



Magnetic stimulation intensity modulates motor inhibition

U. Berger^a, A. Korngreen^{b,c}, I. Bar-Gad^{b,c}, A. Friedman^d, S. Wolfus^d, Y. Yeshurun^d, M. Lavidor^{a,b,e,*}

^a Department of Psychology, Bar Ilan University, Israel

^b The Gonda Brain Sciences Center, Bar Ilan University, Israel

^c Goodam Faculty of Life Sciences, Bar Ilan University, Israel

^d Department of Physics, Bar Ilan University, Israel

^e Department of Psychology, University of Hull, Hull, UK

ARTICLE INFO

Article history:

Received 3 April 2011

Received in revised form 3 September 2011

Accepted 6 September 2011

Keywords:

Repetitive transcranial magnetic

stimulation (rTMS)

Stimulation frequency

Stimulation intensity

Motor threshold (MT)

Motor evoked potentials (MEP)

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a standard tool in neuroscience research and therapy. Here we study one rTMS property that has not received adequate attention, the interaction of subthreshold intensity stimulation and low frequencies. We applied 1 Hz rTMS over the motor cortex at three intensities, 40%, 80% and 100% of the resting motor threshold (rMT), and measured cortical excitability before and after the stimulation sessions. When comparing motor evoked potential (MEP) measured from the abductor pollicis brevis (APB) muscle before and after rTMS stimulation, we found that low intensity (40% MT) stimulation significantly decreased MEP magnitude, some smaller (non-significant) inhibition was found for the 80% MT intensity and increased MEP was found for the high intensity (100% MT) stimulation. Our results indicate that when explaining the input–output relationship of motor cortex induced activation as an intensity-dependent function, there might be a need to split it into separate functions associated with separate processes mediated by different cell types such as interneurons, pyramidal neurons and others.

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Introduction

Repetitive transcranial magnetic stimulation (rTMS), which is based on Faraday's principles of electromagnetic induction, is a non-invasive method of cortical stimulation that changes the activation of the underlying neuronal tissue [2]. In an ongoing attempt to establish causal links between brain functions and observed behavior, rTMS studies complement and overcome some of the shortcomings of brain lesion and imaging studies [21]. For these and other reasons rTMS has had a profound impact on core subject areas of cognitive neuroscience such as perception, visual awareness, numerical processing and action generation to name only a few [21]. Moreover, rTMS was shown in recent years to be a potentially useful clinical tool for addressing psychiatric and neurological disorders [19,24]. Nevertheless there are at least two main areas of uncertainty regarding the way rTMS affects the underlying neuronal elements [11]. Little is known about the specific interactions between the electromagnetic field and single neuron properties such as morphology, molecular structure, and physiology [11,22]. Moreover, the effects of various rTMS parameters such as wave type, duration of treatment, coil configuration, site of action,

frequency, intensity, etc., on cortical excitability have yet to be fully mapped [18].

One rTMS parameter that has not received adequate attention is the interaction between subthreshold intensity and low frequencies. It is widely believed that low-frequency stimulation produces a decrease in cortical excitability whereas high frequency stimulation produces the opposite effect [1]. Inducing a TMS pulse over a subject's motor cortex may cause an activation of corticospinal pyramidal neurons, thus eliciting a descending volley to targeted muscles [9]. The elicited muscle activation, referred to as motor evoked potential (MEP), can be used as a measure of corticospinal neuron excitability. In addition, the recruitment curve (i.e. the growth of MEP size as a function of stimulus intensity), may indicate the involvement of inhibitory interneurons [34].

There is evidence linking the motor cortex inhibition process and TMS when applied below motor threshold (MT). In a paired-pulse paradigm, one pulse is given at MT and is large enough to elicit an MEP response. If a conditioning stimulus below MT is given 1–5 ms beforehand, suppression is evident in the test stimuli response. The opposite effect occurs (i.e. facilitation) if the conditioning stimulus is given above the MT intensity [33]. However, the effect of low intensities (below motor threshold) in low frequency stimulation rTMS has yet to be determined.

The current study thus addresses the intensity question using a 1 Hz 10 min rTMS protocol, which, at high intensities, has been extensively used in establishing structure–function relationships

* Corresponding author at: Department of Psychology, Bar Ilan University, Ramat Gan 52900, Israel. Tel.: +972 0 3 5318171; fax: +44 1482 465599.

