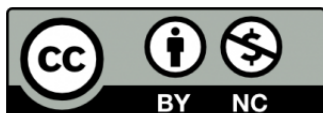




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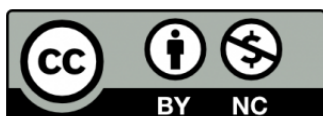
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LOW FREQUENCY (0.5Hz) rTMS OVER THE RIGHT (NON-DOMINANT) MOTOR CORTEX DOES NOT AFFECT IPSILATERAL HAND PERFORMANCE IN HEALTHY HUMANS

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Abstract – Reduction of excitability of the dominant primary motor cortex (M1) improves ipsilateral hand function in healthy subjects. In analogy, inhibition of non-dominant M1 should also improve ipsilateral performance. In order to investigate this hypothesis, we have used slow repetitive transcranial magnetic stimulation (rTMS) and the Purdue Pegboard test. Twenty-eight volunteers underwent 10 minutes of either 0.5Hz rTMS over right M1 or sham rTMS (coil perpendicular to scalp). The motor task was performed before, immediately after, and 20 minutes after rTMS. In both groups, motor performance improved significantly throughout the sessions. rTMS inhibition of the non-dominant M1 had no significant influence over ipsilateral or contralateral manual dexterity, even though the results were limited by unequal performance between groups at baseline. This is in contrast to an improvement in left hand function previously described following slow rTMS over left M1, and suggests a less prominent physiological transcallosal inhibition from right to left M1.

KEY WORDS: low-frequency transcranial magnetic stimulation, rTMS, Purdue Pegboard, primary motor cortex, M1.

A inibição do córtex motor não-dominante por meio da estimulação magnética transcraniana a 0,5Hz não interfere no desempenho manual ipsilateral de sujeitos hígidos

Resumo – A redução da excitabilidade do córtex motor primário (M1) dominante melhora o desempenho manual ipsilateral: a inibição do M1 não-dominante poderia, analogamente, aprimorar a função manual direita. Para investigar esta hipótese, utilizou-se a estimulação magnética transcraniana repetitiva (EMTr) de baixa frequência e o teste Purdue Pegboard. Submetemos 28 voluntários a 10 minutos de EMTr sobre o M1 direito (0,5 Hz) ou a EMTr placebo (bobina perpendicular ao escalpo). O teste foi executado antes, imediatamente após e 20 minutos após a EMTr. Nos dois grupos, o desempenho manual mostrou significativa melhora entre as sessões. A inibição do M1 não-dominante não influenciou significativamente a destreza motora ipsi ou contralateral, apesar da conclusão limitada pelo desempenho discrepante dos grupos na primeira sessão. Este resultado contrasta com a melhora da função manual esquerda descrita após a EMTr sobre o M1 esquerdo e sugere uma inibição transcallosa fisiológica menos intensa do M1 direito para o esquerdo.

PALAVRAS-CHAVE: estimulação magnética transcraniana de baixa frequência, EMTr, córtex motor primário, M1, Purdue Pegboard.

Transcranial magnetic stimulation, first described by Barker et al. in 1985, is a non-invasive painless technique for central nervous system stimulation. It involves a rapidly changing magnetic field, generated by a special coil placed close to the scalp, which induces a secondary and

focal electric current at the cortical level, according to Faraday's law¹. It may be used to apply single pulses of cortical stimulation, paired stimuli at variable intervals or trains of repetitive pulses at various frequencies. The first two are commonly used to study electrophysiological pa-

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rameters such as cortico-spinal tract excitability, motor evoked potentials, silent periods, central motor conduction time, transcallosal conduction². They have been increasingly used for clinical diagnostic purposes³. The latter, namely repetitive transcranial magnetic stimulation (rTMS), produces cortical modulation of excitability associated to measurable effects that usually last beyond the period of stimulation. It has been widely studied as therapy for neurological and psychiatric diseases, such as epilepsy⁴, depression^{5,6}, chronic pain⁷, stroke^{8,9}, dystonia and other movement disorders¹⁰. rTMS is also a useful tool to investigate active neuroplasticity, by altering excitability and function of the stimulated cortex or its connections¹¹. These effects are, however, determined by the frequency of stimuli. Low frequencies (slow rTMS), up to 1 Hz, promote long lasting suppression of motor cortical excitability, while high frequencies (fast rTMS), above 1 Hz, lead to transient increases in cortical excitability^{2,12}. The primary motor cortex (M1) is fundamental for short-term motor learning¹³. Functional studies with single and paired pulse TMS^{13,14} have shown changes in M1 excitability during the acquisition phase of learning complex motor skills, indicating a reorganization process over M1.

