Clinical Neurophysiology (2007) 118(11):2506-2511.

Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation

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Disclosure: none

Keywords: transcranial magnetic stimulation; theta burst stimulation; somatosensory evoked potential; somatosensory cortex; neuroplasticity; human

Acknowledgements: We thank all participants of the study, and Messrs Peter Asselman, Richard Symonds and Peter Owbridge for their special technical support. The author (T. K.) was funded by The Ito Foundation for the Promotion of Medical Science (Sapporo, Japan). The work was funded by the Medical Research Council (UK).

Abstract

Objective: To study the modulation of somatosensory evoked potentials (SEP) using transcranial magnetic intermittent theta burst stimulation (iTBS) over human primary motor (M1) and sensory (S1) cortices.

Methods: Eleven healthy subjects participated to the study. Median nerve SEP were elicited by electrical stimulation at the right wrist before and after 600-pulse iTBS over M1 or S1 of the left hemispheres at the intensity of 80% active motor threshold.

Results: iTBS over S1 facilitated the N20o-N20p, N20p-P25 and P25-N33 amplitudes significantly and the maximal effect appeared 15 minutes after the stimulation. The facilitating effect was observed when the initial phase of the current in the brain was directed antero-medially, whereas the facilitation did not appear when the inverted coil direction was applied. On the other hand, no changes were observed after iTBS over M1. The latencies of the measured onsets and peaks were not affected through the experiments.

Conclusions: iTBS over S1 has the facilitating effect to the central somatosensory pathway, and the position and direction of the coil are the determinant factors of the effects.

Significance: iTBS can be useful technique to induce synaptic plasticity in human central somatosensory pathway.

1. Introduction

Single pulse and repetitive transcranial magnetic stimulation (rTMS) have achieved wide acceptance as non-invasive methods to evaluate human cortical function. The effects of a single pulse of TMS last for less than 1 s, whereas rTMS has prolonged effects on cortical excitability that may outlast the stimulation by 30-60 min or more. Long lasting effects on cortical excitability have also been described after repeated pairings of a TMS pulse with somatosensory input, a procedure termed paired associative stimulation (PAS) (Wolters et al., 2005).

The majority of neurophysiological studies have involved the motor cortex and its connections. In contrast there is relatively little information on the effect of TMS over sensory cortex. Surprisingly, some previous studies have found that somatosensory evoked potentials (SEPs) are unaffected by TMS over the sensory cortex even though stimulation with the same parameters over M1 has powerful effects. Enomoto et al. (2001) used low frequency rTMS (1 Hz) at intensities known to produce suppression of corticospinal excitability when given over motor cortex. When applied over the sensory cortex, there was no effect on the SEP, whereas the SEP was suppressed after stimulation over motor cortex. In contrast, Wolters et al. (2005) used a paired associative method of conditioning the cortex. Repeated pairings of median nerve stimulation with a TMS pulse over sensory cortex increased the SEP if the interstimulus interval was N20 latency; there was no effect if the TMS stimulus was given over M1. Nevertheless, previous work of Tsuji & Rothwell (2002) who paired TMS over M1 with repetitive motor point stimulation of the FDI muscle and found enhanced SEPs, suggests that a weak effect of M1 stimulation in a PAS

protocol can be boosted under certain conditions. Despite the varying results on SEPs, most studies agree that TMS of sensory cortex has repeatable effects on sensory thresholds in tactile (Knecht et al., 2003; Satow et al., 2003; Tegenthoff et al., 2005) and temperature modalities (Oliviero et al., 2005).

Theta burst stimulation (TBS) is a new technique of rTMS (Huang et al., 2005) designed on the basis of animal studies for the long-term potentiation and suppression (LTP/LTD) of synaptic connections. TBS has some advantages compared with regular rTMS: TBS can modulate the excitability of human cortex more effectively and rapidly with relatively weak stimulus intensity (i.e. 80% of active motor threshold) in a short time, and it can evoke either facilitating or inhibiting effects according to the stimulation mode (intermittent [iTBS] or continuous [cTBS], respectively). In a recent paper, Ishikawa et al. (2006) found that cTBS over sensory cortex reduced the amplitude of median nerve SEPs, particularly the P25 and later components, whereas cTBS over M1 had the opposite effect. The present short report complements that previous work by examining the effect of iTBS on SEPs to median nerve stimulation.

