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# REPETITION SUPPRESSION IN TRANSCRANIAL MAGNETIC STIMULATION-INDUCED MOTOR-EVOKED POTENTIALS IS MODULATED BY CORTICAL INHIBITION

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**Abstract—Transcranial magnetic stimulation (TMS) can be applied to modulate cortical phenomena. The modulation effect is dependent on the applied stimulation frequency. Repetition suppression (RS) has been demonstrated in the motor system using TMS with short suprathreshold 1-Hz stimulation trains repeated at long inter-train intervals. RS has been reported to occur in the resting motor-evoked potentials (MEPs) with respect to the first pulse in a train of stimuli. Although this RS in the motor system has been described in previous studies, the neuronal origin of the phenomenon is still poorly understood. The present study evaluated RS in three TMS-induced motor responses; resting and active MEPs as well as corticospinal silent periods (SPs) in order to clarify the mechanism behind TMS-induced RS. We studied 10 healthy right-handed subjects using trains of four stimuli with stimulation intensities of 120% of the resting motor threshold (rMT) and 120% of the silent period threshold for an SP duration of 30 ms (SPT30). Inter-trial interval was 20 s, with a 1-s inter-stimulus interval within the trains. We confirmed that RS appears in resting MEPs ($p < 0.001$), whereas active MEPs did not exhibit RS ($p > 0.792$). SPs, on the contrary, lengthened ($p < 0.001$) indicating modulation of cortical inhibition. The effects of the two stimulation intensities exhibited a similar trend; however, the SPT30 evoked a more profound inhibitory effect compared to that achieved by rMT. Moreover, the resting MEP amplitudes and SP durations correlated (*rho* $\leqslant -0.674$, $p < 0.001$) and the pre-TMS EMG level did not differ between stimuli in resting MEPs ($F = 0.0$, $p \geqslant 0.999$). These results imply that the attenuation of response size seen in resting MEPs might originate from increasing activity of inhibitory GABAergic interneurons which relay the characteristics of SPs.**


**Key words: transcranial magnetic stimulation, motor-evoked potential, silent period, repetition suppression.**

## INTRODUCTION

The primary motor cortex, situated in the precentral gyrus, consists of five layers with an absent layer IV (Brodmann, 1909); of these, layers II and III contain excitatory pyramidal neurons (Di Lazzaro and Ziemann, 2013). These pyramidal neurons make monosynaptic connections to the large excitatory pyramidal tract neurons in layer V (Anderson et al., 2010). In addition to excitatory neurons, the motor cortex possesses a large number of inhibitory interneurons, particularly GABAergic interneurons (Di Lazzaro and Ziemann, 2013). The GABAergic interneurons have both vertical and horizontal projections and the interneurons are intermingled among the pyramidal neurons (DeFelipe and Jones, 1985; Schieber, 2001). The function of the inhibitory neurons is to entrain and control the firing of the excitatory neurons (Douglas et al., 1989).

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method which can be used to study the excitatory and inhibitory mechanisms present in the cortical neurons. Generally, the TMS pulses are applied with at least a three-second inter-stimulus interval, since faster repetition might modulate the induced neuronal responses in a different manner than those induced by a single-pulse (Julkunen et al., 2012). For example, these faster pulse repetitions may be exploited in therapeutic applications, in which long-term effects can be obtained via repetitive TMS (rTMS) (Fitzgerald et al., 2006). It is recognized that high-frequency rTMS can enhance cortical excitability consistently, whereas low-frequency seems to exert inhibitory effects on excitability, although the evidence for inhibition is more inconsistent (Fitzgerald et al., 2006). In addition to the frequency of stimulation, a variable length of the TMS pulse train and stimulation intensity might cause different modulatory effects on cortical neurophysiology (Fitzgerald et al., 2006; Reis et al., 2008).

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*Abbreviations:* ADM, abductor digiti minimi; ANOVA, analysis of variance; APB, abductor pollicis brevis; EMG, electromyography; FDI, first dorsal interosseous; *ICC*, intraclass correlation coefficient; LICI, long-interval intracortical inhibition; MEP, motor-evoked potential; MSO, maximum stimulator output; rMT, resting motor threshold; RS, repetition suppression; rTMS, repetitive transcranial magnetic stimulation; SICI, short-interval intracortical inhibition; SP, silent period; SPT30, silent period threshold for an SP duration of 30 ms; TMS, transcranial magnetic stimulation.

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The modulation of the evoked responses is not a unique characteristic of TMS, for example, in the auditory system, repetition suppression (RS) in response to repeated auditory stimuli has been a widely studied phenomenon (Groves and Thompson, 1970; Grill-spector et al., 2006). RS (or response habituation) is an inhibitory property, i.e. the size of the neuronal response to repeated stimuli is less than the response size to an unexpected, single stimulus (Grill-spector et al., 2006). Recently, RS was also reported to exist in the motor system in response to repeated TMS stimuli (Löfberg et al., 2013), in a similar manner to that encountered in the auditory processes, in which the phenomenon is studied with four repeated stimuli with a long inter-train interval (Näätänen and Picton, 1987). This suggests that RS could be a general neuronal mechanism to allow cortical processes to adapt to both internal and external stimuli (Löfberg et al., 2013). Since the output of the primary motor areas can be easily and objectively measured, the motor system represents an excellent cortical system with which to study the characteristics of RS.

