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# Effects of repetitive transcranial magnetic stimulation on masseter motor-neuron pool excitability

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ABSTRACT

*Objective:* Repetitive transcranial magnetic stimulation (rTMS) has been widely used to modulate the excitability of the cortical control of limbs muscles, but rarely in the cortical control of human masseter muscles. This study aims to investigate the effects of rTMS on masseter motor-neuron pool excitability in humans.

*Materials and methods:* A total of 20 healthy participants were selected and received a total of three rTMS sessions involving stimulation of the right masseter-motor complex: one session of 10-Hz rTMS, one session of 1-Hz rTMS and one session of sham rTMS at an intensity of 80% of the active motor threshold (AMT). The masseter AMT, motor-evoked potentials (MEPs), cortical-silent period (CSP), and short-interval intracortical inhibition (SICI) were measured before and after each rTMS session.

*Results:* The masseter SICI was significantly decreased following 10-Hz rTMS, with no significant changes in AMT, MEPs or CSP. No significant differences in masseter AMT, MEPs, CSP or SICI were observed in either the 1-Hz, or sham rTMS groups.

*Conclusions:* The present findings demonstrate that high-frequency rTMS increases masseter motor-neuron pool excitability.



## 1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) of the cerebral cortex can induce lasting changes in motor-neuron excitability (Veniero, Vossen, Gross, & Thut, 2015). This type of intervention has been used in many studies as a treatment of cerebral dysfunction in patients with movement disorders, such as epilepsy, stroke, or restless legs syndrome (Sun et al., 2012; Klomjai et al., 2015; Altunrende, Yildiz, Cevik, & Yildiz, 2014). However, the vast majority of research into rTMS has focused on the corticospinal system, and, rarely on the corticobulbar system.

The masseter muscles, which are innervated by the trigeminal nerve, are involved in voluntary control of biting, chewing, swallowing and speech. The masseter-motor cortex enables the initiation and control of movements of the lower jaw, or mandible, through descending corticobulbar projections to the trigeminal motor nuclei and brainstem reticular formation (Nordstrom, 2007). Motor-neuron pool excitability is usually assessed using motor-evoked potentials (MEPs) followed by measurements of the cortical-silent period (CSP), the degree of short-intracortical inhibition (SICI) and the extent of intracortical facilitation (ICF), which are evoked using transcranial magnetic stimulation (TMS). Several differences exist between reflex and cortical control of the trigeminal and spinal muscles; therefore, simple extrapolation of rTMS data from the corticospinal system to the corticobulbar system is not appropriate. For example, the masseter CSP is shorter than the hand CSP (Sowman, Flavel, McShane, Miles, & Nordstrom, 2008). Furthermore, recordings of masseter MEPs are a more sensitive method of detecting upper-motor neuron involvement, such as in patients with amyotrophic lateral sclerosis (ALS) than recordings of hand MEPs (Tompetto, Caponnetto, Buccolieri, Marchese, & Abbruzzese, 1998). The existence of such differences suggests that the rTMS of the masseter-motor cortex could be applied to the clinical treatment of muscle dysfunction in the craniofacial region, which is part of the corticobulbar system.

The effects of rTMS are closely dependent upon the stimulation parameters used. Generally, high frequency (>5 Hz) stimulation results in facilitatory effects, whereas low frequency (<1 Hz) stimulation results in inhibitory effects (Fitzgerald, Fountain, &

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Daskalakis, 2006; Peinemann et al., 2004). However, only a few studies to date have reported the effects of rTMS on masseter motor-neuron pool excitability. Therefore, in this study, we investigated two possible hypotheses: Either that high-frequency rTMS has a facilitatory effect on masseter motor-neuron pool excitability; or that low-frequency rTMS has an inhibitory effect on masseter motor-neuron pool excitability. To test these hypotheses, this study focused on the effects of 10-Hz and 1-Hz rTMS, which were delivered to the masseter-motor cortex in healthy human study participants. Effects of rTMS were quantified using standard measures of masseter motor-neuron pool excitability, such as active-motor threshold (AMT), MEPs, duration of CSP, degree of SICI and ICF, which were tested using the paired-pulse technique.

## 2. Materials and methods

### 2.1. Participants

A total of 20 healthy, right-handed individuals (12 males and eight females; mean age: $24.1 \pm 1.1$ years) participated in this study. No participants had any history of neurological or psychiatric disorders or contraindications to use of TMS (Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998). The experimental designs of this study were approved by the Ethics Committee of the University of Tongji, in accordance with the Declaration of Helsinki, and all participants gave their written consent before enrollment into the study.

