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The intensity of continuous theta burst stimulation, but not the waveform used to elicit motor evoked potentials, influences its outcome in the human motor cortex

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ABSTRACT

Background: Responses to continuous theta burst stimulation (cTBS) applied to the human primary motor cortex are highly variable between individuals. However, little is known about how to improve the after-effects of cTBS by adjusting the protocol characteristics.
Objective: We examined whether current directions adopted in the measurement of cortical motor excitability indexed as motor evoked potentials (MEPs) affect the responses to cTBS. We also tested whether the stimulus intensity of cTBS influences the after-effects.
Methods: Thirty-one healthy volunteers participated. The after-effects of cTBS with the conventional intensity of 80% of individual active motor threshold (AMT) ($cTBS_{80\%}$) were tested by measuring MEP amplitudes induced by not only posterior-anterior (PA) but also anterior-posterior (AP) and biphasic (PA-AP) currents. We also investigated cTBS with 65% AMT ($cTBS_{65\%}$) and 100% AMT ($cTBS_{100\%}$) in subjects who showed depression of MEP amplitudes after $cTBS_{80\%}$, as well as $cTBS_{65\%}$ in subjects in whom facilitation of MEPs was induced by $cTBS_{80\%}$.
Results: Current directions in MEP measurement had no influence on the cTBS responses. In subjects whose MEPs were depressed by $cTBS_{80\%}$, $cTBS_{100\%}$ partly induced MEP facilitation, while $cTBS_{65\%}$ abolished the after-effects. In subjects who showed MEP facilitation by $cTBS_{80\%}$, $cTBS_{65\%}$ partly induced MEP depression.
Conclusions: Stimulus intensity of cTBS influenced the responses to cTBS, and lowering stimulus intensity induced the expected after-effects of cTBS in some subjects.

Introduction

Non-invasive brain stimulation (NIBS) is a common technique to induce neuroplasticity reminiscent of the labile early phase of long-term potentiation (LTP) and/or long-term depression (LTD) in human cerebral cortices [1]. Because the effects remain after the period of stimulation, NIBS has a potential for therapeutic use in a variety of neurological and neuropsychiatric disorders. However, a major problem is that the after-effects of any NIBS plasticity-inducing protocol are highly variable between individuals [2–5]. A number of factors have been shown to relate to this variability, including age, time of day, attention, accompanied motor activity, and genetic differences [6]. Although many studies have focused on these biological factors, methodological factors might also be another issue related to the variability of NIBS after-effects.

For example, most of the plasticity studies using repetitive transcranial magnetic stimulation (rTMS) employ biphasic pulses of TMS for its plasticity induction, while monophasic TMS pulses were

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used to measure its effect by motor evoked potential (MEP). Although it is widely accepted that MEP is quite useful to measure the changes in cortical excitability caused by NIBS, it is well known from the previous studies that monophasic and biphasic TMS recruit quite different (albeit overlapped) interneuron circuits within the primary motor cortex [7]. An epidural recording study showed that monophasic pulses with a posterior-to-anterior (PA) direction, which is often used to measure MEP, preferentially recruit early indirect waves (I-waves), while biphasic pulses with the handle pointing 45° away from midline (i.e., the conventionally used coil orientation in rTMS studies) mainly recruit late and early I-waves [7]. This is explained by the fact that in biphasic stimulation, a second depolarizing phase of the biphasic pulse (i.e., anterior-to-posterior, AP) is effective to stimulate cortical neurons, rather than the first phase of the biphasic pulse, which is PA. Given this proviso, it is possible to assume that a test TMS pulse in the same direction as that used in the plasticity induction protocol may be more sensitive to detecting changes in plasticity induced by NIBS. However, there is no study that has systematically investigated this issue to date.

