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Low-frequency rTMS inhibitory effects in the primary motor cortex: Insights from TMS-evoked potentials

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ABSTRACT

The neuromodulatory effects of repetitive transcranial magnetic stimulation (rTMS) have been mostly investigated by peripheral motor-evoked potentials (MEPs). New TMS-compatible EEG systems allow a direct investigation of the stimulation effects through the analysis of TMS-evoked potentials (TEPs).
We investigated the effects of 1-Hz rTMS over the primary motor cortex (M1) of 15 healthy volunteers on TEP evoked by single pulse TMS over the same area. A second experiment in which rTMS was delivered over the primary visual cortex (V1) of 15 healthy volunteers was conducted to examine the spatial specificity of the effects.
Single-pulse TMS evoked four main components: P30, N45, P60 and N100. M1-rTMS resulted in a significant decrease of MEP amplitude and in a significant increase of P60 and N100 amplitude. Such effect was not presented after V1-rTMS.
1-Hz rTMS had increased the amount of inhibition following a TMS pulse, as demonstrated by the higher N100 and P60, which are supposed to originate from the GABAb-mediated inhibitory post-synaptic potentials.
Our results confirm the reliability of TMS-evoked N100 as a marker of cortical inhibition amount and provide insight into the neuromodulatory effects of 1-Hz rTMS. The present finding could be of relevance for therapeutic and diagnostic purposes.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that can produce after-effects on cortical excitability lasting 30 min or more (Ridding and Rothwell, 2007). Over the years, its use for research and therapeutic purposes has increased even though its mechanism of action is still only partially understood (Pascual-Leone et al., 1998; Ridding and Rothwell, 2007; Rossi et al., 2009). In the majority of the TMS/EMG literature, neuromodulatory effects of rTMS have been investigated by analysing motor-evoked potentials (MEPs). However, this is a complex measure reflecting excitability of the whole corticospinal pathway which can be influenced not only by excitability of cortex, but also of spinal cord (Barker et al., 1985). Nowadays, with the current development of TMS-compatible electroencephalography (EEG) systems it is possible to record the cerebral activity evoked by TMS from the entire scalp (Ilmoniemi et al., 1997). These responses, collectively termed as TMS-evoked potentials (TEPs), are unaffected by spinal excitability so they may be a more reliable measure of the response of the brain to TMS and give information about widespread effects throughout the cortex (Ilmoniemi and Kičić, 2010). Indeed, studies have shown that TEPs are sensitive to differences in intensity of stimulation and are reproducible from day to day (Casarotto et al., 2010; Lioumis et al., 2009). Given these advantages, there is a growing interest in using EEG measures during TMS to clarify the effects of stimulation protocols such as: rTMS (Helfrich et al., 2013; Van Der Werf and Paus, 2006), paired-pulse TMS (Daskalakis et al., 2008; Ferreri et al., 2010), transcranial direct current stimulation (Pellicciari et al., 2013) and paired associative stimulation (Bikmullina et al., 2009; Veniero et al., 2013).

Many studies have focused on the time-locked EEG response evoked by stimulation of the primary motor cortex (M1). This consists of a

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; MEP, motor-evoked potential; TEP, TMS-evoked potential; RMT, resting motor threshold.

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sequence of positive and negative components, usually labelled P30, N45, P60, N100 and P180 (Bender et al., 2005; Bonato et al., 2006; Ferreri et al., 2010; Komssi et al., 2002; Lioumis et al., 2009; Paus et al., 2001; Van Der Werf and Paus, 2006). Of these the N100 peak appears to be the most robust and well characterised with little clear evidence about the functional origin of the other components (Komssi and Kähkönen, 2006). Several lines of evidence suggest that the N100 reflects inhibitory processes following the TMS pulse (Bender et al., 2005; Bonnard et al., 2009; Bruckmann et al., 2012; D'Agati et al., 2013; Nikulin et al., 2003; Rogasch et al., 2013). In a simple reaction time task, the N100 is reduced in amplitude just prior to movement onset whilst the evoked MEP is increased (Nikulin et al., 2003); a similar reduction is seen in the late part of the foreperiod in a warned reaction time task (Bender et al., 2005). In both cases, the reduction was interpreted as removal of inhibition during excitatory preparation for a forthcoming movement. Bonnard et al. (2009) found that the N100 was larger during the warning period when participants were instructed to "resist" a forthcoming perturbation applied to the wrist compared with trials where the instruction was to "assist" the perturbation. At the same time, the duration of the cortical silent period in ongoing EMG activity was increased (Chen et al., 1999). Since the latter is thought to be a measure of cortical inhibition following a TMS pulse it was suggested that the increase in N100 also represented an inhibitory process primed by the instruction to "resist". Additional evidence along the same lines have been provided by some very recent studies on ADHD children (Bruckmann et al., 2012; D'Agati et al., 2013). In contrast to this, some studies found an increase in the N100 amplitude evoked by occipital TMS in conditions that presupposed enhanced arousal (Murd et al., 2010; Stamm et al., 2011).