If TMS is applied to the cortical representation area of a resting muscle at a sufficient stimulation intensity, a resting motor-evoked potential (MEP) manifested as a muscle twitch may be evoked in the target muscle. In contrast, if the target muscle is voluntarily contracted, an active MEP might be induced followed by a corticospinal silent period (SP) which is a temporary cessation of muscle activity (Fuhr et al., 1991). The MEPs arise as a result of pyramidal neuron activation and thus, are considered to represent the activity of the corticospinal excitatory system (Rossini et al., 2015). SPs, on the other hand, are thought to originate from the activation of corticospinal GABAergic inhibitory circuits (Fuhr et al., 1991), mediated mainly through $GABA_A$ and $GABA_B$ receptors (Keller, 1993). The early part of the SP up to 50 ms is believed to arise from spinal mechanisms with the later component being of cortical origin (Fuhr et al., 1991; Tergau et al., 1999). Despite the different background processes, MEPs and SPs are closely related to each other and share several characteristics (Orth and Rothwell, 2004; Säisänen et al., 2008). Furthermore, it is the balance between excitatory and inhibitory systems that regulates the normal cortical activity (Chen, 2004).

Although the RS phenomenon has been well characterized in MEPs, its neural origin is still poorly understood (Löfberg et al., 2013). In a previous study, it was hypothesized that the RS was a reflection of the instantaneous feedback from neuronal populations controlling the motor execution (Löfberg et al., 2013). Due to this feedback during the stimulation train, the MEPs could be evoked by a smaller population of firing neurons (Wiggs and Martin, 1998; Löfberg et al., 2013). However, alternative explanations for the phenomenon were also postulated, e.g. RS results from the inhibitory feedback from the somatosensory cortex (Löfberg et al., 2013). Since there is no consensus about the neuronal cause, the present study aimed at elucidating the neural background of RS in TMS-evoked motor responses by examining the phenomenon with both excitatory and inhibitory responses.

## EXPERIMENTAL PROCEDURES

### Subjects and measurement

Ten healthy right-handed volunteers (five females and five males, age range: 24–35 years) with no history of neurological disorders or contraindications for TMS (Rossi et al., 2009) were recruited as subjects. The study was approved by the local ethics council (78/2014) and written informed consent was collected from all the participants. The measurements were performed with an eXimia navigated TMS system (version 3.2.2, Nexstim Plc., Helsinki, Finland) using a figure-of-eight coil with biphasic waveform. During the stimulation, the first phase of the biphasic pulse was in the anterior–posterior direction and the second (stimulating) phase in the posterior–anterior direction. TMS-evoked responses were measured with surface electromyography (EMG) from the first dorsal interosseous (FDI), abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles of the contralateral right hand using an integrated EMG device.

The measurement was started by roughly mapping the primary motor cortex in order to identify the optimal stimulation site, i.e. the location eliciting MEPs with the greatest amplitudes for FDI. At this location, the coil was rotated in the tangential plane to find the optimal coil direction. Thereafter, the resting motor threshold (rMT) and SP threshold for an absolute SP duration of 30 ms (SPT30) (Kallioniemi et al., 2014) were estimated at the FDI target using the TMS Threshold Assessment Tool 2.0 (Awiszus, 2003; Awiszus and Borckardt, 2012) with 20 single-pulses, separately for each threshold. MEPs of at least 50 $\mu$V in amplitude and SPs of 30 ms and above in duration were accepted as responses.

The RS in TMS-induced responses was studied using stimulus trains consisting of four identical single-pulses at 1-s intervals. The trains were repeated every 20 s. The experimental session was divided into three parts. In the first part, stimulation was applied at rest using 30 stimulus trains with a stimulation intensity of 120% of rMT, thus on total 120 stimuli were given (Löfberg et al., 2013). In the second and third parts, stimulation was conducted during voluntary muscle contraction using 20 stimulus trains, with 120% of rMT and 120% of SPT30. The order of the parts was randomized in the subjects. The subject was instructed by the researcher to begin the muscle contraction with equal force in each finger approximately 2 s before the first stimulus, and to continue to contract with constant force until 2 s after the last stimulus in a train. During the session, EMG was examined online from the display screen to ensure that at the rest condition, no muscle tension existed and sufficient, supramaximal level of muscle contraction (approximately 1 mV peak-to-peak) was maintained in the active conditions. There was a few minutes break between the active conditions to avoid muscle fatigue exerting effects on SPs (Hunter et al., 2006). In addition, both hands were contracted concurrently, although EMG was measured only from the right hand, to reduce the effect of interhemispheric inhibition (Fling and Seidler, 2012).