E-mail addresses: michal.lavidor@gmail.com, M.Lavidor@hull.ac.uk (M. Lavidor).

[1]. The targeted protocol was reported to have inhibitory effects on motor [29] and cognitive functions [5,10].

The current study therefore aimed to chart low intensity, inhibitory rTMS protocols and examine the effects of very low intensity 1 Hz rTMS on motor cortex inhibition, as measured by assessment of MEP. It was predicted that a low intensity (40% MT) 10 min 1 Hz rTMS over the motor cortex representation of the contralateral left abductor pollicis brevis (APB) muscle will cause an excitation of inhibitory interneurons, leading to motor inhibition which will be visible in electromyography (EMG) recordings of the APB muscle. Furthermore, two control conditions of 80% and 100% MT stimulation over the same area should generate smaller motor inhibition (at 80% MT), or excitation (100% MT). We hypothesised the excitation is due to activation of pyramidal corticospinal neurons, thus causing an excitatory effect as reflected in EMG recordings of the APB muscle.

Methods

Subjects

Ten healthy right-handed, mean age 31.7 (SD 6.1 years) took part in the study (5 females). Right hand dominance was assessed by the Hebrew version of the Edinburgh Handedness Inventory [20], and the mean score was 90. All subjects were screened for potential TMS-related risks according to safety guidelines [32] and were free of neurological problems, without acute or chronic CNS-affecting medication. Subjects signed informed consent forms. The study was approved by the local ethics committee.

Procedure and equipment

Subjects were seated in a comfortable chair and received a short explanation about the device and protocol to reduce anxiety. A bathing cap was placed on each subject's head in order to mark the motor cortex. EMG recordings from the APB muscle were acquired with adhesive surface electrodes (Thought Technology, Montreal, Canada), using a muscle belly tendon setup. A 1 cm diameter circular ground electrode was placed on the arm, 10 cm from the wrist. The EMG signal from the APB was collected by an A.N.T (Refa 60-channel) EMG device (TMS International, Enschede, the Netherlands). The signal was bandpass filtered (20–500 Hz), with an epoch of 100 ms (beginning with the pulse) and was digitized at a sampling rate of 2 kHz, using a SAS 15 (1989) with a laptop platform. TMS was delivered using a 70 mm figure-8 coil, using a 2000 Super Rapid Magstim Magnetic stimulator (Magstim Company, Dyfed, UK).

To locate the stimulation site, i.e., the motor cortex representation of the APB, the scalp point was identified by a maximal MEP output given for a single TMS pulse, at a constant intensity of 50% machine output (MO). The coil was oriented so that the induced electrical currents flowed approximately perpendicular to the central sulcus, at a 45° angle from the mid-sagittal line. If no MEP was induced, stimulation intensity was gradually raised using 2% MO steps. The resting Motor Threshold (rMT) was defined as the minimal intensity required to elicit MEPs of 50 μ V peak-to-peak amplitude, under muscle relaxation, in 5 out of 10 consecutive trials [25].

Prior to offline stimulation, the baseline motor cortex excitability (the dependent variable) was obtained by recording elicited MEP by 20 single TMS pulses over the primary motor cortex (M1) representation of the APB (pre-rTMS measure). Then a 1 Hz stimulation was applied for 10 min over M1 at 40%, 80% or 100% of MT. After the rTMS sequence, motor cortex excitability was reassessed by twenty 0.25 Hz single TMS pulses which were obtained in an identical

fashion as the baseline to generate the post-rTMS measure. Each subject completed the experiment in 3 separate sessions, with at least a 1-week interval between the sessions. The sessions were identical except for the stimulation intensity (the independent variable). Order of application of the different intensities (40%, 80% and 100% of MT) was counterbalanced across subjects.

Results

Recorded MEPs to single pulse TMS before and after rTMS was applied (at 40%, 80% and 100% of MT) were collected for each subject. MEP analysis was done by calculating the area under the MEP curve (MEP area) for each measurement taken pre/post rTMS. The MEP areas were averaged per subject and stimulation condition. The mean MEPs were analyzed with time (before and after rTMS) and stimulation intensity (40%, 80% and 100% MT) as the within-subject variables. Representative sample traces are presented in Fig. 1.

