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Influence of phasic muscle contraction upon the quadripulse stimulation (QPS) aftereffects

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HIGHLIGHTS

- Voluntary hand movement (VM) just after quadripulse stimulation (QPS) abolished the QPS aftereffects.
- VM at 20 min after QPS briefly weakened the QPS aftereffects but not continuously.
- Subjects should keep the target muscle relaxed soon after rTMS intervention.

ABSTRACT

Objective: Contractions of the target muscle influence the aftereffects of repetitive transcranial magnetic stimulation (rTMS). The aim of this paper is to investigate whether or not voluntary hand movement influences the aftereffects of quadripulse stimulation (QPS) on the hand motor area.
Methods: Thirteen healthy volunteers participated in this study. After QPS-5 or QPS-50 intervention over the motor hot spot for the right first dorsal interosseous muscle (FDI), the subjects performed voluntary motor tasks (opening–closing right hand movements at 1 Hz for 1 min). We compared the time courses of MEP size between the conditions with and without voluntary movement.
Results: When the subjects moved their hands immediately after QPS, both QPS-5 and QPS-50 aftereffects were abolished. However, if they moved their hands at 20 min after QPS, the long-term aftereffects were preserved.
Conclusions: Voluntary hand movement applied after intervention influences QPS aftereffects, but the magnitude of the influence depends on the delay between QPS and the voluntary movement.
Significance: In the plasticity induction experiments, we should always be mindful of the fact that voluntary movement, including the target muscle, seriously influences the induced long-term effects of QPS.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is able to induce long lasting excitability changes in the human motor cortex, which are analogous to synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD). Patterned rTMSs, such as paired associative stimulation (PAS), theta burst stimulation (TBS), or transcranial direct current stimulation (tDCS) can also induce these effects (Stefan et al., 2000; Nitsche and Paulus, 2001; Huang et al., 2005). However, these aftereffects can be readily modulated by various confounding factors (Ridding and Ziemann, 2010), one of which is contraction of the target muscle. Ziemann et al. (2004) reported that ballistic thumb movements prior to PAS converted its LTP-like aftereffect to LTD and enhanced the LTD-like aftereffect. Gentner et al. (2008) demonstrated that continuous isometric contraction of the target muscle before intervention reversed continuous TBS (cTBS)-induced facilitation to depression. Iezzi et al. (2008) reported that phasic voluntary finger movements prior to TBS reversed the aftereffects. Metaplasticity must be responsible for these modulations (Abraham, 2008). Moreover, some previous studies have demonstrated that voluntary muscle contractions during or after plasticity-inducing protocols

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influenced their aftereffects. Huang et al. (2008) reported that static muscle contractions during TBS abolished both facilitative intermittent TBS (iTBS) aftereffects and depressive cTBS aftereffects. Muscle contraction immediately after TBS enhanced LTP by iTBS and reversed LTD by cTBS to LTP. They also reported that muscle contraction at 10 min after cTBS transiently weakened its depressive aftereffects for a few minutes. Thirugnanasambandam et al. (2011) reported that isometric voluntary muscle contraction immediately after tDCS abolished both the anodal tDCS potentiation and cathodal tDCS depression. They considered that depotentiation and de-depression mechanisms can explain these modulations. The ready modulation of rTMS or tDCS aftereffects by target muscle contraction is a serious problem in the interpretation of rTMS or tDCS experimental results, and which is especially critical in its therapeutic application. Therefore, it is important to elucidate how voluntary movements influence plasticity induction in humans.

Hamada et al. (2007) reported a novel patterned rTMS method, quadripulse stimulation (QPS), which can induce bi-directional cortical excitability changes (Hamada et al., 2008). Its effects continued for longer than other rTMS protocols, and, in contrast to the drastic influence of brain derived nerve growth factor (BDNF) polymorphism on rTMS or tDCS aftereffects (Cheeran et al., 2008; Antal et al., 2010), they were unaffected by BDNF polymorphism (Nakamura et al., 2011). Moreover, the inter-individual variability is much smaller in QPS compared with other non-invasive stimulation methods (Ugawa, 2015). Two features may explain the above robustness of QPS to several confounding factors. Firstly, QPS uses monophasic pulses for stimulation. The activated population by monophasic pulses may be more specific than those by bi-phasic pulses usually used in rTMS protocols, and the aftereffects may be more clear or pure. Secondly, QPS takes 30 min but the other methods take a shorter duration, especially cTBS, which takes 40 s. Plasticity induction has several succeeding processes, such as short-term potentiation/depression, early LTP/LTD, late LTP/LTD and consolidation (Ugawa, 2012). Within the intervention of QPS (30 min), some early processes will have started and their effects may be resistant to confounding factors, or such processes will trigger the next step of plasticity induction, which may be resistant to some cofounding factors than the earlier processes. These hypotheses may partly explain the robustness of QPS to several confounding factors compared with other protocols. In the present study, we investigated the influences of voluntary hand movement on QPS aftereffects.

