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# Sustained increase of somatosensory cortex excitability by 5 Hz repetitive transcranial magnetic stimulation studied by paired median nerve stimulation in humans

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**Abstract**

Repetitive transcranial magnetic stimulation (rTMS) has been shown to alter cortical processing within primary motor cortex dependent on the choice of stimulation variables. However, little is known about the effects of TMS in other cortical areas such as the primary somatosensory cortex (SI). Here we asked whether high-frequency (5 Hz) rTMS applied over the left SI evokes sustained changes in cortical excitability. To assess excitability changes, we applied a paired-pulse protocol consisting of paired electrical stimulation of the median nerve using an interstimulus interval of 30 ms and recordings of somatosensory evoked potentials. For ipsilateral SI we found that 1 h after termination of 5 Hz rTMS applied over the left SI with a figure-of-eight coil there was a sustained suppression of the normally present paired-pulse inhibition. Latencies and N20 amplitudes of the first peak remained unchanged. No changes of paired-pulse behavior were observed in the contralateral SI that was not TMS stimulated. The sustained excitability enhancement in SI is discussed in respect to previous findings regarding an improvement of tactile discrimination behavior by rTMS.
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There is convincing evidence that repetitive transcranial magnetic stimulation (rTMS) is capable of altering cortical processing within primary motor cortex dependent on the choice of stimulation variables [1,7,12]. Using paired-pulse techniques, the effects of rTMS are often described in terms of enduring changes of excitability [4]. High-frequency rTMS is known to facilitate corticospinal excitability that persists after termination of rTMS, especially at high stimulation intensities [6]. In contrast, low-frequency rTMS usually results in suppression of corticospinal excitability (for review see Ref. [11]). In most cases, the primary motor cortex has been the target of extensive rTMS studies. Therefore, little is known about the effects of TMS in other cortical areas such as the primary somatosensory cortex (SI). Here we asked whether 5 Hz rTMS over the left SI evokes sustained changes in cortical excitability. To assess excitability changes, we applied a paired-pulse protocol consisting of paired electrical stimulation of the median nerve in combination with recordings of somatosensory evoked potentials (SEPs).

We tested 13 right-handed healthy subjects (eight female, mean age 29 years, range 19–44 years). All subjects gave their written informed consent before participating. The study was approved by the Ethics Committee of the Ruhr-University of Bochum and was performed in accordance with the 1964 Declaration of Helsinki.

To study changes in cortical excitability, we applied a paired-pulse protocol consisting of paired electrical median nerve stimulation with interstimulus intervals (ISIs) of 30 ms. Nerve stimulation was performed with a block electrode placed on the wrist (pulse duration 0.2 ms, repetition rate of the paired stimuli 2 Hz, ISI between paired stimuli 30 ms). Stimulation of the median nerve was chosen to establish a

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link between SEP recordings and the cortical representation of the right index finger (IF) selected for rTMS application. The median nerve stimulation intensity was adjusted to 2.5-fold threshold and was kept constant for each subject before and after rTMS application. Subjects had to report a prickling phenomenon in the thumb, index and middle finger of the stimulated hand to verify correct positioning of the stimulating block electrode. In all subjects, the chosen stimulation intensity induced a small muscular twitch in the thenar muscles. During median nerve stimulation and SEP recordings, subjects were seated in a comfortable chair and were instructed to relax but to stay awake with their eyes closed. SEPs were recorded and stored for offline analysis with conventional Neuropack 8 equipment (Nihon Kohden, bandpass filter 2–2000 Hz, sensitivity 2 μV/division). Paired-pulse SEP recordings were made using a three electrode array. Two electrodes (C3′ and C4′) were located over the left and right SI, 2 cm posterior to C3 and C4 according to the International 10–20 system. A reference electrode was placed over the midfrontal (Fz) position. The electrical potentials were recorded in epochs from 0 to 200 ms after the stimulus. A total number of 400 stimulus-related epochs were recorded. Latencies and peak-to-peak amplitude of the N20 response generated in SI were measured and compared before and after rTMS (see Fig. 1). In addition to an analysis of the raw amplitude data, paired-pulse suppression was expressed as a ratio (A2/A1) of the amplitudes of the second (A2) to the first N20 peak (A1).