A two-way analysis of variance with repeated measures revealed no significant main effects but a significant intensity \times time interaction, ($F(2,8)=7.48$, $p=0.018$, $\eta^2=0.68$). LSD post-hoc comparisons ($p<0.05$) revealed that motor cortex excitability decreased significantly following stimulation at 40%, and increased significantly following stimulation at 100% of MT, while no significant change was observed for the 80% MT stimulation. Excitability following 100% MT stimulation was significantly higher than excitability following the lower intensities stimulation. In addition, all conditions of baseline stimulation, before 40% MT, before 80% and before 100% MT stimulation, did not differ (Fig. 2).

Discussion

In the present study, we have recorded EMG before and after 1 Hz rTMS stimulation of the motor cortex, with three different intensity settings at 40%, 80% and 100% of resting MT. Our results indicate that low intensity rTMS evoke an inhibitory effect in the motor cortex, whereas only the 100% intensity caused an excitatory effect. Although previous studies have reported similar rTMS protocols, to the best of our knowledge, there are no other studies indicating such a differentiation in activation patterns based on stimulation intensity.

High and low intensity differentiation

In the present study, when comparing MEP measured from the APB before and after rTMS stimulation, it was found that low intensity stimulation significantly decreased MEP magnitude; the opposite effect was recorded for high intensity stimulation of 100% MT. Furthermore, the analysis found that the three averaged baseline MEP, which were measured prior to stimulation on different days, were not significantly different. The similar baseline MEP in all intensity conditions (baseline response) rules out alternative explanations related to the different testing periods.

Two types of studies lend weight to our claims. First, there are several studies that have examined 1 Hz rTMS protocols effects on MEP and found sub-threshold rTMS to be inhibitory at intensities ranging from 80% to 90% of MT [29]. Second, a number of studies have utilized the same method at high intensity 1 Hz rTMS and found a full excitatory effect or fluctuating effects [26]. Our claims are also supported by studies which tested the TMS effect in a double-pulse stimulation paradigm. In this paradigm, a pulse at a sub-threshold intensity suppresses a subsequent pulse given 1–5 ms after the first pulse at 100% MT or higher intensity. The opposite effect occurs (i.e. facilitation) if the conditioning

