Brain Stimulation (2011) 4, 261–5

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Interventional repetitive I-wave transcranial magnetic stimulation (TMS): the dimension of stimulation duration

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Background
A range of transcranial magnetic stimulation (TMS) techniques are now available to modulate human corticomotor excitability and plasticity. One presumably critical aspect of these interventions is their duration of application.

Objective
In the current study, we investigated whether doubling the duration of an intervention would offer any additional benefit, or invoke self-limiting mechanisms controlling corticomotor excitability or synaptic plasticity.

Methods
We compared (in a cross-over design) corticomotor excitability (to the first dorsal interosseous muscle) during and after a 15-minute (I15) and 30-minute (I30) TMS intervention targeting indirect (I-) wave interaction (iTMS). The interventions consisted of equi-intensity paired stimuli with an interpulse interval (IPI) of 1.5 milliseconds, corresponding to I-wave periodicity, delivered at a frequency of 0.2 Hz.

Results
During both the I15 and I30 interventions, paired-pulse (I-wave) motor evoked potential (iMEP) amplitude significantly increased (by 98.3% and 120.6%, respectively, last versus first minute, $P = .001$). The increase for I30 occurred in the first 15 minutes, and there was no further change during the remainder of the intervention. Both interventions were equally effective overall. Postintervention, single-pulse MEP amplitude increased by a mean of 91% and 106% (I15 and I30, respectively, $P < .01$) with no significant difference between interventions.

L.M.M. was supported by an Australian Postgraduate Award and an Edith Cowan University Postgraduate Research Scholarship.

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Submitted September 29, 2010; revised December 16, 2010. Accepted for publication December 17, 2010.

1935-861X/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.brs.2010.12.003

Conclusions
We conclude that repetitive iTMS can increase corticomotor excitability after a relatively short intervention period of stimulation, and that a longer stimulation period has no additional benefit or detriment, perhaps as a result of the action of regulatory mechanisms.
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Keywords TMS; I-wave intervention; homeostatic plasticity

A range of transcranial magnetic stimulation (TMS) techniques are now available to examine cortical plasticity mechanisms and to modulate cortical excitability.[1] Although new interventions continue to be developed, even within a given intervention the range of stimulation parameters that can be manipulated is considerable and likely to influence the efficacy of the intervention in complex ways.[2] One presumably critical parameter is the duration of the intervention itself and the manner in which it is applied. For example, in the functioning human brain mechanisms such as homeostatic plasticity are likely to be evoked to control the effects of the intervention, raising the possibility that a longer duration of intervention may be counterproductive, or at least offer no further effect size. Homeostatic effects have been reported in a number of studies using a priming intervention, followed by a test intervention, indicating that priming had an effect consistent with accepted models of homeostatic plasticity such as the Bienenstock-Cooper-Munro (BCM) model.[3-5] More recently Hamada et al.,[6] using a quadruple-pulse intervention, have suggested that the first phase of an ongoing intervention can be thought of as priming the response to the latter phase of the intervention.

A TMS intervention that has been described makes use of indirect (I-) wave dynamics to target time-dependent plasticity mechanisms.[7] The intervention is based on the short intracortical facilitation (SICF) that arises when pairs of pulses are delivered at a periodicity that parallels that of the volley of I-waves arising from transynaptic inputs to principle cells of motor cortex.[8-10] The paired-pulse interaction that occurs at I-wave periodicity together with the presumed transynaptic mechanism of I-wave generation, suggests that this interval (1.5 milliseconds) is conducive to synaptic transmission. The I-wave TMS (iTMS) intervention thus consists of repeatedly delivering (at 0.2 Hz) pairs of stimuli at an interpulse interval (IPI) of 1.5 milliseconds.[7,11-14]

The original description of this intervention used a 30-minute period of stimulation, and described a large increase in motor evoked potential (MEP) amplitude during and after the intervention.[7] Subsequent studies have shown more modest increases associated with interventions of 13 minutes[12] and 15 minutes[11,14] duration. The magnitude of the effect described in the initial study has not been replicated, and a direct comparison of shorter and longer duration interventions has not been made. In the current study, we compared (in a cross-over design) the effect of a 15-minute (I15) and 30-minute (I30) intervention on corticomotor excitability during the interventions and for 30 minutes thereafter.

