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Modulation of electrically induced pain by paired pulse transcranial magnetic stimulation of the medial frontal cortex

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Abstract

Objective: Aim of this study was to investigate whether paired pulse transcranial magnetic stimulation (ppTMS) applied over the medial frontal cortex (MFC) affects acute Aδ fiber-mediated electrically induced pain. In addition, we investigated whether this effect depends on the time course of the stimulation, on the noxious stimulus intensity or on the ppTMS intensity.

Methods: For painful stimulation, the electrical stimulus for the nociceptive flexion reflex (NFR) was used. PpTMS (ISI: 50 ms) was applied over the medial frontal cortex at different intervals ranging from 0 to 1000 ms following the previous elicited NFR in 10 healthy volunteers. Three sequences at 3 different NFR stimulus intensities (at NFR threshold, 1.3× and 1.6×NFR threshold) with a ppTMS stimulus intensity at 1.2×resting motor threshold (RMT) and one sequence with elevated ppTMS at 1.6×RMT stimulus intensity were performed. Pain intensity and pain unpleasantness were assessed by visual analogue scales.

Results: Pain ratings differed in dependence of the interstimulus interval between NFR and ppTMS. Post-hoc *t*-tests revealed an increased verbal pain report within interstimulus intervals from 25 to 75 ms at NFR threshold as well as for 25 ms at 1.3×NFR threshold when ppTMS was applied at 1.2×RMT and from 0 to 75 ms at 1.6×NFR threshold when ppTMS was applied at 1.6×RMT.

Conclusions: The present data suggest that ppTMS over MFC—applied in a certain time window—can enhance pain perception of acute Aδ fiber-mediated electrically induced pain. We hypothesize that the increase of pain is due to interference between ppTMS and the incoming nociceptive input. Further pain processing might be modulated by direct effects on MFC or indirect effects on anterior cingulate cortex (ACC) or spinal nociception.

Significance: Brain areas involved in cognitive and emotional adaptation to pain can be used, in place of primary motor areas, as cortical targets in TMS trials of experimental or ongoing pain.

Keywords: Medial frontal cortex; Anterior cingulate cortex; Paired pulse TMS; Nociception; Pain processing

1. Introduction

Repetitive-transcranial magnetic stimulation (rTMS) and paired-pulse transcranial magnetic stimulation (ppTMS) have been shown to modulate nociceptive processing of the cerebral cortex in chronic pain and in acute experimentally induced pain. The effect on perceived pain has been found to depend mainly on the stimulation parameters, the cortical target and the nature of pain. Reduction of chronic pain was reported for high frequency rTMS of the motor cortex by some investigators (Lefaucheur et al., 2001, 2004; Pleger et al., 2004), while others did not find such an inhibitory effect (Rollnik et al., 2002).

Low frequency 1 Hz rTMS of the motor cortex resulted in an increase of acute Aδ fiber-mediated laser induced pain and a decrease of acute C fiber-mediated capsaicin induced pain (Tamura et al., 2004a,b). These different effects were

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assumed to be due to different cortical representations of first and second pain as described by Ploner et al. (2002). Since, Aδ fiber-mediated pain is more closely related to the somatosensory cortex, 1 Hz repetitive stimulation might enhance noxious Aδ fiber-mediated input (Tamura et al., 2004a). On the other hand, the inhibitory effect of rTMS on C fiber-mediated pain was assumed to be caused by changes in medial pain pathways (Tamura et al., 2004b).

Focal ppTMS over the medial frontal cortex (MFC) was found to have an inhibitory effect on CO_2 laser induced pain when applied with an interstimulus interval (ISI) of 50 ms to prior noxious stimulation. The converse effect was observed when ppTMS was applied over the sensorimotor cortex using an ISI of 150 ms (Kanda et al., 2003). It has been concluded that ppTMS disrupts pain processing on the level of the MFC or on the level of the anterior cingulate cortex (ACC). However, so far little is known about the conditions of this interaction between ppTMS over MFC and pain perception. Thus, we aimed to investigate whether the modulation of acute electrically induced pain by ppTMS over the MFC depends on the noxious stimulus characteristics, on the intensity of the ppTMS or on the time course of the stimulation. In order to obtain a well-defined noxious induction method, we used the Aδ fiber-mediated nociceptive flexion reflex (NFR) of the lower limb. Pain intensity and pain unpleasantness were assessed using visual analogue scales.