2. Subjects and methods

2.1. Subjects

Eleven healthy subjects (9 men and 2 women, aged 24-33 [mean ± SD; 28.5 ± 2.7 years]) participated to the study and seven out of the eleven subjects completed all conditions of the experiments. The three experiments for a subject were carried out

on separate three days at intervals of more than several days. The informed consent was obtained from each subject. The study was approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery.

2.2. SEP

The subject was seated on a reclining chair during the experiment. SEPs were elicited by electrical stimulation of the right median nerve at the wrist at 3 Hz with a pulse width of 0.2 ms using a bipolar stimulator. At first, we obtained the conventional SEPs with the electrical stimulus intensity enough to evoke brisk muscle twitches at the thenar muscle. Second, less intense stimuli were given to evoke 'unsaturated' SEP, which had approximately 70-80% amplitude of the conventional one. The unsaturated SEPs were needed to assure the predicted facilitating effects of TBS. The stimulus intensities were usually about the mean value between the sensory and the motor threshold.

The active and reference Ag-AgCl surface electrodes were put on the C3' (2 cm posterior to C3 of International 10-20 system) and Fz, respectively. This montage was adopted according to the previous report (Enomoto et al., 2001). The impedance between the electrodes was kept below 5 kOhm. The peripheral sensory nerve action potentials (SNAP) were also recorded simultaneously with a pair of the surface electrodes put along the right median nerve at the cubital fossa to verify the stimulus intensity. The cathode electrode was put 3 cm distal to the anode.

SEP and SNAP were recorded in epochs from -10 to 90 ms triggered by the electrical stimuli. The sampling rate was set at 5 kHz, and the potentials were amplified and filtered between 1.6 and 3000 Hz (-3 dB).

We collected and averaged 250 responses in each trial, and more than two trials were examined in each session to ascertain the reproducibility. SEPs were recorded in four sessions (before TBS, 0, 15 and 30 minutes after TBS).

2.3. Single-pulse TMS

The detail of the technique of TMS and TBS is described in the previous report (Huang, 2005).

We used a standard double (figure-of-eight) 70 mm coil (P/N 3191-00) connected to Magstim 200 rapid^2 stimulator (Magstim Co., Whitland, Dyfed, UK) which generates biphasic outputs.

We put the surface recording electrodes on the right abductor pollicis brevis (APB) muscle with the belly-tendon method. The subject made the steady contraction of the muscle at approximately 10-20% of the maximal force during the measurement of the active motor threshold (AMT).

The coil was placed tangentially to the scalp over the hand motor cortex (M1) of the left hemisphere and the handle of the coil was directed posterolaterally, when the initial phase of the electrical current in the centre of the coil was directed towards the handle.

The series of single pulse TMS were delivered over M1 to obtain the maximal response from the APB muscle. The optimal position ('hot spot') and direction of the coil was confirmed. The stimulus intensity was controlled 1% stepwise with the stimulator's output indicator panel.

AMT was defined as the minimal single pulse intensity required producing motor evoked potentials (MEP) of greater than 200 μV on more than five out of ten trials.

2.4. TBS

TBS is magnetic stimulation with triplets of 50 Hz in a 5 Hz rhythm. In iTBS, a 2-sec train of TBS was repeated every 10 sec for a total of 190 s (600 pulses). The intensity of iTBS was set at 80%AMT. For the stimulation of M1, the coil was placed over the hot spot with the handle directed posterolaterally. In case of the stimulation of the sensory cortex (S1), the centre of the coil (the intersection of the wing) was put over C3' with the handle directed posterolaterally. The recording electrode on C3' was not removed during iTBS. The subject kept the muscle relaxation during iTBS in order to prevent the voluntary muscle contraction from interfering iTBS. The electromyographic silence of the APB muscle was monitored during iTBS. When we tried the reverse direction of iTBS over S1, the handle of the coil was directed anteromedially, with the centre of the coil placed over C3'. The following text adopts the direction of the handle to describe the stimulus orientation.