Materials and methods

Participants and study design

Ten healthy individuals (7 female; 21-27 years of age) participated in the study. All were right-hand dominant according to the Oldfield handedness questionnaire.[15] Participants were excluded if they were on any medication known to affect the central nervous system (eg, antidepressants, sedatives), had any known medical problems, or showed any contraindications to TMS. They were asked to avoid exercise and caffeine intake before each experiment. The study had the approval from the local Human Research Ethics Committee and conformed to the standards set out by the 1964 Declaration of Helsinki. Consenting participants underwent 15 and 30 minutes of interventional iTMS on separate occasions no less than a week apart in a randomized order.

Experimental setup and electromyography

Participants were seated on a chair with feet placed on a footrest. The right arm was placed in a pronated position supported by a lap cushion, fingers outstretched, while comfortably resting the left arm across the body. Participants were asked to keep their eyes open and to remain relaxed throughout the study.

MEP amplitude was recorded through pairs of surface electrodes placed over the motor point of the first dorsal interosseous (FDI) muscle of the right hand and the bony projection of the metacarpophalangeal joint. A reference (grounding) pad was positioned around the upper forearm just below the elbow crease.

Electromyographic (EMG) activity was recorded for 100 milliseconds before TMS (to confirm relaxation) and 100 milliseconds after each TMS (gain 1000; band pass 20-2 kHz; digitized 2 kHz), and stored on a computer for offline data analysis. All recordings were made at rest and any trials with EMG activity prestimulus were discarded.

TMS

A comfortably fitting latex cap with premarked grid spaces of 1 cm in a latitude/longitude coordinate system (origin at

the vertex) was placed on the participant's head. The stimulus was delivered by a Magstim Bistim 200^2 unit (Magstim Ltd, Whitland, Dyfed, UK) connected to a 70 mm figure-of-eight coil placed over the hot spot for the right FDI (over left motor cortex and determined from initial exploration), with the coil handle in the parasagittal plane.

The TMS intervention consisted of paired-pulse stimulation delivered at an IPI of 1.5 milliseconds at 0.2 Hz for 15 or 30 minutes. Paired pulses were equi-intensity and adjusted in strength so that the paired (I-wave) MEP amplitude (iMEP) was approximately 0.5 mV at baseline. Single-pulse TMS measurements before and after the intervention were collected in blocks of 12 stimuli (1 minute total collection time per block) at an intensity that gave a MEP amplitude of approximately 0.5 mV at preintervention baseline. The protocol consisted of two baseline blocks of single-pulse TMS separated by 1 minute, followed by either 15 or 30 minutes of iTMS. After the intervention, two consecutive single-pulse blocks were collected (total collection time 2 minutes; 24 pulses), followed by 1-minute blocks starting at 3, 5, 7, 9, 14, 19, 24, and 29 minutes postintervention.

Data analysis

Peak-to-peak MEP and iMEP amplitude was manually cursored and averaged for each minute, excluding the first two responses in the blocks of 12 stimuli (to allow responses to settle). The mean iMEP amplitude across the first minute of the intervention was used as a baseline for the remainder of the intervention. Post-MEP amplitudes were expressed as a percentage of the mean of the two averaged baseline blocks.

Statistical analysis

A two-tailed paired t test was used to compare baseline MEP amplitude between interventions and at selected time points during interventions. iMEP amplitude was averaged for each minute during each intervention, and changes over time were analyzed with a one-way repeated measures ANOVA (rmANOVA) for I15 and I30 separately. Changes in iMEP amplitude during I15 and the first 15 minutes of I30 were compared using a two-way rmANOVA. A one-way rmANOVA was used during the first and second 15-minute periods of I30. Post-MEP amplitudes were compared between interventions and time by a two-way rmANOVA. When the rmANOVAs found a significant effect, a Bonferroni post hoc test was applied.

Statistical analysis was carried out with Predictive Analytics SoftWare (PASW) Statistics Version 18.0. Results were presented mean ± standard error of mean (SEM) unless otherwise stated. Differences were considered significant at $P < .05$.