2. Materials and methods

2.1. Subjects

Ten healthy young subjects (female: 7, male: 3) between the age of 20 and 30 years (mean ± SE; 23.4 ± 1.7) were recruited. Eight of them were right handed, two were left handed. None of the subjects had taken any analgesic medication for at least 24 h prior to the sessions. All subjects gave written informed consent. The study protocol was approved by the local ethics commission.

2.2. Nociceptive flexion reflex (NFR)

Electrophysiological recordings were performed using a standard electro-diagnostic device (Viking IV D, VIASYS Healthcare) with modified software. In order to localize the sural nerve for reflex stimulation and to exclude patients with sensory polyneuropathy, sural neurography was performed. Stimulation was done by surface electrodes attached on the left calf over the subcutaneous course of the sural nerve (cathode inferior). For recording, surface electrodes were fixed to the left leg over the retromalleolar course of the nerve. Twenty consecutive recordings were averaged. A nerve conduction velocity of at least 40 m/s and amplitude of at least 5 μV were required for inclusion.

For recording of the nociceptive flexion reflex (NFR), surface electrodes were attached on the left calf (anode inferior, same localization as for sural nerve neurography). The recording electrode was attached ipsilateral over the short head of the biceps femoris muscle, and the reference electrode was fixed near the tendon of the biceps femoris muscle at the head of the fibula. Stimulation of the sural nerve elicits two responses in the biceps femoris muscle, the first is of short latency (40–70 ms, RII) and low threshold reflecting a tactile reflex, the second of longer latency (80–150 ms, RIII) and higher threshold corresponding to a nociceptive reflex (Willer, 1977). A time window of 80–150 ms was selected in order to exclude RII responses and voluntary limb movements (France et al., 2002; Garcia-Larrea et al., 1999; Willer, 1977). Furthermore, an amplitude of at least 40 μV (corresponding to a level of 150% of baseline fluctuations) within 100 ms after reflex onset was required to distinguish with certainty reflex responses from baseline fluctuations. As described previously, a stimulus train of 5 impulses of 1 ms duration at a frequency of 250 Hz was used (Sandrini et al., 1993; Schepelmann et al., 1998). Stimulus trains were applied at intervals varying from 10 to 15 s in order to avoid habituation.

The nociceptive flexion reflex threshold was assessed using the up–down staircase method (France et al., 2002; Levitt, 1971). Stimulation intensity was increased in 3 mA increments until the flexion reflex RIII component was detected the first time. Next, we lowered stimulus intensity in 2 mA steps until the reflex disappeared. After that, steps of 1 mA were used and the procedure was repeated until the reflex appeared and subsided two more times. Mean values of 3 peaks (current intensity that just elicited a reflex) and 3 troughs (current intensity that no longer elicited a reflex) determined the reflex threshold.

2.3. Transcranial magnetic stimulation (TMS)

TMS was delivered through a focal 9 cm figure-8-shaped magnetic coil (external diameter) connected with either a single Magstim-200 or two Magstim-200 connected by a Bistim module (Whitland, Dyfed, UK). Motor evoked potentials were recorded by surface electrodes from abductor digiti minimi muscle contralateral to the dominant site of the motor cortex using a belly-tendon montage. The coil was placed flat on the skull over the dominant motor cortex at the site optimal for abductor minimi muscle activation. The resting motor threshold (RMT) was defined as the lowest stimulator output needed to induce a MEP of >50 μV peak-to-peak amplitude in at least 5 of 10 consecutive trials.

The ppTMS intensity was set to 1.2 and 1.6 × RMT with a fixed ISI of 50 ms between the two stimuli. The ISI of 50 ms was chosen in order to reach a prolongation of the disruptive effect of each single stimulus as suggested by Jahanshahi and Rothwell (2000).