There is growing evidence for asymmetries in the role of the dominant vs. the non-dominant M1 for unimanual tasks performed with either the left or the right hand, especially among right-handers¹⁵⁻¹⁷. Hanna-Pladdy et al.¹⁸, while investigating precise coordinated finger movements in patients with damaged right or left hemisphere, showed more substantial impairment of ipsilateral deftness in those subjects that had lesion in the left hemisphere. Slow rTMS above motor threshold decreases transcallosal interhemispheric inhibition¹⁹, in an effect thought to be bidirectional, more significant from the stimulated to the non-stimulated side. Some authors suggest that there is an interhemispheric rivalry, demonstrated by improvement in performance of the ipsilateral hand (left) following 10 minutes of slow rTMS over the dominant motor cortex²⁰. The improved performance is explained by a disinhibition of the contralateral M1 (non-dominant), due to a transient decrease in transcallosal inhibition. However, most studies dealing with interhemispheric motor physiology have evaluated the influence of dominant (left) M1 over ipsilateral hand function and there are still uncertainties concerning the exact dynamics of the physiological balance between the cerebral hemispheres^{21,22}. Here we intended to investigate, then, functional consequences of manipulating the excitability of the non-dominant, right, cerebral hemisphere of normal human subjects. Specifically, we verified whether inhibition of the non-dominant M1 with repetitive transcranial magnetic stimulation (rTMS) affected ipsilateral fine motor performance in a classical

hand coordination task (Purdue Pegboard test), compared to the effect over contralateral performance.

We expected that slow rTMS would impair performance gains of the contralateral hand – it should be able to decrease cortical excitability during motor learning, competing with the practice-dependent increase in M1 excitability that usually occurs. We also hypothesized that ipsilateral hand performance would be improved by rTMS – possibly by releasing the left hemisphere from transcallosal inhibition exerted by right M1.

METHOD

Subjects

Twenty-eight healthy male volunteers, ranging in age from 18 to 29 years (mean age=21.93±2.29 years), all right-handed according to the Edinburgh Handedness Inventory²³ (Mean laterality quotient=+78.87±18.06), were recruited. Just dextrals were included because of higher heterogeneity for hemisphere dominance in sinistrals: 90–95% of the right-handers have left-hemisphere dominance while right-hemisphere dominance is found in 27% of left-handers²⁴. No subject had a history of neurological or psychiatric disease or contraindications for TMS, such as intracranial metallic or magnetic implants, pacemakers, or any other implanted devices²⁵. They gave written informed consent prior to the study and were naïve as to the task and to the TMS. The protocol was approved by the local institutional ethics committee.

Apparatus

Subjects were submitted to a fine motor learning task, using the Purdue Pegboard (Lafayette Instruments model 32020, Lafayette, IN, USA). The height of the chair and position of the pegboard were adjusted to allow unrestricted, comfortable movement of the arm over the entire surface of the pegboard. The task was performed in a quiet room, free of noise. Only one of the authors, present in the room at the moment of the task, gave instructions and recorded task scores. This investigator was blind to the group (experimental or sham) to which each subject belonged.

rTMS procedure

For the rTMS paradigm, subjects were sitting comfortably in a chair, in another quiet room. A Dantec MagLite magnetic stimulator (Skovlunde, Denmark) connected to a figure-of-eight shaped coil, placed tangentially to the subject's scalp with the handle pointing backward and laterally at an approximate angle of 45° to the midsagittal line, was used to deliver stimuli at an intensity of 80% of the subject's resting motor threshold (MT). The volunteers were instructed to maintain muscle relaxation throughout the stimulation period. The MT was defined as the lowest stimulus intensity capable of producing at least 5 visible contractions of the relaxed first *dorsal interosseus* (FDI) muscle, in a total of 10 stimuli.

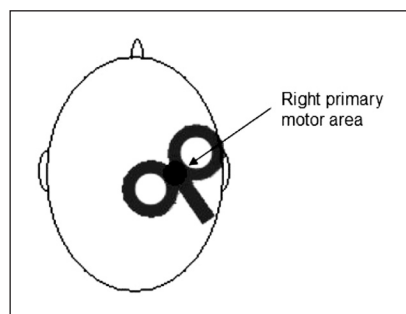


Fig 1. Site of the low frequency 0.5 Hz repetitive transcranial magnetic stimulation.