Results

During intervention

Mean iMEP amplitude during the I15 and I30 interventions are shown in Figure 1. Mean iMEP amplitude for the initial minute of each intervention was not significantly different between I15 (0.61 ± 0.07 mV) and I30 (0.58 ± 0.07 mV; $P = .75$). Both the I15 and I30 interventions significantly increased excitability over time (I15 $F_{14,126} = 4.03$, $P < .001$; I30 $F_{29,261} = 2.09$, $P = .001$) with the mean iMEP amplitude increasing by 98.3% and 120.6%, respectively, by the end of the intervention periods.

During the first 15 minutes of I30, iMEP amplitude also significantly increased ($F_{14,126} = 2.67$, $P < .002$), and there was no significant difference between this increase and that for I15 ($F_{1,9} = 2.35$, $P = .16$).

At the 15-minute mark, mean iMEP amplitude for I15 (1.21 ± 0.16 mV) and I30 (1.04 ± 0.21 mV) were similar between interventions ($P = .51$). For I30, the last 15 minutes did not lead to any further significant increase in iMEP amplitude ($F_{14,126} = 1.49$, $P = .13$). Nor was there any significant difference ($P = .81$) between the final collection minute of I15 (1.21 ± 0.16 mV) and the final collection minute of I30 (1.29 ± 0.28 mV).

Pre- versus postintervention

The preintervention single-pulse MEP amplitude was not significantly different between I15 (0.60 ± 0.03 mV) and I30 (0.65 ± 0.03 mV; $P = .33$; Figure 2). For the first 2 minutes postintervention, MEP amplitude (collected every 5 seconds) did not change over time for either I15 or I30 ($F_{19,171} = 1.11$, $P = .34$) and was not different between interventions ($F_{1,9} = 0.02$, $P = .91$). Mean MEP amplitude over this period was 0.61 ± 0.08 mV for I15 and 0.64 ± 0.09 mV for I30, and neither of these values were significantly different to baseline (I15 $P = .88$; I30 $P = .93$).

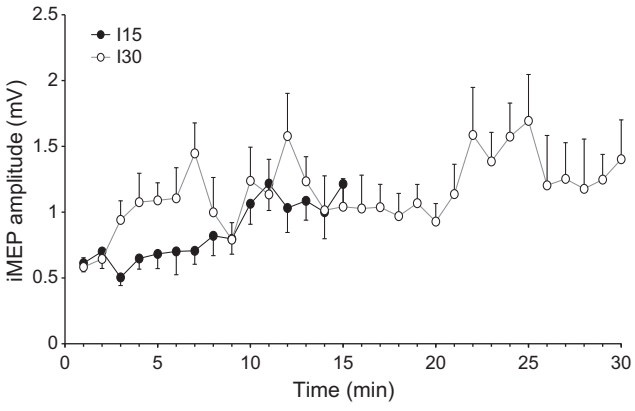

Figure 1 Changes in paired-pulse (I-wave) motor evoked potential (iMEP) amplitude (mean ± standard error of mean) during the 15 (I15) and 30 (I30) minute interventions.

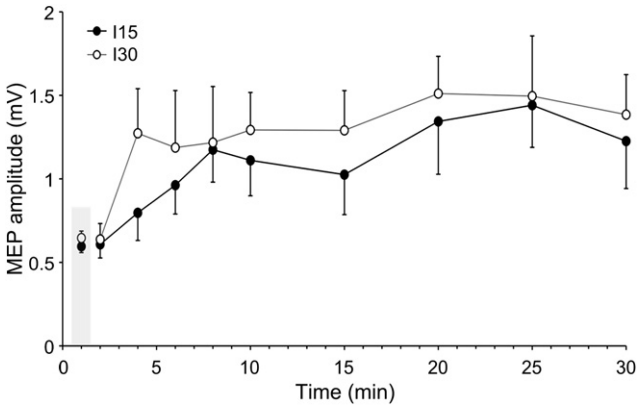

Figure 2 Single-pulse motor evoked potential (MEP) amplitude (mean ± standard error of mean) at baseline (shaded; mean of 2 baseline blocks), and for 30 minutes after the 15 (I15) and 30 (I30) minute interventions. The postintervention 0-2 minute collection has been averaged and presented at the 1-minute time point.

