Interaction between finger opposition movements and aftereffects of 1Hz-rTMS on ipsilateral motor cortex

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Abstract

1Hz-repetitive transcranial magnetic stimulation (1Hz-rTMS) over ipsilateral motor cortex is able to modify up to 30 minutes the motor performance of repetitive finger opposition movements paced with a metronome at 2Hz. We investigated whether the long lasting rTMS effect on motor behaviour can be modulated by subsequent engagement of the contralateral sensorimotor system. Motor task was performed in different experimental conditions: immediately after rTMS, 30 minutes after rTMS or when real rTMS was substituted with sham rTMS. Subjects performing the motor task immediately after rTMS showed modifications in motor behaviour up to 30 minutes after rTMS. On the other hand, when real rTMS was substituted with sham stimulation or when subjects performed the motor task 30 minutes after the rTMS session, the effect was no longer present. These findings suggest that the combination of ipsilateral 1Hz-rTMS and voluntary movement is crucial to endure the effect of rTMS on the movement itself probably acting on synaptic plasticity-like mechanism. This finding might provide some useful hints for neurorehabilitation protocols.
Introduction

In the last years repetitive transcranial magnetic stimulation (rTMS) has been extensively used to better understand the physiopathology of movement and explore therapeutic opportunities in a variety of conditions. When TMS is applied in trains of multiple stimuli (rTMS), cortical excitability can be modified in a sustained fashion outlasting the repetitive stimulation. Fast rTMS (frequency >1Hz) tends to increase, whereas slow rTMS (frequency ≤ 1Hz) tends to decrease motor cortical excitability (Abbruzzese et al. 2002, Siebner and Rothwell 2003, Ridding and Rothwell 2007).

Long lasting effects of rTMS probably involve changes in the effectiveness of synapses between cortical neurons (long term depression, LTD, and long term potentiation, LTP, of synaptic connections) (Huang et al., 2005; Lee et al., 2006; Huang et al., 2007). The aftereffects of rTMS have been demonstrated to be strictly dependent on the state of the brain when rTMS is applied. As an example, low frequency (0.1 Hz) stimulation over the arm area had no aftereffect on biceps excitability when applied in normal subjects, while it increased the excitability when the forearm was anaesthetized (Ziemann et al., 1998). The effect of 1 Hz-rTMS can be reversed if it is applied after a short period of cathodal transcranial DC stimulation (Siebner et al., 2004). Further, in a recent work, Stefan and coworkers (2006) demonstrated that prior motor training can reduce the response to subsequent facilitatory motor protocol highlighting the possibility of interaction between rTMS and natural behaviour.

It is well known that ipsilateral motor cortex (ipsiM1) plays a pivotal role in the control of movement in normal subjects (Pollok et al. 2006, Verstynen et al. 2005, Kobayashi et al. 2004, Chen et al. 1997) and that it plays an important role in motor recovery in stroke patients. Indeed, 1Hz-rTMS on ipsilateral motor cortex improved simple reaction time with the contralateral hand in patients with stroke (Mansur et al., 2005). In a recent paper, we have demonstrated that 1Hz-rTMS over ipsiM1 is able to influence the performance of sequential finger opposition movements and this effect lasted up to 30 minutes after rTMS (Avanzino et al., 2008). These long term effects might
rely on the interaction between finger movement and rTMS itself. Therefore, we decided to analyze if the long lasting effect on motor behaviour, due to 1Hz-rTMS on ipsiM1, was the consequence only of the conditioning train of rTMS or if it depended on the subsequent engagement of the contralateral sensorimotor system. To answer this question different experimental conditions were considered in which finger opposition movements were performed immediately, 30min after rTMS or when real rTMS was substituted with sham rTMS.

Material and Methods

Seven healthy subjects were recruited (3 males and 4 females, mean age 28.3 years, range 25-32 years). Subjects had no contraindication to TMS and they participated in this study after giving an informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Motor task

Subjects were seated in a comfortable chair in a quiet and darkened room. They wore a sensor-engineered glove (patent pending, number: TO2005A00368, 31/05/2005) on their right hand. The glove was based on thin and flexible conductive electrodes, one for each finger, set on a Lycra™ glove. The electrodes were connected to a customized conditioning electronic system able to amplify, record and detect the contact between thumb and another finger. Data were processed with a customized software (GAS, eTT s.r.l.) able to evaluate for each finger movement the Touch Duration (TD), computed as the contact time between thumb and another finger and the Inter Tapping Interval (ITI), defined as the time between the end of the contact of thumb and another finger and the beginning of the successive contact (Bove et al., 2007). An eyes closed paradigm was chosen to avoid possible confounding effects due to the integration of acoustic and visual information. Subjects were instructed through a video showing a finger opposition movement sequence (thumb to index, medium, ring and little fingers). Then they practiced the task and the
training ended generally within two minutes, when they were able to execute the task without errors at their own pace.