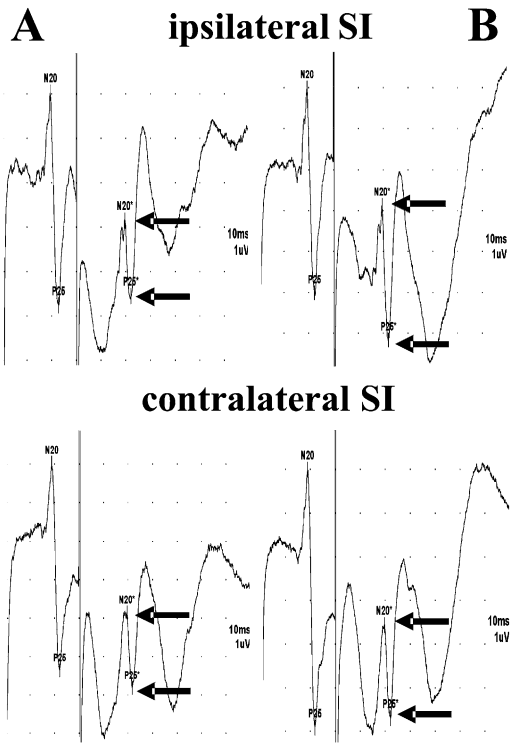


Fig. 1. Paired-pulse behavior as revealed by SEPs recorded in SI before (A) and after (B) 5 Hz rTMS over the left SI IF representation. We found a significant suppression of paired-pulse inhibition after rTMS on the ipsilateral but not on the contralateral side (repeated measures ANOVA (with factor paired-pulse ratio pre/post rTMS): $F_{(1,12)} = 15.250$, $P = 0.002$). The ISI of the paired median nerve stimulation was 30 ms.

The application of the 5 Hz rTMS protocol was the same as described previously [8]. A MAGSTIM Rapid Stimulator (Magstim, Whitland, Dyfed, UK) connected to an eight-shaped coil was used for application of rTMS. During the rTMS sessions, subjects were seated in a comfortable chair and were instructed to keep their eyes closed and to try to relax. Subjects wore a tight-fitted cap with a 1 cm grid referenced to the vertex (Cz). First, the subject's motor thresholds (MTs) were measured at the relaxed first dorsal interosseous (FDI) muscle of the right hand using single pulse TMS. During searching the cortical FDI muscle representation, TMS stimuli were presented within a 2 × 2 cm array 5 cm away from Cz along the central sulcus. The FDI muscle representation was identified at that scalp position, where TMS induced the highest motor evoked potentials (MEPs). MT was defined as the lowest intensity capable of evoking five out of ten MEPs with an amplitude of at least 50 μV. Next, to position the coil as close as possible to the right IF representation in the left SI, we used the coordinates of the sensorimotor representations of the fingers provided by Maldjian et al. [5]. To this end, from the point of maximum stimulation of the contralateral FDI muscle we moved the magnetic coil 1–2 cm posterior in a parasagittal direction to a position where subjects reported sensible sensations in their right IF induced by single pulse TMS. After having encircled the location of the right IF representation, the position of the figure-of-eight coil was fixed. This location is denoted $SI_{right\ IF}$ in the following. The rTMS intensity was set at 90% of the MT. During subsequent rTMS stimulation, surface EMGs were recorded from the FDI muscle of the right hand using silver–silver electrodes.

For rTMS, 25 trains of TMS pulses were applied through the tangentially oriented coil grip backwards positioned over $SI_{right\ IF}$. A single train consisted of 50 single pulses of 5 Hz lasting 10 s with an inter-train interval of 5 s. Five consecutive trains were grouped into one block. Between each block was a rest period of 1 min. Forty-five minutes after the termination of this rTMS session, $SI_{right\ IF}$ stimulation was repeated in a second rTMS session, with stimulation intensity, magnetic coil position and parameter settings kept constant. To be able to apply 2500 TMS pulses, rTMS sessions were separated by 45 min to ensure that TMS stimulation was well tolerated.