Another methodological factor regarding stimulation protocol per se is the stimulation parameters. For instance, in the original report of theta burst stimulation (TBS), which is one of the most frequently used rTMS methods, stimulation intensity was set at 80% of active motor threshold (AMT) [8]. Surprisingly, stimulation intensity, which is a very important factor to determine plasticity [9], has not been systematically investigated in TBS to date. It is also known from the previous studies that much of the inter-individual variation in responses to TBS plasticity protocols is due to differences in the recruitment of early and late I-waves [3]. In other words, the people in whom late I-waves are preferentially recruited have the “expected” responses to TBS, while those in whom early I-waves are recruited demonstrate the “opposite” responses to TBS protocols. Although it is still unclear why TBS produces different responses depending on early and late I-waves, it has been shown that late I-waves are more sensitive to short interval intracortical inhibition (SICI) than early I-waves [10]. Thus, given different neuronal characteristics among I-waves, the ease of recruitment of early and late I-waves might be another important factor to determine the direction of plasticity of TBS [3]. Arguably, an epidural recording study clearly demonstrated that recruitment of early and late I-waves substantially differ among individuals depending on stimulation intensity [7,11]. It is, therefore, possible to assume that the stimulus intensity of TBS in subjects showing opposite responses may not be optimal. For instance, the conventional stimulus intensity may be too high to preferentially recruit late I-waves, and thus, simultaneous recruitment of early I-waves would be induced.

To obtain some insight into these issues, we examined the effects of continuous TBS (cTBS), which has been shown to suppress cortical excitability [8]. Importantly, we measured MEP with test TMS pulses with different coil orientation and configuration, such as PA, AP, and biphasic (PA-AP) pulses. We predicted that expected MEP suppression might be clearly proven by applying AP and/or biphasic currents compared with PA because cTBS is applied with biphasic pulses in which AP currents are dominant. This possibility is also supported by the fact that the after-effects of cTBS are related to the recruitment of late I-waves, but not early I-waves [3], so that adopting AP currents which relate to late I-waves might be suitable in evaluation of cTBS responses. Another possibility is that PA currents are suitable to detect MEP suppression by cTBS, given that early but not late I-wave is predominantly suppressed by cTBS [12]. In the second set of experiments, we investigated the effects of stimulus intensity on the cTBS protocol. We hypothesized that changing the stimulation intensity may have a substantial impact on the recruitment of early and late I-waves [7,11], and that firm stimulation of, for example, late I-waves by adjusting stimulus intensity would lead to expected cTBS responses of MEP depression, given that late I-wave recruitment is important for cTBS [3]. We, therefore, exploratorily performed cTBS with different stimulus intensities for 2 groups of subjects: people in whom cTBS responses showed expected depression of MEP after conventional cTBS and those in whom it demonstrated opposite responses, i.e., MEP facilitation.

Subjects and methods

Subjects

We recruited 31 right-handed participants (10 women; 18–54 years old; mean ± SD: 24.7 ± 8.6) with no history of neurological or psychiatric diseases and no contraindications to TMS [13]. All participants gave written informed consent in accordance with the ethical standards of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the University of Tokyo.

EMG recordings

Participants were seated in a comfortable chair during the experiment. The electromyogram (EMG) activity from the right first dorsal interosseous (FDI) was recorded via Ag/AgCl cup electrodes in a belly-tendon montage. The raw signal was amplified and filtered with a bandpass filter of 20 Hz to 3 kHz (Biotop; GE Marquette Medical Systems, Japan). Signals were digitized at 10 kHz and stored on a computer for off-line analysis (TMS bistim tester; Medical Try System, Japan).

Transcranial magnetic stimulation

Monophasic TMS was performed using Magstim 200^2 stimulator (Magstim) connected to a figure-of-eight coil with an internal wing diameter of 7 cm. For biphasic TMS, Magstim Super Rapid (Magstim) connected to another coil was used. The following 3 currents induced by TMS were used in this study: (1) PA currents produced by monophasic TMS with the coil held posterolaterally at an angle of approximately 45° to the midline; (2) AP currents elicited by monophasic TMS with the coil rotating 180° to that in PA currents; and (3) biphasic currents produced by biphasic TMS with the coil placed in the same as monophasic PA currents, consisting of smaller PA currents in the first phase and larger AP currents in the second phase. The hotspot in the left primary motor cortex (M1) was identified as the position where the largest MEP responses in the right FDI were elicited with PA currents. This position was marked on the scalp for exact coil repositioning. All following measurements and interventions were performed at this hotspot determined with PA currents since the current direction does not significantly influence the position of the hotspot [14,15]. The resting motor threshold (RMT) for each current (RMTpa, RMTap, and RMTbi) was determined as the minimum stimulation intensity needed to evoke an MEP of no less than 50 μV in 5 out of 10 trials when the FDI muscle was completely relaxed. AMT for biphasic currents (AMTbi) was defined as the lowest intensity to evoke an MEP of at least 200 μV in 5 out of 10 trials while subjects maintained approximately 10% of their maximal voluntary contraction in the target muscle.

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