Transcranial magnetic stimulation (TMS) of the sensorimotor cortex and medial frontal cortex modifies human pain perception

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Abstract

Objective: Although recent neuroimaging studies have shown that painful stimuli can produce activity in multiple cortical areas, the question remains as to the role of each area in particular aspects of human pain perception. To solve this problem we used transcranial magnetic stimulation (TMS) as an ‘interference approach’ tool to test the consequence on pain perception of disrupting activity in several areas of cortex known to be activated by painful input.

Methods: Weak CO₂ laser stimuli at an intensity around the threshold for pain were given to the dorsum of the left hand in 9 normal subjects. At variable delays (50, 150, 250, 350 ms) after the onset of the laser stimulus, pairs of TMS pulses (dTMS: interpulse interval of 50 ms, and stimulus intensity of 120% resting motor threshold) were applied in separate blocks of trials over either the right sensorimotor cortex (SMI), midline occipital cortex (OCC), second somatosensory cortex (SII), or medial frontal cortex (MFC). Subjects were instructed to judge whether or not the stimulus was painful and to point to the stimulated spot on a drawing of subject’s hand.

Results: Subjects judged that the stimulus was painful on more trials than control when dTMS was delivered over SMI at 150–200 ms after the laser stimulus; the opposite occurred when dTMS was delivered over MFC at 50–100 ms. dTMS over the SII or OCC failed to alter the pain threshold.

Conclusions: These results suggest that TMS to SMI can facilitate whereas stimulation over MFC suppresses central processing of pain perception. Since there was no effect of dTMS at any of the scalp sites on the localization task, the cortical locus for point localization of pain may be different from that for perception of pain intensity or may involve a more complex mechanism than the latter.

Significance: This is the first report that TMS of SMI facilitates while that of MFC suppresses the central processing of pain perception. This raises the possibility of using TMS as a therapeutic device to control pain.

Keywords: Pain; Transcranial magnetic stimulation (TMS); Sensorimotor cortex; Anterior cingulate cortex; Facilitation; Inhibition

1. Introduction

The concept of multiple dimensions of pain is consistent with results from a number of neuroimaging studies that have shown pain-related activations in multiple cortical regions including primary somatosensory cortex (SI), second somatosensory cortex (SII), parietal operculum, insular cortex, anterior cingulate cortex (ACC), thalamus and cerebellum (Talbot et al., 1991; Derbyshire et al., 1997; Rainville et al., 1997; Xu et al., 1997; Tolle et al., 1999; Kwan et al., 2000; Sawamoto et al., 2000; Brooks et al. 2002; for review see, e.g. Peyron et al., 2000). Human electroencephalographic (EEG) or magnetoencephalographic (MEG) studies using short pulse CO₂ laser stimuli have investigated the time course of pain processing in these cortical areas and have revealed activities in a series of serial and parallel pathways starting as early as 80 ms after
stimulus onset (Bromm and Treede, 1987; Treede et al., 1988; Kakigi et al., 1989; Kanda et al., 1999, 2000; Ploner et al., 1999; Ploner et al., 2000; Valeriani et al., 2000; Timmermann et al., 2001). MEG source analysis has revealed activation in SI and SII at approximately 200 ms after painful stimulation of hand by a CO2 laser (Ploner et al., 1999; Kanda et al., 2000). Recent human studies with epicortical EEG recording suggest that not only SI and SII but also the ACC are active at a similar peak latency of about 200 ms after the CO2 laser stimulation (Lenz et al., 1998a,b; Kanda et al., 2000). The question we ask here is whether these different pathways process different aspects of the pain signal.

Transcranial magnetic stimulation (TMS) is a powerful, non-invasive tool for studying human brain functions (Barker et al., 1985; for review see, e.g. Jahanshahi and Rothwell, 2000; Hallett, 2000). A single pulse or short train of TMS given outside the skull creates current flow in the brain and can temporarily excite or inhibit targeted areas and alter their normal activity for a short period. It has been reported that, if given at a suitable time during the task, TMS could briefly modulate (usually attenuate) somatosensory or visual perception (Amassian et al., 1989; Cohen et al., 1991; Andre-Obadia et al., 1999). In the present study we have applied this 'interference' approach to the activity in sensorimotor cortex (SMI), SII and ACC to test whether disruption of processing of each area at particular times differentially affects the characteristics of the painful sensation produced by each stimulus.