2.5. Data analysis

The data were stored in a personal computer. After the identification of N20 onset (N20o), N20 peak (N20p), P25 and N33 on the waveform, we measured the latencies of the points and the amplitudes of N20o-N20p, N20p-P25 and P25-N33 components. N20o was distinguished carefully from the preceding small positive deflation (P15) (Sonoo et al., 1996). The latencies and inter-peak amplitudes of SNAP were also measured. The effects of TBS on SEPs were evaluated with repeated-measures ANOVA (analysis of variance) with the SEP components, time-course, site and the

direction of the stimulation. The statistical analysis was performed with SPSS 11.5 for Windows software (SPSS Inc., Chicago, Illinois, US). When necessary, the Greenhouse-Geisser correction was used for non-sphericity of the data. A P-value of less than 0.05 was considered significant for all statistical analyses.

The grand average waveforms were reconstructed by adjusting the time scale with respect to the peak latencies of the N20p for the correction of the inter-individual difference.

The mean amplitudes of each component of SEPs during these three time periods after TBS were expressed in a graphic form as a ratio of size compared with the control values before TBS.

3. Results

The subjects did not experience any serious side effects or clear subjective sensory changes from the stimulation.

The grand average waveforms before and after iTBS over S1 are shown in Figure 1 (n=10). The amplitudes of N20o-N20p, N20p-P25 and P25-N33 were facilitated significantly after iTBS over S1 (see Table 1 and 2).

The graphs in Figure 2 illustrate the mean data from all subjects, with the amplitudes of the components normalized to that measured in the pre-conditioning control data. Following iTBS over S1, the amplitudes of N20o-N20p, N20p-P25 and P25-N33 were enhanced with maximal after-effects at 15 min after iTBS. On the other hand, iTBS over M1 did not change any of the SEP components (Figure 2, Table 1 and 2). This was confirmed in the statistical analysis detailed in Table 3.

The facilitating effect of iTBS over S1 occurred only when the handle of the coil was directed posterolaterally, but not anteromedially (Figure 2, Table 1 and 2). The result of a 2-way ANOVA revealed a significant interaction between the direction and time periods about the effect on N20o-N20p (Table 4). The latencies were not affected after TBS in any condition (p>0.05; full data not shown).

4. Discussion

The main result of the present experiment complements that of Ishikawa et al. (2007): iTBS over S1 facilitates SEPs, whereas cTBS suppresses them (Ishikawa et al., 2007). Thus, TBS over sensory cortex has effects on SEPs that are parallel to its effects on MEPs when applied over M1 where cTBS suppresses MEPs and iTBS facilitates them (Huang et al., 2005). However, in contrast to the previous study, where opposite effects on the SEP were observed when cTBS was moved to M1, here we saw no effect on SEPs if iTBS was performed on M1. Finally, a novel observation of the present study was that the effect of iTBS disappeared if the initial direction of induced current in the brain was reversed from anteromedial to posterolateral.

The experiments employed a submaximal stimulus to the median nerve in order to avoid saturation in the amplitude of the SEP. It is difficult to monitor the consistency of such weak stimulation pulses during the course of each experiment, and there was a slight (non-significant) increase in SNAP amplitude. However since this occurred in all three experiments (iTBS-S1, iTBS-M1, and reversed iTBS-S1) it seems unlikely to have been responsible for the effects on SEP amplitude since these were observed only after iTBS-S1.

As argued by Ishikawa et al. (2007), it seems reasonable to think that the effect of iTBS was mediated via a direct action on the sensory cortex. The very low intensity of the iTBS pulses means that there is little effective physical spread of the current to other cortical areas, and probably little direct activation of output connections from the stimulated site. Thus we think that the major effect of iTBS on the P25 component of the SEP is due to modulation of excitability in somatosensory cortex. It should be noted though that although the montage adopted in this study can provide a clear distinction between N20-P25-N33 waveforms it does not clearly differentiate between P22 and P25. Therefore, it is possible that changes in activity in either/both of them could potentially contribute to the present results. Additionally, in the present study we observed a small effect on the N20 amplitude that was not seen after cTBS. It is not clear why this difference occurs. Any effect on the N20, however, is likely to be small since it is generated in area 3b (Allison et al., 1989; 1991) which is some distance from the cortical surface within the central sulcus and therefore less likely to be stimulated directly by low intensity TBS.