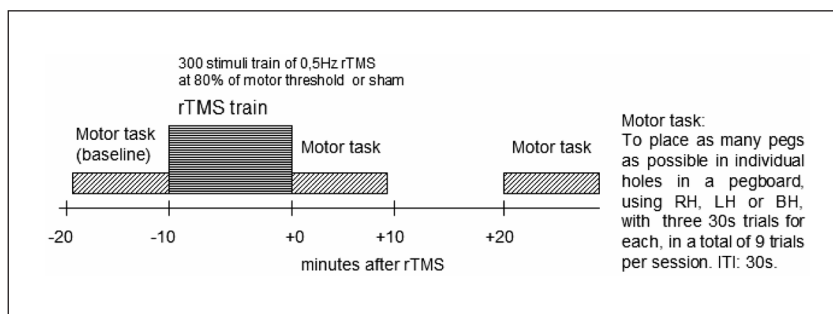


Fig 2. Experimental design - subjects' motor performance was tested in the Purdue Pegboard test before (Pre-rTMS or baseline), immediately after (+0), and 20 minutes after rTMS (+20). rTMS, repetitive transcranial magnetic stimulation; RH, right hand; LH, left hand; BH, both hands; ITI, inter-trial interval.

Table. Motor performance in the pegboard following 0.5 Hz rTMS over the right motor cortex or sham stimulation.*

Stimulation protocol	Pegboard score [means (standard deviation)]		
	Pre-rTMS (baseline)	After rTMS (+0)	20 min after rTMS (+20)
Real rTMS (n=14)			
Right hand	15.79 (1.54)	16.12 (1.52)	16.64 (1.58)
Left hand	14.33 (1.21)	14.83 (0.57)	15.21 (1.31)
Both hands	11.71 (1.03)	11.88 (1.18)	12.38 (1.12)
SHAM (n=14)			
Right hand	17.07 (1.40)	17.76 (1.76)	18.07 (1.70)
Left hand	15.05 (1.51)	15.81 (1.24)	16.00 (1.86)
Both hands	12.12 (1.31)	13.17 (1.25)	13.48 (1.75)

*See text for statistical analyses descriptions.

Experimental group

Focal 0.5 Hz rTMS was performed, according to current safety recommendations²⁵. The rTMS train consisted of 300 pulses, during 10 minutes, and was delivered to the right M1 (Fig 1), defined as the optimal scalp position to activate the FDI muscle of the contralateral hand.

Sham (Placebo) group

The coil was oriented in a perpendicular position over the scalp, for ten minutes, with a stimulus intensity of 10% of MT. This position and intensity were chosen because they maintain the "click" noise, although they are devoid of neurophysiologic effect²⁶.

Assessment of motor performance

Each subject was submitted to 3 sessions of testing in the pegboard (Fig 2), at 3 different times: before rTMS (Pre or baseline), immediately after rTMS (+0), and 20 minutes after rTMS (+20).

Each session consisted of nine 30 seconds trials of the Purdue Pegboard test, assessing fine movements of the right hand (RH), left hand (LH) and both hands (BH). RH, LH and BH were combined in a random sequence and, in each session, the sequence was repeated 3 times, i.e. the subject had to perform a total of 9 trials. The intertrial interval (ITI) was approximately 30 s,

to minimize fatigue. The procedure was carried out as follows: the subject picked individual pegs from a well using the thumb and index finger and placed them in individual holes in the pegboard. Subjects were encouraged to place as many pegs as possible and the number of pegs placed on each trial was recorded. The order of the hand tested was counterbalanced across subjects. One minute of practice was allowed for each subject before the first session, in order to make him acquainted with the experimental setup.

Statistical analysis

The mean score of the three trials for each hand during each session was calculated for each subject. These data were analyzed in a mixed-design three-way ANOVA (session × hand × group). Baseline for each condition was calculated as the mean score in the Pegboard of the three trials for each hand before rTMS. Significance level for all tests was set at $p < 0.05$. Bonferroni method for adjustment of the significance level was used where applicable.

RESULTS

None of the subjects experienced any adverse effects during or after the rTMS procedure. The means and stan-

dard deviation of the pegboard scores for each intervention are summarized, in Table, and divided by session and hand used.

We found a significant effect for the session factor ($p < 0.001$) over performance. The multiple comparisons procedure showed significant differences between all sessions, being the performance in (Pre-rTMS) worse than that at [+0], which, in turn, was worse than that at (+20) ($p < 0.004$ for all comparisons).

The hand factor (right, left or both) also influenced performance ($p < 0.001$). The multiple comparisons procedure showed significant statistical difference between the three conditions; the mean pegboard score with the right hand was better than that for the left hand, which in turn was better than that for both hands ($p < 0.001$ for all comparisons).