2. Methods

2.1. Subjects

Nine normal subjects (all males; age 35.9 ± 4.6 (mean ± standard deviation) years; all right-handed) volunteered for this study. All subjects gave informed consent in a written form, according to the protocol approved by the Committee of Medical Ethics, Graduate School of Medicine and Faculty of Medicine, Kyoto University. The subject was seated in a reclining armchair with his eyes open without fixing on any point, in a quiet and electrically shielded room, with the ambient temperature controlled at about 24°C.

2.2. Pain perception and localization task

Pain stimuli were delivered with a special CO2 laser stimulator (Nippon Infrared Industries Co. Ltd, Kawasaki, Japan) (Kakigi et al., 1989; Kanda et al., 1999, 2000). The laser wavelength was 10.6 μm, and its constant power output was 6 W with the irradiation duration of 20 ms, while the irradiation beam was adjusted to 6 mm in diameter on the skin with the aid of a helium-neon laser (Kakigi et al., 1989; Kanda et al., 1999).

The CO2 laser stimuli were delivered to the left hand dorsum at the interval of 4–6 s, which was occasionally followed by TMS with various intervals. Twenty-five spots were marked on the left hand dorsum in a 5 × 5 grid pattern while each spot was arrayed at 1 cm interval. A Xerox copy of the hand with these marks was presented in front of the subject and served as a tool to examine the localization of each stimulated spot, i.e. the subject was instructed to point to the corresponding spot on that copy with a pointer (Localization Task) (Fig. 1). The subject was also instructed to make an oral report on stimulus intensity according to the following criteria; 0, no sensation at all; 1, some feelings but no pain; and 2, pain (Pain Task). In response to any CO2 laser stimulus, the Pain Task was instructed to carry out first, and then the Localization Task only when the oral report on intensity of the CO2 laser stimulus for the Pain Task corresponded to 1 or 2 according to the criteria.

2.3. TMS

TMS was delivered with either a Magstim Super Rapid or two Magstim-200 connected by a Bistim module using a 7-cm figure-eight-shape coil, which enabled a focal cortical stimulation. At first, the optimal position to elicit motor evoked potentials (MEPs) in the left first dorsal interosseous muscle (FDI) was determined. The motor threshold at rest was defined as the minimum stimulator output that can evoke a MEP of >50 μV in at least 5 out of 10 trials. The intensity of TMS was set at 1.2 times the relaxed motor threshold. Since the first arrival of pain impulse arising from CO2 laser stimulus to the cerebral cortex has been reported to be about 80–200 ms (Bromm and Treede, 1987; Treede et al., 1988; Kakigi et al., 1989; Kanda et al., 1999, 2000; Ploner et al., 1999, 2000; Valeriani et al., 2000; Timmermann et al., 2001), a temporal resolution of approximately
100 ms is required to study the effect of TMS on pain processing. Since disruption caused by a single pulse of TMS lasts for only 50–150 ms (Jahanshahi and Rothwell, 2000; Hallett, 2000), we chose double pulse TMS (dTMS) with the interpulse interval of 50 ms to increase the duration of the effect. This interval was the shortest that our system was able to provide at the maximal power output.

Stimulated cortical sites were the right SMI (the hot spot for the left FDI) and occipital cortex (OCC: Oz of the 10–20 International System for EEG electrode location) for a session of the experiment 1, and the right SII (2.5 cm anterior and 6.5 cm superior to the right preauricular point) and medial frontal cortex (MFC: Fz of the 10–20 International System) for a session of the experiment 2. The SII position was derived from the mean MEG source at 210 ms over the second somatosensory cortex following the hand pain stimulation (Kanda et al., 2000, n = 10). The MFC position was found to be located 1.5 cm anterior to the anterior commissure point, which is the nearest scalp position to the ACC activation associated with pain (Sawamoto et al., 2000).

2.4. Experimental design

Eight out of 9 subjects participated in the experiment 1 which was conducted to examine effects of dTMS over the right SMI or OCC on the two tasks (Pain Task or Localization Task) while applying the CO₂ laser stimuli on the left hand. One session consisted of two sets of 5 trials for each of SMI and OCC, while trials of these sets were mixed together so that each of 10 trials in total was given for SMI or OCC in a random sequence. For a set for each of SMI or OCC, session-dependent 4 out of 5 CO₂ laser stimuli were followed by dTMSs with the stimulus onset asynchronies (SOAs) of 50, 150, 250 and 350 ms between the CO₂ laser stimulus and the dTMS, while the order of trials with different SOAs was randomized. The remaining one trial without any following dTMS served as a control. Ten sessions involving such 10 trials were preformed. In the experiment 2, 8 out of 9 subjects were examined on effects of dTMS on the two tasks over the SII and MFC in the similar fashion designed for the experiment 1. Seven subjects in this experiment were the participants in the experiment 1.