In contrast to Ishikawa et al. (2007) who found opposite effects of cTBS when moving the TMS coil anterior onto M1, we did not find any significant effect on SEPs when iTBS was applied over M1. A similar finding has been reported in abstract form by Murakami et al. (2006). We did not evaluate whether M1 iTBS had any effect on MEPs because of concerns that this might interfere with SEP. However, since the same stimulus parameters produced clear effects on the SEP when applied over S1, it seems likely that stimulation over M1 would have produced the usual facilitation of MEPs reported by Huang et al. (2005). Thus one explanation of these

results is that motor cortex circuits responsible for modulating SEPs after cTBS over M1 are not affected by iTBS over M1. Another explanation is that modulation of SEPs after iTBS over M1 was limited by a "floor" effect on SEPs, so SEPs could not be further suppressed.

A new finding in this study was that the facilitating effect of iTBS over S1 depended on the initial direction of current induced in the brain. A similar effect of current orientation has been described on MEPs evoked by single biphasic pulses from M1 (Kammer et al., 2001) where anteromedially directed initial current has a slightly higher threshold and generates smaller MEPs than posterolateral current. Direct recordings of descending motor volleys evoked by the stimuli show that this is because different orientations of the stimulus evoke different combinations of I-wave volleys in the corticospinal tract (Di Lazzaro et al., 2001). It is thought that even though the pulse is biphasic, stimulation occurs best on the reversing phase of the current, and hence has a directional component that can interact with directional anisotropies in the distribution of excitable elements in the cortex. This leads to preferential activation of particular circuits in the cortex when the direction of the stimulus is changed. Presumably, the elements involved in effects on the SEP are preferentially activated by an initially antero-medially directed pulse. Interestingly, as with SEPs in the present experiment, the effect of iTBS on MEPs is also reduced by reversing the current from anteromedial to posterolateral (Talelli et al., 2007), suggesting further similarities in the action on the sensory and motor cortices.

In conclusion, we have found that iTBS over S1 at 80%AMT increases the amplitude of the N20o-N20p, N20p-P25 and P25-N33 components of SEP, and the

effects depend on the stimulus site and direction of induced current in the brain. This provides further evidence that TMS can modulate synaptic function in human central somatosensory pathways similarly to its actions on corticospinal output from motor cortex.

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Legends

Figure 1

Grand averaged waveforms before and after iTBS over S1 (N=10). The grey line is the waveform of the pre-conditioning time period, and the dotted and black lines are those recorded 0 and 15 min after iTBS, respectively. Note the temporal change of the facilitation in the amplitudes of N20o-N20p, N20p-P25 and P25-N33 after iTBS.

Figure 2

Mean (±standard deviation (SD)) time courses of effects of iTBS over S1, iTBS over M1, and iTBS with reverse (R) direction over S1. The amplitude of each component is normalized to that measured in the pre-conditioning control periods. Note the facilitating effect on N20o-N20p, N20p-P25 and P25-N33 after iTBS over S1, whereas no effects were observed in other conditions. The significant changes are indicated by the asterisks which are drawn with the plain [*], bold [**] and grey styles for N20o-N20p, N20p-P25 and P25-N33, respectively ($p<0.05$, see table 2).

Table 1
The results of one-way repeated-measures ANOVA and follow up paired comparisons at individual time points on SNAP and SEP amplitude

	df	*F*	*P*
iTBS-S1			
SNAP	1.621	2.097	0.163
N20o-N20p	3	3.266	0.037 *
Pre vs 0 min	1	1.319	0.280
Pre vs 15 min	1	7.031	0.026 *
Pre vs 30 min	1	0.913	0.364
N20p-P25	3	5.274	0.005 *
Pre vs 0 min	1	0.189	0.189
Pre vs 15 min	1	12.339	0.007 *
Pre vs 30 min	1	5.787	0.040 *
P25-N33	3	3.705	0.024 *
Pre vs 0 min	1	4.013	0.076
Pre vs 15 min	1	5.658	0.041 *
Pre vs 30 min	1	7.013	0.027 *
iTBS-M1			
SNAP	3	1.952	0.143
N20o-N20p	3	1.953	0.142
N20p-P25	3	0.229	0.875
P25-N33	3	1.380	0.268
iTBS-S1 (reverse direction)			
SNAP	3	0.758	0.532
N20o-N20p	3	0.499	0.688
N20p-P25	3	0.367	0.778
P25-N33	3	0.601	0.623