Subjects were asked to perform repetitive finger opposition movements with their right hand and to pace their movements with the tone of a metronome fixed at 2 Hz. This rate value was chosen as the most comfortable one since in a previous study it was shown that the normal subjects had a frequency during self paced finger opposition movements which was around 2 Hz (Bove et al., 2007).

Motor task consisted in the execution of the sequence lasting 1 min in which 120 finger movements were recorded and processed. All subjects underwent three different experiments in three different days separated by two weeks, according to the experimental paradigm (Figure 1). The order of the experiments was randomized.

In the first condition (BASIC) subjects were tested before (PRE) and immediately after (POST) the ipsilateral slow 1Hz-rTMS, and at 15 minutes (POST-15) and 30 minutes (POST-30) afterwards.

In the second condition (no rTMS, i.e. SHAM) the complete time course was considered, but subjects underwent a sham stimulation. Then, in the third condition (no movement i.e. REST) subjects underwent real rTMS but performed the task only before (PRE) the ipsilateral 1Hz- rTMS and 30 minutes (POST-30) after it. We asked them to maintain the dominant hand in a rest condition during both the 1Hz-rTMS session and 30min after it.

In general, at the beginning of each block, three tones were given to signal the task pacing; subjects were instructed to wait for these three tones and to start pacing their first movement with the fourth tone. Subjects were instructed to stop a sequence and to quickly re-start from the first finger of the sequence when they made errors.

**EMG recording and Cortical stimulation**

EMG was recorded bilaterally with silver disc surface electrodes placed in a tendon belly arrangement over the first dorsal interosseous (FDI) muscle. The ground electrode was placed at
the wrist. EMG signals were amplified and filtered (20 Hz to 1 kHz) with a D360 amplifier (Digitimer Limited, Welwyn Garden City, UK). The signals were sampled at 5000 Hz, digitised using a laboratory interface (Power1401, Cambridge Electronics Design, CED, Cambridge, UK) and stored on a personal computer for display and later off-line data analysis.

TMS was performed with a Magstim Rapid magnetic stimulator (Magstim Company, Whitland, Dyfed, UK) connected to a figure-of-eight coil (wing diameters of 90 mm) placed over the right hemi-scalp, with the handle pointed backward at approximately 30° to the midsagittal line. The coil was positioned over a point where the largest motor evoked potentials in the left FDI were obtained (hot spot). Resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a motor evoked potential of at least 50 µV in 5 out of 10 consecutive trials.

The slow rTMS protocol consisted of two conditioning trains of 1 Hz (1500 stimuli in total) with a stimulation intensity corresponding to 90% of RMT. Background EMG of the right FDI muscle was continuously monitored with audio speakers throughout the entire rTMS session. When subjects underwent to SHAM session the real coil was substitute with the sham one.

**Statistical analysis**

The changes in ITI and TD after rTMS (BASIC condition) were subjected to analysis of variance (ANOVA) with TIME as main factor. Then, in order to compare the BASIC condition to the other two conditions (SHAM and REST) normalised data (POST-30/ PRE) were entered in a ANOVA with factor TYPE OF EXPERIMENT (BASIC, REST and SHAM) as main factor. For all ANOVAs, the Greenhouse-Geisser method was used if necessary to correct for non-sphericity and post-hoc Tukey (LSD) tests were done for significant results to compare directly the experimental conditions. Significance for all procedures was set at a level of 0.05. All statistical analysis was conducted with SPSS 12.0 (SPSS for Windows 12.0 Chicago: SPSS; 2004). Numerical data are mean ± SEM unless otherwise stated.
Results

*BASIC* condition: effects of ipsilateral 1Hz-rTMS on unilateral finger movements

1Hz-rTMS was able to influence motor behaviour of dominant hand thus confirming previous observations (Avanzino et al., 2008). ANOVA showed that ITI significantly decreased after rTMS (TIME: F(3,18) = 5.542, p = 0.007) (Fig. 2A); post hoc tests indicated a significant difference between pre-stimulation values (PRE) and post-stimulation values (p always < 0.03). As expected, the same analysis showed a significant increase of TD after rTMS (TIME: F(3.18) = 5.385, p = 0.008) (Fig. 2B). Post hoc tests indicated a significant difference between pre-stimulation and post-stimulation values (p always <0.05).

*SHAM* and *REST* conditions

Motor performance was significantly modified 30 minutes after the stimulation only when subjects underwent a real stimulation and performed the motor task at all the intervals (immediately, after 15 and 30 minutes) following the ipsilateral 1Hz-rTMS (Fig. 3A-D). In fact, ANOVA showed a significant effect of “TYPE OF EXPERIMENT” both for ITI (F (2,12) = 9.26, p = 0.004) and TD (F (2,12) = 4.22, p = 0.04). Post hoc tests showed that the ITI of the *BASIC* experiment was different from *REST* (p=0.006) and *SHAM* (p=0.03) conditions while no difference was found between *REST* and *SHAM* (p=0.21). Similarly, for TD post hoc tests showed that *BASIC* experiment was different from *REST* (p=0.03), and *SHAM* ( p= 0.05) while *REST* and *SHAM* were not significantly different (p=0.4).