2.5. Data analysis

As regards the Pain Task, the number of trials reported as pain (number of pain), which corresponded to ‘2’ according to the criteria, was used for analysis. In the Localization Task, location error was defined by the distance between the two spots on the Xerox copy of the subject’s hand, one actually stimulated and the other pointed to in response to a CO₂ laser stimulus, excluding the trials in which the subject felt nothing. In each of these data sets, differences among different SOAs were tested with Friedman repeated measures of analysis on ranks, followed by Wilcoxon’s signed-rank test (two-sided) comparing each data of different SOAs with that of the control. Significance level was set at P < 0.05.

3. Results

In one subject, the nearest cortical areas to the TMS location were confirmed by the anatomical MRI scan of the brain (Fig. 2).

3.1. Pain Task

Across the 10 sessions of the two experiments, the numbers of control trials (no TMS) that were reported as painful were counted separately for SMI, OCC, SII and MFC. Their mean numbers across subjects were 4.0, 5.3, 3.9 and 6.4, respectively, and were subtracted from the data at different SOAs. Wilcoxon’s signed-rank test showed no significant difference between these controls for SMI and OCC nor between those for SII and MFC (P = 0.242 and P = 0.070, respectively). The adjusted values were plotted against different SOAs along with their standard errors (Fig. 3). dTMS over SMI at a SOA of 150 ms lead to an increase in the number of trials judged as painful whereas dTMS over MFD at a SOA of 50 ms decreased number of trials identified as painful (see Fig. 3). Friedman repeated measures of analysis on ranks showed that the numbers of trials regarded as painful were significantly different among various SOAs for the SMI (P = 0.015) and for the MFC (P = 0.017), but not for the OCC (P = 0.380) or for the SII (P = 0.392). Wilcoxon’s signed-rank test showed that, while the number of trials identified as painful after dTMS of SMI (SOA of 150 ms) was significantly larger than

Fig. 2. The nearest cortical areas to the TMS location confirmed by the anatomical MRI scan of the brain. Positions of TMS were marked with capsules containing oil, which are shown as small white spots. A, B and C: coronal, axial and sagittal views for the right SMI and SII. D: sagittal view for the MFC and OCC. An arrow indicates the right SMI and an arrowhead indicates the right SII. An asterisk indicates the MFC and a triangle indicates the OCC.
4. Discussion

The present study showed that TMS over SMI with a delay of 150–200 ms from onset of the laser stimulus decreased pain threshold, while it was increased by dTMS of the MFC at 50–100 ms post-stimulus. We also showed that there was no effect of TMS over any of 4 positions on the localization task.

4.1. Effects of MSI stimulation

In human EEG and MEG studies using painful CO₂ laser stimulation, initial SI activation was recorded at a latency of 150–200 ms (Ploner et al., 1999, 2000; Kanda et al., 2000). This has been confirmed by epicortical recording in an epilepsy patient (Kanda et al., 2000). Thus it is possible that TMS given to SMI at this timing interferes with the initial processing of painful input to SI. Interestingly, painful input is also known to have an influence on motor cortex. Valeriani et al. (2001) found that painful CO₂ laser stimuli delivered to the hand reduced significantly the amplitude of motor evoked potentials evoked by the TMS of the contralateral primary motor area.

Previous studies have already shown that TMS over SI can attenuate somatosensory inputs if it is given before, during, and after cortical arrival of a somatosensory afferent volley (Cohen et al., 1991; Andre-Obadia et al., 1999). However, in the present study, TMS enhanced rather than reduced perception of painful input. One possible reason for this difference could be the different location of the primary receiving areas for non-painful and painful somatosensory inputs (Ploner et al., 2000). Animal studies showed that neurons responsive to nociceptive inputs are distributed in the crown of the postcentral gyrus (Brodmann’s areas 2 and 1) (Tommerdahl et al., 1996; Kenshalo et al., 2000), while those of other sensory modalities are located in its wall (area 3b) (Tommerdahl et al., 1996; DiCarlo et al., 1998; Kenshalo et al., 2000). The results of human direct cortical recording are also compatible with the importance of areas 2 and 1 for pain processing (Kanda et al., 2000). It is therefore possible that TMS has a different effect on signal processing of superficially located neurons in areas 1 and 2 compared with those located in the posterior bank of the central sulcus. Kujirai et al. (1993) found that a TMS conditioning stimulus caused a large increase in the positive component of somatosensory evoked potentials at 25 ms following electric stimulation of the median nerve at wrist, the generator of which is located at areas 2 and 1 (Allison et al., 1989, 1991). This would be consistent with a possible enhancement of processing in this area, resulting in facilitation of pain.
Differential processing of pain and other inputs was also reported by Tommerdahl et al. (1996). They found in monkey SI that the presence of noxious heat, which evoked an increase in the intrinsic optical-imaging signal in area 2, reduced the signal in area 3b/1 evoked by low-threshold mechanical stimulation. Psychophysical data also show that the presence of pain reduces tactile perception (Apkarian et al., 1994). These data suggest that sensations of pain are inversely correlated with other sensations, and would be compatible with the difference in effects of TMS on pain and other sensations (Cohen et al., 1991; Andre-Obadie et al., 1999).

