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Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms

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ABSTRACT

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that activates neurons via generation of brief pulses of high-intensity magnetic field. If these pulses are applied in a repetitive fashion (rTMS), persistent modulation of neural excitability can be achieved. The technique has proved beneficial in the treatment of a number of neurological and psychiatric conditions. However, the effect of rTMS on excitability and the other performance indicators shows a considerable degree of variability across different sessions and subjects.

The frequency of stimulation has always been considered as the main determinant of the direction of excitability modulation. However, interactions exist between frequency and several other stimulation parameters that also influence the degree of modulation. In addition, the spatial interaction of the transient electric field induced by the TMS pulse with the cortical neurons is another contributor to variability. Consideration of all of these factors is necessary in order to improve the consistency of the conditioning effect and to better understand the outcomes of investigations with rTMS. These user-controlled sources of variability are discussed against the background of the mechanisms that are believed to drive the excitability changes. The mechanism behind synaptic plasticity is commonly accepted as the driver of sustained excitability modulation for rTMS and indeed, plasticity and rTMS share many characteristics, but definitive evidence is lacking for this. It is more likely that there is a multiplicity of mechanisms behind the action of rTMS. The different mechanisms interact with each other and this will contribute to the variability of rTMS-induced excitability changes. This review investigates the links between rTMS and synaptic plasticity, describes their similarities and differences, and highlights a neglected contribution of the membrane potential.

In summary, the principal aims of this review are (i) to discuss the different experimental and subject-related factors that contribute to the variability of excitability modulation induced by rTMS, and (ii) to discuss a generalized underlying mechanism for the excitability modulation.

Abbreviations: AMPA, amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; AMT, active motor threshold; AP, anterior–posterior; Bi_{PA}, biphasic pulse with initial phase of induced current anteriorly directed (second phase posteriorly directed); Bi_{AP}, biphasic pulse with initial phase of induced current posteriorly directed (second phase anteriorly directed); BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CMAP, compound muscle action potential; cMEP, contralateral MEP; cSP, cortical silent period; CSF, cerebrospinal fluid; cTBS, continuous TBS; D–H, depolarization–hyperpolarization biphasic pulse; DTI, diffusion tensor imaging; EMG, electromyogram; EP, evoked potential; EPSP, excitatory postsynaptic potential; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; GABA-R, GABA receptor; GFAB, glial fibrillary acidic protein; H–D, hyperpolarization–depolarization biphasic pulse; HF, high frequency; ICF, intracortical facilitation; IHI, inter-hemispheric inhibition; INB, ischemic nerve block; IPSP, inhibitory post-synaptic potential; ISI, inter-stimulus interval; iMEP, ipsilateral MEP; iTBS, intermittent TBS; iTMS, TMS at I-wave periodicity; LF, low frequency; LFP, local field potential; LM, lateral-medial; LTD, long term depression; LTP, long term potentiation; M1, primary motor cortex; MEP, motor evoked potential; ML, medial–lateral; $Mono_{AP}$, monophasic pulse with induced current posteriorly directed; $Mono_{PA}$, monophasic pulse with induced current anteriorly directed; MRI, magnetic resonance imaging; *N*/*A*, non-applicable; NMDA, N-methyl-D-aspartate; NMDA-R, NMDA receptor; *N*/*S*, information not supplied; qTMS, quadripulse TMS; PA, posterior–anterior; PAS, paired associative stimulation; PBS, primed burst stimulation; PMC, premotor cortex; RDP, rate dependent plasticity; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SICF, short interval cortical facilitation; SICI, short interval cortical inhibition; STDP, spike-timing dependent plasticity; tDCS, transcranial direct current stimulation; TBS, theta burst stimulation; TMS, transcranial magnetic stimulation; V_m, transmembrane potential.

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Contents

1. Introduction

Transcranial magnetic stimulation (TMS) is a technique for non-invasive stimulation of neurons via generation of a pulse of high-intensity magnetic field by passing a brief electric current through an inductive coil. The induced current can be sufficient to cause depolarization of corticospinal tract neurons either directly at the axon hillock or indirectly via depolarization of interneurons. Single TMS pulses can depolarize neurons transiently, but when these pulses are applied repetitively—an approach known as repetitive TMS (rTMS)—cortical excitability can be increased or decreased depending on the parameters of stimulation. Trains of rTMS pulses applied at specific frequencies are able to induce persistent modulation of cortical excitability as well as of other physiological, metabolic, and behavioral measures (Bäumer et al., 2003; Chen et al., 1997; Pascual-Leone et al., 1994; Ziemann, 2004b). In addition to the "conventional" rTMS technique based on the delivery of pulses at equal inter-stimulus intervals, several "alternative" TMS protocols have been introduced. These include "patterned" protocols with more complex timings such as those based on the theta frequency and those based on combinations with other interventions such as peripheral nerve stimulation. It has not been established whether the origin of the clinical benefit of any of the rTMS schemes is as a direct or indirect consequence of the modulation of excitability. It is believed that the associated release of neuromodulators (for example, dopamine) and growth factors (for example, brain derived neurotrophic factor (BDNF)) play an important role in the mechanism of rTMS (Wassermann and Lisanby, 2001). This ability of rTMS to modulate cortical function in a persistent fashion has opened the door to the potential treatment of a variety of psychiatric and neurological disorders.

The underlying mechanisms that drive the conditioning effect of rTMS (i.e., the sustained excitability modulation) are not fully understood. This is reflected by the considerable degree of both inter-subject and inter-session variability observed in the excitability modulation induced by rTMS (Gangitano et al., 2002; Hiscock et al., 2008; Maeda et al., 2000a). Synaptic plasticity in the form of long term potentiation (LTP) and long term depression (LTD) is commonly accepted as the most likely mechanism behind the conditioning effect of rTMS and this review expands upon the basis of this belief. It is more likely that there are a number of mechanisms driving the excitability modulation and that the interactions between these mechanisms and the stimulation parameters will act as an additional source of variability. In order to gain a deeper appreciation of the scope of the different mechanisms that may be involved, it is important to comprehend the sources of variability in rTMS that are under the control of the experimenter. TMS can be delivered in a wide number of different forms and patterns. The variety of experimental parameters, such as coil geometry, stimulus amplitude, frequency and duration lead to a large number of experimental permutations and this will also contribute to the variability of the conditioning effect. The parameters that influence the degree and polarity of modulation can be divided into two principal categories—geometry (for example, TMS coil shape, orientation) and timing (for example, frequency, stimulus duration). The latter category refers to the direct influence of the timing of the stimulus pattern, while the former refers to the interaction of the spatial distribution and orientation of the induced electric field with the cortical neuroanatomy. This review aims to summarize the sources of variability of excitability modulation induced by rTMS (Section 2) against the background of the mechanisms that are believed to drive the excitability changes (Section 3).