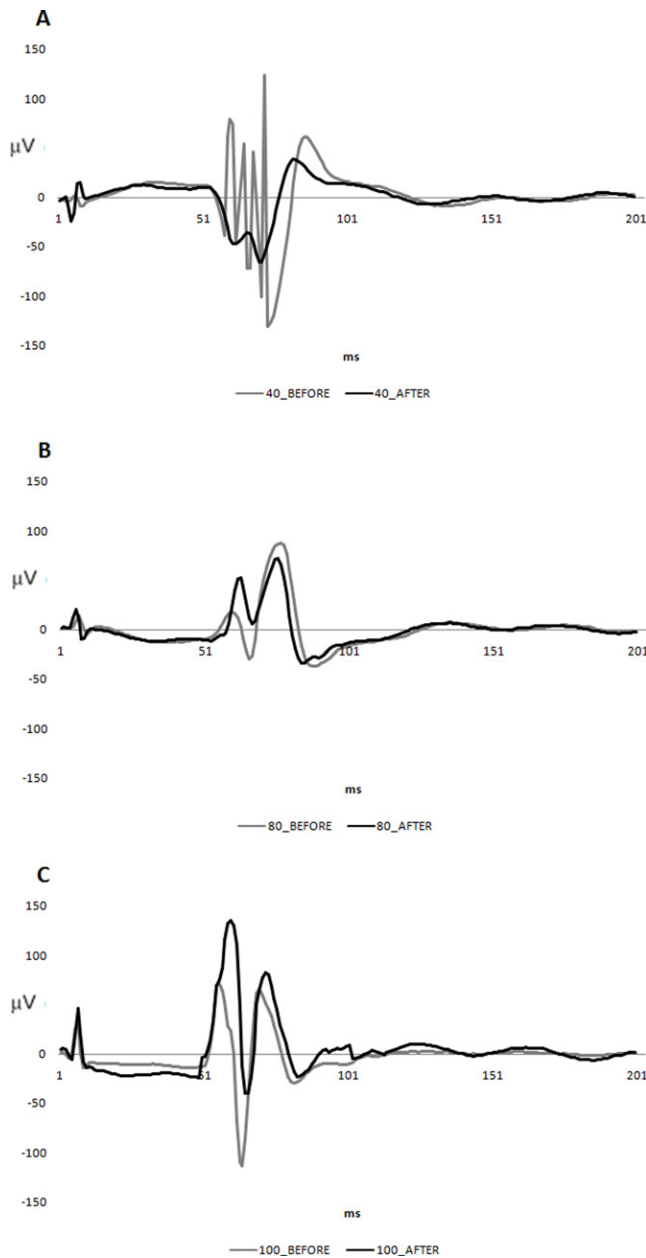


Fig. 1. TMS-induced changes in motor cortex excitability as a function of magnetic stimulation intensity in one subject. MEP following (A) TMS at 40% MT, (B) TMS at 80% MT, and (C) TMS at 100% MT, gray lines denote the excitability before rTMS sequence, black lines denote the activity after rTMS sequence.

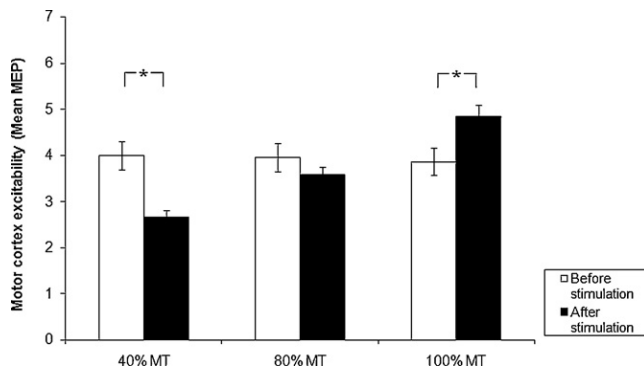


Fig. 2. Motor cortex excitability measured by mean MEP as a function of time (before or after the 1 Hz TMS) and stimulation intensity ($p < 0.05$).

stimulus is given above the MT intensity; these phenomena are known as intracortical inhibition (ICI) and intracortical facilitation, respectively [6,34].

The few previous studies that have employed very low intensities are not conclusive. One study examined the effects of 60% active MT intensity, (with 1 Hz rTMS) on corticospinal excitability and intracortical inhibition and yielded null results [31]. Similarly, Gerschlagler et al. [14] assessed three participants and intensities of 60–70% of active MT and the results were not significant. These studies, however, did not include a control condition of additional intensity and had a small sample size.

This range of results implies that the effect of stimulation intensities may depend upon the types of neurons at the targeted region. Some previous studies have indicated that low frequency and low intensity rTMS inhibitory effects may be mediated by interneuron activation [8]. Given this assumption, it seems reasonable to posit that this phenomenon may have an effective range in which it occurs. The upper bound is the pyramidal cell threshold; i.e. activation of pyramidal cells will cancel out the exclusive effect of the inhibitory interneurons. The lower bound is dependent on a combination of interneuron depth within the neuronal tissue, the specific cell morphology and other features that might impact the cell's electromagnetic conduction.

Consistent with neurological studies suggesting that motor cortex interneurons and γ -aminobutyric acid A (GABA-A) receptors are crucial components of motor inhibition [8], repetitive activation of inhibitory interneurons in the motor cortex might be summated, causing an inhibitory effect.

In line with the lack of significant change observed for the 80% level, some studies that measured MEP after medium intensity rTMS stimulation (85–90% of MT) also did not find a significant effect [11,14]. One possible explanation for this null activation might be that 80–90% of MT and RMT are the point of equilibrium for facilitation and inhibition. However, it might also be argued that low intensity is not sufficient to cause any change. Such claims of non-activation can be discounted by taking into account Komssi et al.'s [16] findings, showing that TMS can evoke an EEG response at intensities under 60% of MT. Similar support is provided by Fox et al. [12], who found undifferentiated levels of brain activation (as measured by positron-emission tomography – PET) after a 3 Hz rTMS stimulation at 75% MT and 100% MT over M1. Furthermore, Fox et al.'s [12] results indicate that stimulation at 75% MT caused an increase in local blood flow. Similar reports of blood flow increases in subthreshold magnetic stimulations have been reported using PET and fMRI [27,30].