df, degrees of freedom; *F*, *F* values; *P*, *p* values. * $p<0.05$

Table 2
Mean (± SD) amplitudes of SNAP, N20o-N20p, N20p-P25 and P25-N33 (μV)
* $p<0.05$

iTBS-S1 (n=10)

	Pre	0 min	15 min	30 min
SNAP	7.24 ± 3.84	7.61 ± 4.00	7.73 ± 4.14	7.90 ± 4.57
N20o-N20p	0.80 ± 0.23	0.76 ± 0.20	0.87 ± 0.24 *	0.83 ± 0.23
N20p-P25	1.83 ± 0.86	1.92 ± 0.94	2.11 ± 0.88 *	1.95 ± 0.96 *
P25-N33	1.25 ± 0.65	1.41 ± 0.72	1.50 ± 0.70 *	1.43 ± 0.74 *

iTBS-M1 (n=11)

	Pre	0 min	15 min	30 min
SNAP	7.16 ± 5.56	7.43 ± 6.19	7.95 ± 6.18	7.60 ± 5.98
N20o-N20p	0.82 ± 0.24	0.79 ± 0.26	0.74 ± 0.56	0.78 ± 0.20
N20p-P25	1.95 ± 0.86	1.91 ± 0.90	1.91 ± 0.85	1.92 ± 0.84
P25-N33	1.23 ± 0.63	1.26 ± 0.68	1.33 ± 0.69	1.34 ± 0.66

iTBS-S1 (reverse direction) (n=7)

	Pre	0 min	15 min	30 min
SNAP	5.51 ± 2.59	5.74 ± 2.89	5.77 ± 3.21	5.83 ± 3.22
N20o-N20p	0.74 ± 0.24	0.75 ± 0.29	0.72 ± 0.26	0.77 ± 0.27
N20p-P25	1.76 ± 0.80	1.79 ± 0.97	1.70 ± 0.94	1.74 ± 0.95
P25-N33	1.38 ± 0.75	1.25 ± 0.73	1.30 ± 0.69	1.36 ± 0.74

Table 3
Main result and contrasts of the 2-way factorial repeated-measures ANOVA of the interaction between "stimulation site" and "time" for the N20p-P25 component

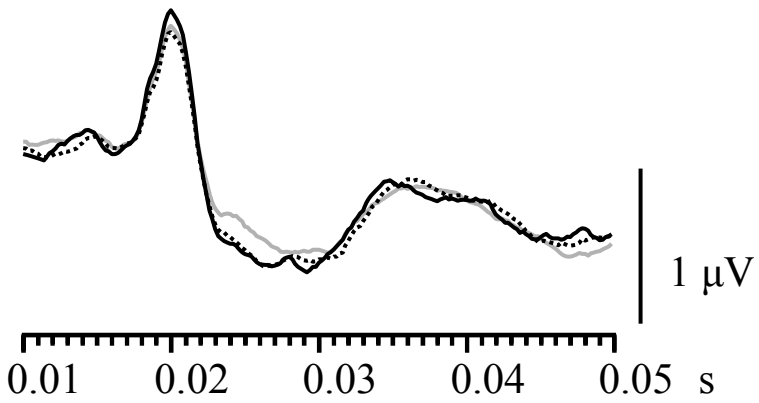
	df	*F*	*P*
Site	1	0.614	0.453
Time	3	1.793	0.172
Site x time	3	6.241	0.002 *
iTBS-S1 vs iTBS-M1			
Pre vs 0 min	1	3.647	0.089
Pre vs 15 min	1	14.907	0.004 *
Pre vs 30 min	1	5.494	0.044 *