It is also possible that, in the present experiments, the movement induced by suprathreshold TMS over SMI may modulate the pain perception. Here, the present result cannot be explained by this peripheral mechanism because the gating caused by the movement, if any, would attenuate the pain sense (Kakigi and Shibasaki, 1992).

4.2. Effects of MFC stimulation

There is good evidence from PET, fMRI and even single cell recordings during surgery that MFC is activated by painful stimuli (Rainville et al., 1997; Derbyshire et al., 1997; Tolle et al., 1999; Kwan et al., 2000; Brooks et al., 2002; Hutchison et al., 1999). Since the early cortical activity associated with a point localization task has a mean latency of 83 ms (Valeriani et al., 2000), it is possible that TMS of MFC at 50 and 100 ms disrupts pain processing. The ACC is critical for normal pain-related behavior (Devinsky et al., 1995). Therefore, inhibition of pain might be due to disruption of activity in the MFC and/or ACC by TMS. It was found that TMS over the MFC/ACC impaired cognitive processing of angry, but not happy, facial expressions of emotion (Harmer et al., 2001). Thus, in the present experiment, it could be hypothesized that TMS reduced effective pain sensation by affecting the emotional aspect of pain. While it has been found that repetitive TMS of 10 Hz over the motor cortex can reduce chronic pain (Lefaucheur et al., 2001), the present result suggests that the MFC may also be a possible target site of TMS for relief of chronic pain.

4.3. Effects of SII stimulation

TMS over SII failed to show any effects on pain sensation, although patients with lesions including the parietal operculum and posterior insula have impaired pain perception (Greenspan et al., 1999). So-called pain-related SII activity, however, involves much wider region comprising the depth of the Sylvian fissure and the parietal and frontal operculi (Xu et al., 1997; Peyron et al., 2000). Thus, the reason why the present TMS of SII did not affect pain perception may be that its effect was too localized to disrupt all neuronal activities in the parietal and frontal operculi and posterior insula. It is also possible that the unstimulated SII in the other hemisphere may compensate for the effect of unilateral SII stimulation, because pain-related SII activation is seen bilaterally and almost simultaneously (Ploner et al., 1999; Kanda et al., 2000).

4.4. Effect on localization of pain

Localization of the pain spot was insensitive to the TMS, suggesting that the cortical channel for localization of pain is different from that for pain intensity. Both SI and SII have been thought to be important for the sensory-discriminative dimension of pain processing, because animal studies showed that SI and SII contain neurons that code spatial, temporal, and intensive aspects of noxious as well as innocuous somatosensory stimuli (Kenshalo and Isensee, 1983; Chudler et al., 1990; Craig et al., 1994; Dong et al., 1994; Shi and Apkarian, 1995). Previous MEG studies suggest that the contralateral SI and the bilateral SII most likely process pain information in a parallel way (Ploner et al., 1999; Kanda et al., 2000). Thus, it is likely that information about pain localization may be relayed simultaneously at both SI and SII and that pain localization requires activity throughout this distributed cortical network. Since the peak latency of a cortical potential regarding the point localization following painful CO2 laser stimulation was over 600 ms (Kanda et al., 1999), the important timing for localization may be 400 ms post-stimulus or even later, which may be beyond the scope of the present study where we focused on the earlier phase of pain processing.

The present study has demonstrated that TMS can be used to investigate cortical mechanisms of pain processing, complementing other neuroimaging studies using PET, fMRI and MEG. Modulating effects of TMS on pain suggest that TMS could be used in the future (in conjunction with other methods) to control pain in certain conditions. As proposed by Pridmore and Oberoi (2000), studies would also be justified to determine whether TMS can correct or compensate for neuroplastic changes in the central nervous system that may be at least in part responsible for chronic pain.

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