Paired-pulse SEPs were recorded after stimulation of the left (control) and right median nerves approximately 15 min before the rTMS sessions. Thereafter, rTMS was applied over the left SI in two sessions separated by 45 min as described above. One hour after the termination of 5 Hz rTMS, paired-pulse SEP measurements were repeated in order to study possible intracortical excitability changes in terms of changes of paired-pulse behavior. During rTMS application, SEP electrodes and block electrodes were removed, however, exact electrode positions were marked on the wrist before removal.

Under control conditions, prior to rTMS, we found a significant paired-pulse inhibition. The mean N20 responses (A1) to a paired median nerve stimulation at an ISI of 30 ms were substantially larger in amplitude than the responses to the second stimulus (A2) (4.85 ± 0.83 μV (SEM) versus 1.75 ± 0.32 μV within ipsilateral SI, *t*-test: $P < 0.0001$, Fig. 2). The mean paired-pulse ratio (A2/A1) of the N20 responses after electrical stimulation of the right median nerve was 0.39 ± 0.05 (SEM), indicating a paired-pulse inhibition of 61.04 ± 5.27% (Fig. 3). For the contralateral SI, A1 responses were also significantly larger in amplitude than the response to A2 (4.38 ± 0.69 μV (SEM) for A1 versus 1.9 ± 0.32 μV for A2 (SEM), *t*-test: $P < 0.0001$). The mean paired-pulse ratio after electrical stimulation of the left (control) median nerve was 0.48 ± 0.05 (51.16 ± 5.97% (SEM) paired-pulse inhibition).

Reassessment of the paired-pulse behavior 1 h after 5 Hz rTMS application revealed a suppression of paired-pulse inhibition of the N20 response (A2) ipsilateral to rTMS in comparison to the N20 response of the non-stimulated SI contralateral to rTMS (*t*-test: $P = 0.001$). Generally, rTMS application over the left SI was well tolerated in all subjects, and no side-effects could be observed. Paired-pulse ratios of A2/A1 were 0.39 ± 0.05 (SEM) before and 0.65 ± 0.06 (SEM) after rTMS on the ipsilateral side (repeated measures ANOVA (with factor paired-pulse ratio pre/post rTMS): $F_{(1,12)} = 15.250$, $P = 0.002$; Fig. 3). However, latencies of the N20 responses before and after rTMS did not differ.

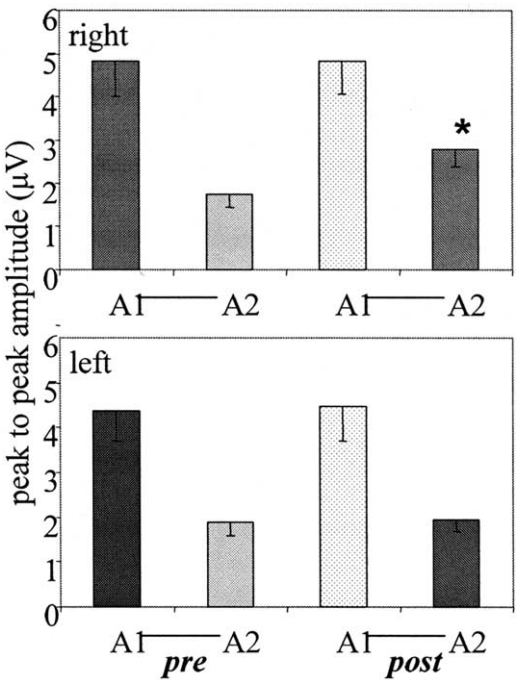


Fig. 2. Peak-to-peak amplitudes of the first and second N20 responses (A1 and A2) evoked by paired median nerve stimulation before (pre) and after (post) 5 Hz rTMS over $SI_{right\ IF}$ ($n = 13$). rTMS induced a significant increase of the A2 response of the left SI. However, peak-to-peak amplitudes remained unchanged within the SI contralateral to rTMS ($P = 0.01$). The ISI of the paired median nerve stimulation was 30 ms.