2. Methods

2.1. Subjects

Thirteen healthy volunteers (26–61 years old; mean age 36.3) participated in the present study. Seven of the 13 subjects participated in more than one experiment. They had no contraindications to TMS and provided written informed consent to take part in the present study. The experiments were performed according to the Declaration of Helsinki. The procedures were approved by the Ethics Committee of Fukushima Medical University (receipt number: 1427). In each subject who took part in several experiments, two successive experiments were separated by at least one week. No side effects were noted in any individuals.

2.2. MEP recording

The subjects sat on a comfortable armchair during the experiments. Electromyograms (EMGs) were recorded from the right first dorsal interosseous muscle (FDI) (filtered between 16 and 3000 Hz and sampled with 20 kHz) using Ag/AgCl electrodes placed in a conventional belly-tendon arrangement. EMGs were input to a computer running TMS Bistim Tester software (Medical Try System, Japan) through a multichannel amplifier (MA-1000; TEAC, Japan) for offline analyses. In order to record motor evoked potentials (MEPs), single TMS pulses were applied to the left motor cortex with a 70-mm diameter figure-of-eight coil (The Magstim Co. Ltd, Whitland, Dyfed, UK) combined with a monophasic magnetic stimulator (Magstim 200; The Magstim Co. Ltd). We placed the coil tangentially on the scalp in the same direction in which an electric current was induced from lateral-posterior to medial-anterior in the motor cortex. The right FDI motor hot spot was defined as the optimal site for eliciting the largest MEP. The stimulation intensity was adjusted to elicit MEPs as large as 0.5–1 mV in the relaxed condition. Before each intervention, voluntary movement, or QPS (as described below), we recorded 20 MEPs using single TMS pulses every 4.5–5.5 s (MEP_{pre}) to obtain the baseline MEPs. At each time point after any intervention, we recorded 20 MEPs in the same way (MEP_{post}). The cortical excitability was estimated by the MEP size ratio, which was the ratio of the peak-to-peak amplitude of MEP_{post} to that of MEP_{pre}.

2.3. Quadripulse stimulation (QPS)

QPS consists of 360 bursts of four monophasic TMS pulses separated by several different inter-stimulus intervals (ISIs). Bursts were repeatedly given every 5 s for 30 min. Four monophasic magnetic stimulation pulses were combined with a specially customized module (The Magstim Co. Ltd) to deliver four consecutive monophasic TMS pulses through one figure-of-eight coil. Hamada et al. (2008) reported that the direction of QPS-induced motor cortical excitability changes depended on the inter-stimulus interval (ISI) of TMS pulses. When the ISI is relatively short ($\leqslant$10 ms), QPS induces potentiation aftereffects, and when the ISI is relatively long ($\geqslant$30 ms), QPS induces depression aftereffects. We employed the most effective QPS-5 (ISI = 5 ms) for LTP-like effect induction and QPS-50 (ISI = 50 ms) for LTD-like effect induction (Hamada et al., 2008). The intensity of TMS pulses for QPS was set at 90% of the active motor threshold (AMT). The AMT was the lowest intensity to elicit MEPs in the right FDI larger than 100 μV in at least five of ten consecutive TMS pulses while the subjects maintained a weak voluntary contraction of the target muscle (right FDI). The time points for MEP recordings after the intervention were every 5 min until 30 min and every 10 min until 60 min (see Fig. 1). As control experiments, we performed the standard QPS-5 and QPS-50 experiments (called *QPS-5 alone* and *QPS-50 alone* sessions).

2.4. Voluntary hand movement (VM) task

In the present study, we used a repetitive opening–closing cyclic movement of the right hand (VM). Subjects sat on a comfortable armchair and placed their right arm onto the arm of the chair. During VM intervention, subjects were instructed to perform an opening–closing movement of their right hand at 1 Hz guided by a metronome for 60 s. We used this task because it had more influence on the plasticity than a single FDI muscle contraction in our preliminary experiments. The movement used here had no considerable effects on MEP when applied alone (shown below).

2.5. Experimental paradigm (Fig. 1)

2.5.1. Experiment 1: effects of voluntary hand movement alone (VM alone)

Six subjects participated in this study. First, 20 MEPs (MEP_{pre}) were recorded for the baseline. Then, subjects performed voluntary hand movements (VMs: 60 cycles) for one minute, and 20 MEPs were recorded immediately after VM. MEPs were recorded at 2 min, 5 min and every 5 min until 30 min, then every 10 min until 60 min (MEP_{post}).