As opposed to the agreement our results have with many previous studies testing (separately) lower and 80% MT intensities, there is a set of findings disputing our claim regarding the facilitation observed with the 100% MT. Some previous studies reported inhibitory effects for a 1 Hz rTMS protocol at an intensity of 100% MT or higher [11]. However some other authors [28] concluded that high intensities of stimulation lead to facilitative after effects on corticospinal excitability. A possible account for what seems like lack of consistency was proposed [11] and it is based on accumulative stimulation effects, that is the total number of pulses that might modulate stimulation intensity effects. Out of eight studies that match our stimulation characteristics that were reviewed by Fitzgerald et al. [11], the three which found an excitatory effect, also had the smallest number of pulses. Maeda et al. [17], for example, reported no inhibitory effect for a 90% stimulation after 240 pulses, however inhibitory effects were found after 1600 pulses with the same intensity. This account is plausible yet needs to be explicitly tested with a variety of stimulation intensities.

In the remaining paragraphs we proposed a possible dose-dependent model to account for the results of 1 Hz rTMS effects we reported.

TMS effect on inhibitory interneurons in the motor cortex

There is indirect evidence that some cortical inhibitory interneurons have greater susceptibility to activation by low intensity TMS, in comparison to excitatory cells. Previous findings suggest that certain types of inhibition are predominately mediated by low threshold cortical neurons [6,22]. Furthermore, there is strong evidence linking one inhibitory protocol (short intracortical inhibition, SICI) to more specific mechanisms within the motor cortex. The putative explanation for this link is that SICI can be elicited by low-intensity conditioning pulses that are sub-threshold for the activation of corticospinal neurons [7]. Studies show that SICI originates at the interneuronal circuit level, employing inhibitory cells, which are known to have lower firing thresholds [33]. In studies which examined subtypes and features of GABAergic interneurons, it was found that several subtypes have a lower threshold when activated by current injection [15].

The link between TMS intensity and MEP response was explained by Capaday and colleagues' theory [3,4] that claims that M1 stimulus-response (input–output) profile to intensity-graded TMS is a sigmoid function (see also [28]). It has a ceiling level at which the MEP response saturates and a floor level below which there is no measurable MEP. Our results indicate that when explaining such phenomena as a sigmoid function, it makes more sense to split the function theoretically into at least two separate functions: one for interneurons involved in inhibition and one for pyramidal neurons involved in excitation. Since low threshold interneurons have lower thresholds than excitatory neurons, repetitive activation at subthreshold intensities might only recruit interneurons. By ramping up intensity levels, more pyramidal cells will begin to fire, whereas the number of interneurons remains the same. Thus low intensity single pulses will not yield any MEP response, because no excitatory cells are activated. Nevertheless, when used in a repetitive protocol, low intensities will activate the inhibitory cells which will be summed and generate inhibition. High intensities will always be evident in single pulses and in repetitive protocols. At this stage what we suggest is only a speculative model as we do not show direct physiological data regarding the TMS effects on different cell types. The importance of cell types was established with reports of different stimulation effects for corticospinal and cortical neurons [8,28], and inhibitory GABAergic and excitatory glutamatergic neurons [23]. Also, Funke and Benali [13] recently suggested that the suppressive action of rTMS on the expression of calcium-binding proteins reflecting hypoactivity of the affected interneurons and also plasticity of the GABAergic synapse due to the reduced expression of the calcium-binding proteins. It has to be tested further if different stimulation protocols (for example, dose-dependent protocols as we suggest) may indeed lead to opposite effects.

In summary, based on previous contrasting evidence regarding TMS intensity effects, coupled with the current findings reporting significant intensity-dependent stimulation effects on motor cortical excitability, we propose a speculative model of two separate sigmoid functions, one for interneurons involved inhibition and one for pyramidal neurons involved in excitation. Future system level and cellular level studies should be conducted to further explain these observed phenomena and their possible uses.

Conflict of interests

The authors declare no competing financial interests.

Acknowledgment

This study was supported by the ISF converging Technologies grant no. 1698-07.

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