MEP amplitude increased after 3 minutes postintervention for I15 and I30, and did not vary with time over the subsequent 30-minute period for I15 ($F_{7,63} = 1.09$, $P = .38$) or I30 ($F_{7,63} = 0.32$, $P = .94$). The mean increase in MEP amplitude (compared with baseline) over this period was 91% for I15 and 106% for I30, both of which were significant increases ($P = .002$ and $P = .011$, respectively), but not significantly different to each other ($P = .37$).

Discussion

We compared the effectiveness of 15- and 30-minute interventional TMS targeting I-wave facilitation. During both interventions, corticospinal excitability (as assessed by iMEP amplitude) increased by a similar amount for 15 minutes; however, there was no further increase in excitability during the subsequent 15 minutes of I30, and the time course and magnitude of excitability changes after both interventions were comparable. The results indicate that the shorter period of intervention is effective in modulating corticomotor excitability, and that a longer duration conferred no additional advantage, or was it detrimental to effect size.

Previous studies have reported various durations of intervention and effect sizes.[7,11-14] In the original report,[7] a substantial (4-fold) but short-lived (10-minute) effect was described. Hamada et al.[13] also used a 30-minute duration and found a 90% increase in excitability postintervention. Cash et al.[14] and Benwell et al.[11] used 15-minute interventions and reported a 36% and 54%, respectively, increase in excitability after the intervention. In contrast, Di Lazzaro et al.[12] reported a substantial increase in excitability during and after just a 13-minute period of intervention. It remains to be resolved what aspects of the protocol are critical to the effect size, and the current study has investigated the duration of the intervention, showing a plateau in effect size for the longer intervention.

Two mechanisms could be put forward to explain the plateau in iMEP amplitude during the second-half of I30. First, plasticity mechanisms associated with I-wave facilitation (the target of the intervention) may have reached a limit and effect size was maintained as a result of a ceiling effect. However, this seems unlikely as larger effect sizes have been observed with this type of intervention,[7,12] and the increase in iMEP amplitude was modest (98-120%) and probably well within the scaling range for I-wave facilitation. Alternatively, effect size may have been maintained at this level by a more active process such as a homeostatic regulation. Homeostatic mechanisms are a powerful feature of brain function and may not only stabilize activity but may even facilitate plasticity by maintaining the system within a dynamic range that permits modulation and opposes saturation.

The importance of duration, breaks in stimulation and priming have been highlighted in recent studies. Hamada et al.[6] reported that 30 minutes of quadripulse stimulation increased cortical excitability after the intervention but 40 minutes had no effect, and proposed that homeostatic mechanisms maybe involved. Similarly, Gentner et al.[16] found increasing the duration of continuous theta burst stimulation (TBS) from 20 to 40 seconds changed the after effect from potentiation to depression. In a study by Gamboa et al.,[17] facilitatory intermittent TBS became inhibitory when it was applied for twice as long, whereas inhibitory continuous TBS became facilitatory. The current study likewise suggests that the duration of the intervention is a factor influencing effect size and time course, and that the manner of measuring corticospinal excitability after the interventional period may also be important.

As part of the study of time course of the excitability changes postintervention, we explored the initial two consecutive minutes immediately postintervention in detail, recording MEP amplitude every 5 seconds during this period. No significant differences were found between these MEP amplitudes postintervention and baseline collections, and an increase from baseline was only detected after a 1-minute break in recording. It was not our intention to compare postintervention effects with and without this period of single-pulse stimulation, but rather to plot the time course of the immediate postintervention effect, and the absence of an effect at all was unexpected. It would seem that a break in stimulation is a factor to take into consideration, although the mechanisms underlying this are not certain. There may be some differences in the mechanism underlying the increase in I-wave facilitation during the intervention, and the increased MEP amplitude postintervention. Alternatively, there may have been an interaction between postintervention effects and cortical excitability measurements, bearing in mind that even single-pulse TMS is activating motor cortex and perhaps interfering with the consolidation of after effects.

We conclude that repetitive iTMS can increase corticomotor excitability after a relatively short intervention period of stimulation, and that a longer stimulation period has no additional benefit or detriment, perhaps as a result of the action of regulatory mechanisms. Further studies are warranted to explore these interactions and to determine optimal strategies for patterns of stimulation both during and after the intervention.

Acknowledgment

Professor Frank Mastaglia is thanked for helpful comments.

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