df, degrees of freedom; *F*, *F* values; *P*, *p* values. * $p<0.05$

Table 4
Main result and contrasts of the 2-way factorial repeated-measures ANOVA of the interaction between "stimulation direction" and "time" for the N20p-P25 component after iTBS over S1

	df	*F*	*P*
Direction	1	4.306	0.083
Time	3	1.124	0.366
Direction x time	3	4.464	0.016 *
Posterolateral vs anteromedial			
Pre vs 0 min	1	0.539	0.491
Pre vs 15 min	1	5.957	0.050 *
Pre vs 30 min	1	2.162	0.192

df, degrees of freedom; *F*, *F* values; *P*, *p* values. * $p<0.05$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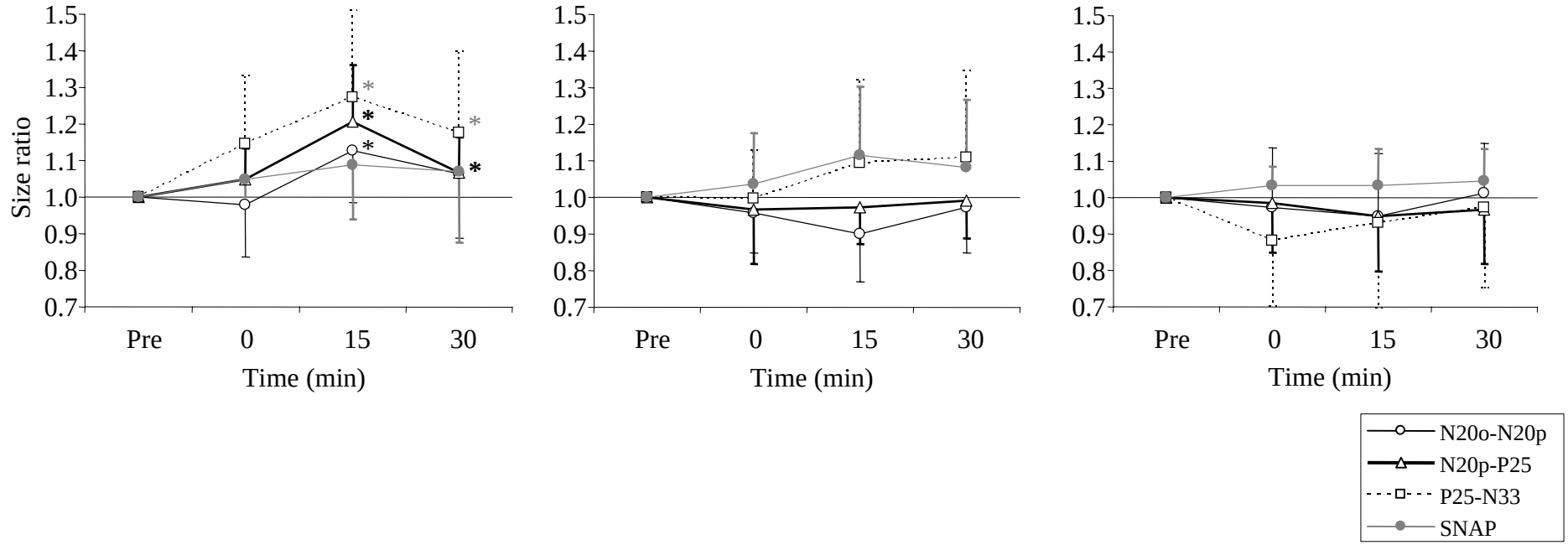
iTBS-S1
iTBS-M1
iTBS-S1 (R)
Size ratio
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
Pre
0
15
30
Time (min)
N20o-N20p
N20p-P25
P25-N33
SNAP

Abstract

Objective: To study the modulation of somatosensory evoked potentials (SEP) using transcranial magnetic intermittent theta burst stimulation (iTBS) over human primary motor (M1) and sensory (S1) cortices.

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Conclusions: iTBS over S1 has the facilitating effect to the central somatosensory pathway, and the position and direction of the coil are the determinant factors of the effects.

Significance: iTBS can be useful technique to induce synaptic plasticity in human central somatosensory pathway.