### 2.2. Preparation

Electromyographic (EMG) were recorded from masseter muscles using with surface electrodes. A reference electrode was placed at the mandibular angle and an active electrode over the muscle belly, 1–2 cm frontally and cranially to the position of reference electrode (Guggisberg, Dubach, Hess, Wuthrich, & Mathis, 2001). The earth electrode was placed over the forehead. Skin impedance was $<10\,k\Omega$. The signals were amplified and filtered (20–5000 Hz) using an amplifier (KeyPoint, Medtronic, Dantec).

Subjects were seated in the upright position on a comfortable chair. They activated their masseters by clenching in the intercuspal position at approximately 10% of maximal voluntary contraction for the single and paired TMS, with the aid of visual feedback of the EMG activity of the left and right masster muscles on the computer screen.

### 2.3. TMS

TMS (single, paired and repetitive pulses) were performed using a figure-eight-shaped coil (the diameter of each wing was 8 cm) connected to a Magnetic Stimulator (MagPro X100, Medtronic, Dantec). The coil was placed tangentially to the skull over the right hemisphere with the handle pointing forwards and laterally at an angle of approximately 120° relative to the midline. The optimal area for masseter activation was determined as the site where we could evoke the largest responses in the left masseter muscle. Generally, the optimal site was 0–9 cm lateral to the vertex and 0–4 cm anterior to the interaural line (Guggisberg et al., 2001). In this position, TMS could activate the presumptive corticobulbar descending fibers that produced a long-latency and a low-amplitude response in the contralateral MEP (c-MEP), and directly excited the ipsilateral trigeminal root, as evidenced by appearance of a short-latency response in the ipsilateral masseter EMG (r-MEP) (Cruccu, Berardelli, Inghiller, & Manfredi, 1989).

### 2.4. rTMS

This aspect of the study consisted of three separate sessions, two of which involved real rTMS sessions and one sham rTMS session. Sessions were conducted >1 week apart. In real rTMS sessions, the subjects received 1200 pulses of 1-Hz stimulation and 20 trains of 10-Hz stimuli delivered with a duration of 1.5 s and a 55 s intertrain interval. rTMS was applied at 80% of the AMT. AMT was defined as the minimal intensity that evoked MEP greater than 0.1 mV at least 5 out of 10 trials when the subjects maintained contraction of the left masseter muscle at approximately 10% of maximal voluntary contraction (Ortu et al., 2008). The sham rTMS procedure involved a 'mock' 10-Hz or 1-Hz stimulation, except that the coil was placed at an angle of 90° relative to the skull and only one edge of the coil was rested on the scalp (Ahna, Kim, & Kim, 2013). During the sham rTMS session, half of all subjects received 'mock' 10-Hz stimulation and half received 'mock' 1-Hz stimulation.

### 2.5. Measurement procedures

MEPs and CSP were induced using a single TMS at an intensity 130% of that of the AMT, a total of 10 trials were recorded. The latency of MEPs was measured from the start of magnetic stimulation to the onset of the first part of the potential; the MEPs amplitude was measured from peak to peak; and the duration of CSP was measured by the same investigator using rectified EMG signals from the start of the MEPs until the return of constant voluntary EMG activity to at least 20% of the pre-stimulus level. The root-mean-square (RMS) value for the pre-stimulus EMG was calculated from rectified signals measured during a 100 ms pre-stimulus epoch.

SICI and ICF were induced using a paired-pulse technique. The technique consists of a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS). The CS intensity was 70% of the AMT, while TS intensity was adjusted to elicit a left-masseter MEP of 0.3 mV. A 3-ms interstimulus interval (ISI) was used for SICI tests, and a 10-ms ISI for ICF. A total of 30 trials were recorded (10 trials for each of the two ISIs and 10 trials for unconditioned MEPs). The mean amplitude of conditioned MEPs was expressed as a percentage of the average test MEPs.

Finally, immediately after the end of the rTMS intervention, MEPs and CSP (post-rTMS) were assessed again with the same parameters used for the pre-rTMS assessments of MEPs and CSP. The AMT, SICI and ICF were also reevaluated.

### 2.6. Statistical analysis

Data are expressed as mean and standard deviation. The measured pre-rTMS and post-rTMS results of AMT, RMS, latency, amplitude of MEPs, duration of CSP and SICI were compared using a two-factor repeated-measures analysis of variance (ANOVA) with time (pre-rTMS, post-rTMS) and rTMS condition (1-Hz and 'mock' 1-Hz stimulation, or 10-Hz and 'mock' 10-Hz stimulation) as within-group independent variables. When a significant interaction was present, individual effects were analysed across the groups using paired Student's *t*-tests. Comparisons between the amplitude of test r-MEPs and conditioned r-MEPs (at 3-ms and 10-ms ISIs) were conducted using a one-way ANOVA, and the post-hoc analysis was based on the LSD test. All statistical procedures were two-tailed and the level of significance level was set to $P<0.05$.

## 3. Results

All participants completed all phases of the study and none of the participants experienced any adverse events. Data on r-MEPs