In this study we investigated in a group of healthy volunteers the effect of an rTMS protocol (1 Hz), which usually reduces motor cortical excitability (e.g. Chen et al., 1997; Maeda et al., 2000), on the local brain activation and on the amplitude of TEPs evoked by single pulse TMS over the same area. In order to examine the spatial specificity of the effect we also tested whether applying rTMS over V1 would also affect the N100 evoked by stimulation of M1.

Methods

Participants and procedure

Fifteen right-handed healthy volunteers (seven females, mean age 25 ± 5 years) were enrolled for this experiment (experiment 1) after giving written informed consent. All participants were tested for TMS exclusion criteria (Rossi et al., 2009) and had normal or corrected-to-normal vision. The experimental procedure was approved by the Institutional Review Board of the University of Padua, and was in accordance with the Declaration of Helsinki (Sixth revision, 2008). Each participant underwent an experimental session consisting of three blocks of TMS during multichannel EEG and EMG recordings. The first and the third blocks of stimulation ("pre-rTMS" and "post-rTMS" respectively) consisted of 50 single-pulses delivered before and immediately after a 1-Hz rTMS block (Fig. 1). During the entire session participants were seated on a comfortable armchair in front of a monitor at 80 cm distance. They were asked to fixate on a white cross (6 × 6 cm) in the middle of a black screen and to keep their right arm in a relaxed position. During TMS participants wore in-ear plugs which continuously played a white noise that reproduced the specific time-varying frequencies of the TMS click, in order to mask the click and avoid possible auditory ERP responses (Massimini et al., 2005). The intensity of the white noise was adjusted for each subject by increasing the volume (always below 90 dB) until the participant was sure that s/he could no longer hear the click (Paus et al., 2001). To reduce the bone-conducted sound we used an EEG cap with a 4 mm plastic sheet that reduced the transmission of mechanical vibration produced by the coil (Esser et al., 2006; Nikouline et al., 1999).

Transcranial magnetic stimulation (TMS)

TMS was carried out using a Magstim R^2 stimulator with a 70 mm figure-of-eight coil (Magstim Company Limited, Whitland, UK), which produced a biphasic waveform with a pulse width of ~0.1 ms. The position of the coil on the scalp was functionally defined as the M1 site in which TMS evoked the largest MEPs in the relaxed first dorsal interosseous (FDI) muscle of the right hand. The coil was placed tangentially to the scalp at about 45° angle away from the midline, so that the direction of current flow in the most effective (second) phase was posterolateral–anteromedial. To ensure the same stimulation conditions during the entire experiment, coil positioning and orientation on the optimal hotspot were constantly monitored by means of the Brainsight neuronavigation system (using the ICBM152 template), coupled with a Polaris Vicra infrared camera (NDI, Waterloo, Canada). Stimulation intensity varied across the blocks of stimulation (see below) and was determined relative to the resting motor threshold (RMT), defined as the lowest TMS intensity which evoked at least five out of ten MEPs with an amplitude >50 μV peak-to-peak in the contralateral FDI at rest (Rossini et al., 1994). Single-pulses were delivered with an interstimulus interval (ISI) of 4–6 s, intensity was set at 120% RMT to obtain

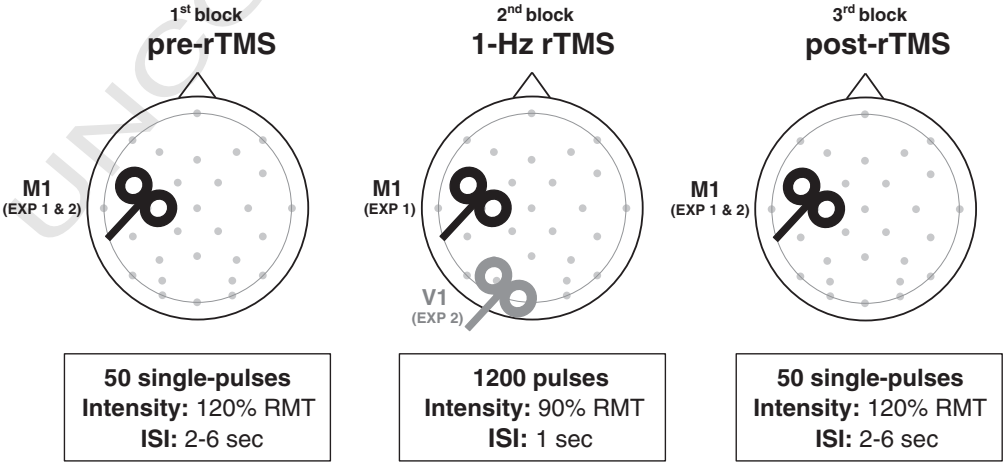

Fig. 1. Schematic representation of the experimental procedure. Each participant underwent three blocks of stimulation. In the first block (pre-rTMS), 50 TMS single pulses were delivered over the left M1. In the second block (rTMS), 20 min of rTMS at 1 Hz of frequency were delivered over the left M1 (for the fifteen participants of experiment 1) or over the left V1 (for the fifteen participants of experiment 2). In the third block (post-rTMS), 50 TMS single pulses were delivered over the left M1, immediately after the rTMS block. rTMS, repetitive transcranial magnetic stimulation; RMT, resting motor threshold; ISI, interstimulus interval.

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