Discussion

1Hz-rTMS over ipsiM1 influenced the kinematics of metronome paced finger opposition movements reducing ITI (duration of the transition phase from a finger to the successive one of the sequence) and increasing TD (duration of the finger touching phase); notably, this effect lasted up to
30 minutes after the rTMS conditioning protocol (Avanzino et al., 2008). Conversely, when real rTMS was substituted with a sham stimulation or when subjects performed the motor task 30 minutes after the rTMS session, the effect was no longer present. These findings suggest that the long lasting rTMS effect on motor behaviour can be modulated by subsequent engagement of the contralateral sensorimotor cortex. Two recent studies demonstrated that physiological activity can influence the effectiveness of cortical plasticity in humans (Gentner et al., 2007; Huang et al., 2008). Indeed, voluntary muscle contraction performed before, during and after a theta burst stimulation (TBS), was able to interact with the aftereffects of intermittent TBS (LTP) or continuous TBS (LTD) on corticospinal excitability. More precisely, a voluntary muscle contraction immediately after continuous TBS reversed the usual effect from suppression to facilitation and enhanced the facilitatory effect of intermittent TBS (Huang et al., 2008). Conversely, contraction after 10min had no permanent effect on corticospinal excitability after continuous TBS. The Authors suggested that these phenomena occur because the ongoing neural activity in the brain interacts with synaptic plasticity-like processes in the conscious human brain.

The present study confirms and expands these findings pointing out that motor performance and ipsilateral 1Hz-rTMS strongly interact between them in enduring the rTMS aftereffects on the movement itself. However, how this phenomenon occurs is not yet known. Inhibition of ipsiM1 due to 1Hz-rTMS induces a subsequent reduction of the activity of the transcallosal inhibitory pathway removing the “functional brake” on the contralateral motor cortex (Gilio et al., 2003). Thus, this rTMS-induced changes in the ipsilateral hemisphere affects the contralateral one enhancing the relative corticospinal excitability.

Following this finding we can assume that there is an interaction between the voluntary finger movements and the aftereffects of 1Hz-rTMS on ipsiM1 and that this could be located both in the contralateral and ipsilateral motor cortices. Here two possible explanations are presented. The former deals with plasticity phenomena induced in the contralateral hemisphere. The dysinhibition of the transcallosal pathway due to 1Hz-rTMS intervention on ipsiM1 and the engagement of the
sensorimotor system induced by the execution of voluntary movement could act together in inducing a positive aftereffect on contralateral motor cortex through an Hebbian potentiation mechanism (Hebb, 1949). Conversely, the latter explanation takes into account the main involvement of the ipsiM1. Inhibitory rTMS on ipsiM1 reduces intermespheric inhibition from this cortex to the contralateral one. On the other hand, during the execution of finger movement the contralateral motor cortex inhibits the ipsilateral one through the transcallosal pathway (Duque et al., 2005). It is possible to speculate that this inhibitory effect from contralateral motor cortex reinforces the already present inhibitory effect of rTMS on ipsiM1 inducing synaptic-like processes able to cause long lasting aftereffects on motor behaviour. However, neither we can discern between these two explanations nor we can exclude that these two mechanisms act together. Moreover further studies in which cortico-spinal excitability and transcallosal inhibition are analysed together with motor behaviour parameters could be useful to provide evidences to confirm a mechanism for the improvement of motor hand performance.

In conclusions, we have demonstrated that long lasting aftereffects of ipsilateral 1Hz-rTMS on motor performance occur only if subjects perform voluntarily the movement immediately after the conditioning protocol. We think that this new finding about the interaction between ipsilateral rTMS and voluntary movements could give an important hint into the field of neurorehabilitation.

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References


Figure Legends

Figure 1. Experimental paradigm. All subjects participated in BASIC, REST and SHAM conditions. PRE, POST, POST15 and POST30 indicate the time of motor performance with respect to conditioning stimulation.

Figure 2A-B. BASIC condition: effects of ipsilateral 1Hz-rTMS on unilateral finger movements. Effect of the conditioning stimulation on ITI (A) and TD (B). Abscissa indicates the time of motor performance with respect to conditioning stimulation. Ordinate indicates the value of ITI and TD expressed in milliseconds.

Figure 3A-B-C-D. BASIC, SHAM and REST conditions. Mean and normalized ITI (A-C) and TD (B-D) values obtained in the three different conditions. Abscissa indicates the condition while ordinate indicates the mean values expressed in milliseconds + S.E. (A-B) and normalised value (POST 30/ PRE values) (C-D). Horizontal dotted line indicates when the value at POST30 is equal with the PRE value.