The group factor also had a significant influence on overall performance. It was found that the group submitted to the slow rTMS paradigm had a worse performance when compared to the sham group ($p = 0.028$). However, it was noted that baseline performance had been better in the sham group, and this was a potentially confounding factor.

Interactions between session \times group, hand \times group, session \times hand, session \times hand \times group did not exert any significant effect over the pegboard performance ($p < 0.107$ for all comparisons).

A second analysis was, then, performed: a mixed design ANOVA $2 \times 3 \times 2$ (session \times hand \times group), including the performance with the right hand in the baseline session (RH-s1) as a confounding variable.

There was a significant effect of the session factor over performance ($p = 0.033$). The multiple comparisons procedure showed that there was an increase in performance from time (+0) to (+20) ($p = 0.001$).

As in the previous analysis, we also encountered an effect of the hand factor over performance ($p = 0.042$), scores with the right hand being better than those with the left hand, which were better than when both hands were used ($p < 0.001$).

The variable RH-s1 exerted a statistically significant influence ($p < 0.001$), meaning that the difference seen in the baseline results between groups might be affecting the results in an independent manner.

After including the control for the confounding factor (RH-s1) in the analysis, the group factor no longer had a significant influence over the pegboard score, i.e., the general performance of the sham group did not significantly differ from that of the real rTMS group ($p = 0.347$).

DISCUSSION

Subjects improved their performance on the pegboard task progressively over the three sessions. This result indi-

cates that simple practice alone improves performance on the pegboard task, i.e. there is a discernible motor learning effect.

We have also shown an overall better performance with the right hand than with the left or both hands. This might be expected given the right-handedness of the subjects.

It is reasonable to assume that the task involved predominantly "short-term learning", as the subjects had no intensive practice before the experiment and it was not long enough to produce a motor learning stagnation, i.e. the pegboard score did not reach a plateau. Our main hypothesis was that 0.5Hz rTMS might hinder performance gains by impairing the already proven practice-dependent increase in M1 excitability associated with learning of new motor skills¹³. On the other hand, a decrease in transcallosal inhibition might result in performance improvements of the ipsilateral (right) hand.

Our results show, however, that slow rTMS over the right M1 did not significantly influence manual dexterity in the Purdue Pegboard test; moreover, it did not seem to affect short-term motor learning.

This result raises the question: does the concept of inter-hemispheric rivalry also apply when we analyze interference from the non-dominant cerebral hemisphere upon the dominant one?

Previous studies have shown that transcallosal inhibition of the contralateral M1 plays a more relevant role when exerted by the left, dominant, hemisphere, which inhibits the right hemisphere and prevents mirror activity and overflow of movements^{20,27,28}. Our 0.5Hz rTMS protocol may have failed to reveal changes in ipsilateral performance because the non-dominant M1 exerts a much weaker transcallosal inhibitory effect^{29,30}, especially if in association with performance of skilled movements³¹. Stronger transcallosal excitability transfer from the dominant M1 to the non-dominant M1 may be also noticed when exploring post-exercise ipsilateral facilitation of motor evoked potentials, a phenomenon that is present if the exercised hand is the right and absent if it is the left hand^{28,30}.

Our results differ from those reported by Kobayashi et al.²⁰, who reported improvement in performance of the left hand after slow rTMS over the left M1. This again seems to confirm the hypothesis that it is the left hemisphere that exerts a significant degree of inhibition upon the non-dominant (right) motor cortex.

High frequency rTMS at 80% of MT, applied to the contralateral motor cortex (right), significantly improved motor learning and facilitated complex movements of the left hand³². It could be expected that, in analogy, low fre-

quency rTMS might have the inverse effect, but no changes in performance gains were produced in our study.

Previous investigations have demonstrated an improvement in hand function of hemiparetic stroke patients when the unaffected hemisphere was inhibited by low-frequency rTMS, even when the deficits were on the right side of the body^{8,9}. It is possible that, when there is damage to the left cerebral hemisphere, the normally weak transcallosal inhibitory effects exerted by the right hemisphere become much more significant.

In summary, slow rTMS applied over the right M1 did not lead to impairments or improvements in hand dexterity in normal human volunteers, as assessed by the Purdue Pegboard test. We suggest that, in normal subjects, transcallosal inhibitory phenomena are much more prominent from the left to the right M1, but that this may change in neurological patients. It would be interesting to see if these results also hold when only left-handers are studied; the dominant hemisphere, however, would have to be ascertained by methods such as high-frequency rTMS over Broca's area, which is able to call speech arrest³³. A more detailed knowledge of inter-hemispheric relationships will be very important for the design of new therapeutic interventions for stroke and other hemispheric pathologies.

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