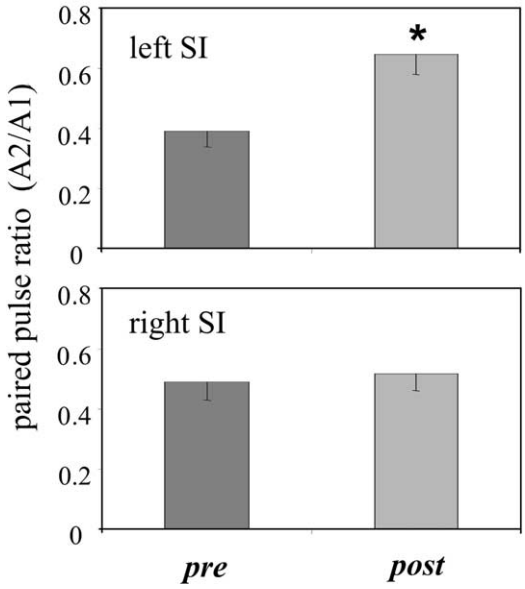


Fig. 3. Average paired-pulse ratios (A2/A1) before (pre) and after (post) 5 Hz rTMS ($n = 13$). We found a significant increase in the paired-pulse ratio of 0.26 ± 0.07 indicative of enhanced excitation 1 h after termination of 5 Hz rTMS over the left SI (repeated measures ANOVA (with factor paired-pulse ratio pre/post rTMS): $F_{(1,12)} = 15.250$, $P = 0.002$). Paired-pulse ratios on the contralateral SI remained unchanged.

In comparison to the contralateral, left median nerve representation no significant differences could be observed after rTMS for the paired-pulse ratio (0.49 ± 0.06 (SEM); *t*-test (pre versus post): $P = 0.19$; Fig. 3), amplitude differences (4.38 ± 0.69 μV (SEM) for A1 (*t*-test (pre versus post): $P = 0.31$) and 1.9 ± 0.32 μV (SEM) for A2 (*t*-test (pre versus post): $P = 0.67$)) and paired-pulse inhibition (51.16 ± 5.97% (SEM); *t*-test (pre versus post): $P = 0.47$).

The present results demonstrate a similar degree of altered paired-pulse behavior for SI using 5 Hz rTMS as described previously for human motor cortex [7]. Peinemann and co-workers described a reduction of paired-pulse inhibition after application of a paired-pulse TMS protocol according to the procedure suggested by Kujirai et al. [4]. In contrast, we found an enhancement of excitability 1 h after the termination of rTMS in the ipsilateral SI using a paired median nerve stimulation protocol that activates SI via the entire peripheral sensory pathway. However, latencies of N20 responses (A1/A2) as well as the contralateral paired-pulse inhibition in SI remained unchanged. To our knowledge, no previous studies have tested lasting effects of 5 Hz rTMS on intracortical excitability in human SI using paired peripheral nerve stimulation in combination with SEP recordings. Low-frequency (1 Hz) rTMS has been shown to suppress the excitability of SI [2]. Psychophysically, it has been demonstrated that low-frequency rTMS application over the sensorimotor cortex caused impairments of tactile perception lasting for 15 min [3,10]. While Satow and co-workers demonstrated that 0.9 Hz rTMS over the sensorimotor cortex induced a short-lasting impairment of tactile perception, median nerve SEPs remained unaffected [10].

The observed excitability changes described in this paper might be due to different mechanisms that can not be resolved by SEP recordings alone. Excitability increase has been discussed in terms of a reduction of intracortical, presumably GABAergic inhibition, or in terms of an enhancement of intracortical, presumably glutamatergic excitation, or by a mixture of both. Based on animal data, high-frequency rTMS has been reported to induce LTP (long-term potentiation)-like mechanisms [13] that would be compatible with a glutamatergic mediated increase in excitability. Using 5 Hz rTMS, we have previously shown that a combination of rTMS together with tactile coactivation boosts tactile discrimination performance in humans [8]. Furthermore, application of 5 Hz rTMS alone improved tactile discrimination [9]. These studies together with our present findings suggest that perceptual changes might develop in parallel to sustained excitability enhancement in SI. Further studies have to be performed to explore the time course and reversibility of the 5 Hz rTMS-induced changes of paired-pulse behavior in somatosensory cortex.

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