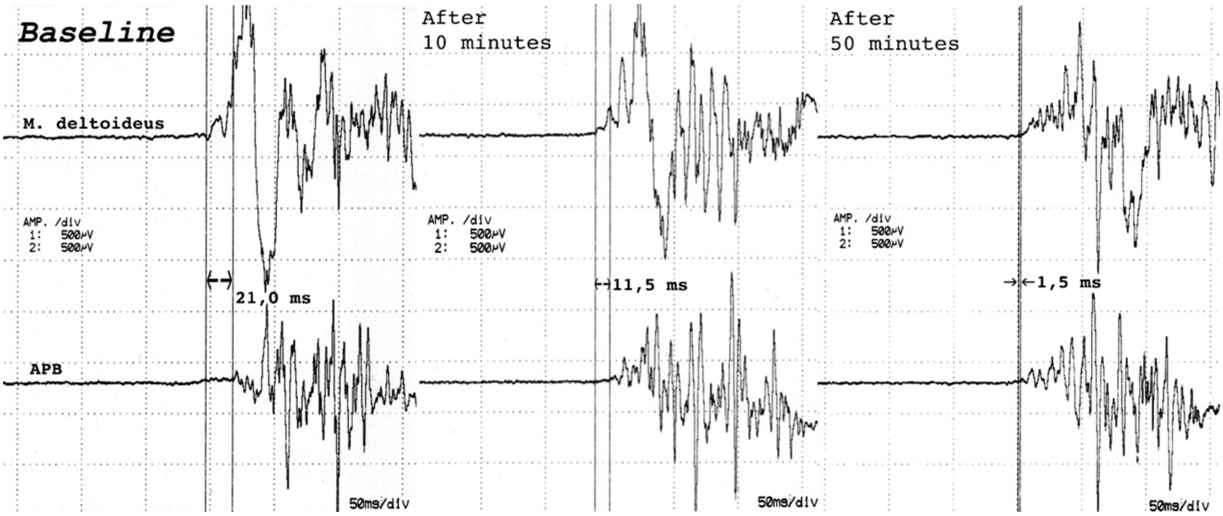

Fig. 1. Example of an original EMG registration showing the measurement of latencies between the onsets of contractions of the deltoid and the abductor pollicis brevis muscle in a single subject of the "sham" rTMS group in the course of motor training (baseline, after 10 and after 50 min). Vertical dashed lines indicate onsets of EMG signals, numbers under each arrow indicate latencies between the onsets of EMG signals in milliseconds. Note the substantial shortening of the latencies between the onsets of muscle contractions during training.

rTMS application, a Magstim Rapid stimulator (Magstim, Whitland, Dyfed, U.K.) and a figure-of-eight shaped coil (outside diameter 8.7 cm, peak magnetic field strength 2.2 T, peak electric field strength 660 V/m) was used, which predominantly stimulates neural structures under its centre. During the entire stimulation procedure the coil was held tangentially to the head in an anterior–posterior direction, with the grip pointing backwards. The participants wore a tight fitting silicone cap with a 1 cm × 1 cm grid referenced to the vertex (C_Z). The dominant hemisphere was stimulated in all subjects. Motor evoked potentials (MEP) were recorded with surface electrodes from the contralateral abductor pollicis brevis muscle (APB) using a standard electromyography (EMG) device (Neuropack 8; Nihon Kohden, Tokyo, Japan). During the entire stimulation, the subjects were seated comfortably in a chair, and muscle relaxation was continuously monitored with surface electrodes by EMG (gain 0.1 mV/D).

First, resting motor threshold (RMT) was determined with single pulse TMS to the nearest 1% of the stimulator output, and was defined as the minimum intensity which produced four MEP > 50 µV out of eight trials [22]. RMT was determined at the scalp position where suprathreshold single pulse TMS previously elicited the highest MEP amplitude (hotspot of the APB). Additionally, in a subgroup of 10 subjects (5 of them receiving "real" rTMS, 5 "sham" rTMS), motor evoked potentials (MEP) were elicited in the completely relaxed APB muscle applying single pulse TMS to the APB hotspot at 120% of the individual RMT. Peak-to-peak amplitudes of sixteen consecutive MEP were measured, and the mean MEP amplitude was calculated.

Thereafter, rTMS was applied to the APB hotspot using a "real" or "sham" stimulation protocol. The APB hotspot was chosen, since it had previously been shown that the motor training used in our present study is accompanied by plastic changes in the APB cortical representation, which we sought to enhance by rTMS [26,27]. For "real" rTMS, stimulation intensity was set at 90% of the individual RMT. 25 trains of TMS pulses were applied. A single train consisted of 50 single pulses of 5 Hz lasting 10 s, with an inter-train interval of 5 s. Five consecutive trains were grouped into one block. Between each of five blocks was a resting period of 60 s. The whole stimulation session lasted about 590 s, with a total of 1250 pulses being applied. For "sham" stimulation, the same stimulation parameters were used, except for the stimulation intensity, which was set at the lowest possible stimulation intensity (10% of maximal stimulator output), assuming that this stimulation intensity would only have local effects at the scalp, but not affect neuronal excitability in the motor cortex. Immediately after terminating "real" or "sham" rTMS, the individual RMT and the mean MEP amplitude after single pulse TMS applied at 120% of RMT were assessed again in the subgroup of 10 subjects, in order to look for possible rTMS effects on corticospinal excitability.

Subsequently, each subject started with the motor training. The aim was to learn an uncommon motor task consisting of a synchronized co-contraction of the right deltoid and APB muscle [5]. The subjects were seated in a comfortable chair in relaxed position and in a silent room sitting in the front of the EMG-monitor as visual feedback. The participants were instructed to make brisk and short movements of both muscles as synchronously as possible. Approximately three co-contractions per minute had to be performed over 60 min. After each single co-contraction, the latency between the onsets of muscle contractions was determined using EMG-monitoring with surface electrodes from both muscles (gain 0.5 mV/D). These latencies of voluntary EMG-activity allowed us to evaluate the training effect. The subjects were informed about the results of their performance and encouraged to improve it.

To evaluate the time course of learning, the mean latencies between the onsets of muscle contractions during the time intervals 0–10, 11–20, 21–30, 31–40, 41–50 and 51–60 min were calculated for each subject. For statistical analysis of motor learning, ANOVA for repeated measurements was used, with "group" ("real" versus "sham") as between-subjects factor, and "time interval" as within-subject factor. The analysis of MEP amplitudes considered "group" ("real" versus "sham") as between-subjects factor, and "MEP amplitude" (pre versus post-rTMS) as within-subject factor. Post hoc *t*-tests were used if ANOVA revealed a significant effect for one of the factors, or a significant interaction between factors. For all tests, significance was assumed at the 5% level.

The mean stimulation intensity in the "real" rTMS group was 57% of maximal stimulator output (S.D.: ±7.56%), whereas in the "sham" session the stimulation intensity was fixed at 10%.

Looking at the training effect in both groups, ANOVA for repeated measurements revealed a significant effect for the factor "time interval" ($F_{5,140}$ = 34.866, p < 0.001), but not for the factor "group" ($F_{1,28}$ = 0.032, p = 0.86) or the interaction between "time interval" and "group" ($F_{5,140}$ = 0.37, p = 0.869) (Figs. 1 and 2). Given this lack of difference between the two groups, all subjects were considered