Neuroscience Letters 356 (2004) 87–90

Neuroscience Letters

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Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I

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Received 15 August 2003; received in revised form 9 October 2003; accepted 13 November 2003

Abstract

In complex regional pain syndrome (CRPS) many clinical symptoms suggest involvement of the central nervous system. Neuropathic pain as the leading symptom is often resistant to therapy. In the present study we investigated the analgesic efficiency of repetitive transcranial magnetic simulation (rTMS) applied to the motor cortex contralateral to the CRPS-affected side. Seven out of ten patients reported decreased pain intensities. Pain relief occurred 30 s after stimulation, whereas the maximum effect was found 15 min later. Pain re-intensified increasingly 45 min after rTMS. In contrast, sham rTMS did not alter pain perception. These findings provide evidence that in CRPS I pain perception can be modulated by repetitive motor cortex stimulation.

Keywords: Complex regional pain syndrome; Pain; Cortical reorganization; Repetitive transcranial magnetic stimulation; Precentral stimulation; Motor cortex

Complex regional pain syndrome (CRPS) is a syndrome that develops after trauma to a bone, nerve, plexus, or soft tissue. Clinically, it is subdivided into two types: type I occurs without any peripheral nerve lesions, whereas in type II a definable nerve lesion is obligatory [21]. The traumatized limb is characteristically affected by a series of complex symptoms including edema, increased bone metabolism, changes in skin blood flow and trophism [2,23]. However, spontaneous pain and allodynia are the most difficult symptoms to treat [19]. Changes in central somatosensory [9,17,18], autonomic ([1], for a review see ref. [8]) and motor processing [20] are discussed as mechanism sustaining pain perception, and alterations on a thalamic level might be crucial [3,4].

Precentral stimulation by epidurally implanted electrodes has already proven efficiency in treating multi-resistant neuropathic pain [12]. Repetitive transcranial magnetic stimulation (rTMS) offers us the opportunity to stimulate precentral gyrus (primary motor cortex, M1) in a non-invasive manner with limited side-effects [24]. Lefaucheur et al. previously reported a significant reduction in pain levels due to precentral rTMS in miscellaneous neuropathic pain syndromes [10,11].

The present study is the first approach investigating the analgesic effect of placebo-controlled 10 Hz rTMS applied to the motor cortex in a homologous group of patients with unilateral CRPS I of the hand.

Ten right-handed patients (seven female, three male, age: mean 51; ranging from 29 to 72) were included. They fulfilled the criteria of The International Association for the Study of Pain (IASP) taxonomy [21]. All patients therefore underwent clinical neurological and electroneurographical examination (for further clinical data see Table 1). 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. All patients gave their written informed consent. The duration of CRPS was between 24 and 72 months (mean 35 months). Patients had not taken central acting drugs for at least 48 h before participating in the study. In order to avoid longer-term intermission of drug administration we evaluated current pain intensities over 90 min even though the analgesic effect may endure over some days [11].

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0304-3940/03/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2003.11.037

Table 1
The table shows the clinical data, individual pain intensities before and after verum rTMS application and the side effects (below, are listed the mean values, the standard deviations (SD) and the standard errors (SE))

Case	Affected upper limb	CRPS initiated by	Pain intensity (VAS) before verum rTMS	Pain intensity (VAS) after verum rTMS (30 s)	Pain intensity (VAS) after verum rTMS (15 min)	Pain intensity (VAS) after verum rTMS (45 min)	Pain intensity (VAS) after verum rTMS (90 min)	Side effects due to verum rTMS
1	ri	Minor trauma	6	4	5	5	5	Right hemihyperthermaesthesy
2	ri	Minor trauma	2.5	1.6	1.4	1.3	1.4	None
3	ri	Radial fracture	9	9	9	9	9	None
4	ri	Radial fracture	6	5.1	3.8	2.2	2.2	Prickling pareastesia, CRPS-limb
5	ri	Radial fracture	2.7	2	1.6	1.6	1.6	None
6	ri	Luxation of DII, III	0.8	0.7	0.5	0.3	0.3	Prickling pareastesia, CRPS-limb
7	le	Fracture of Os navic.	3.6	3.7	3.6	3.6	3.6	Tiredness
8	le	Minor trauma	4.7	4.8	4	3.3	3.2	Light dizziness
9	ri	Radial fracture	7.2	7.2	7.3	7.3	7.3	Light headache
10	le	Fracture of Os navic.	4	2.2	2.8	3	3.7	Left hemihyperthermaesthesy
Mean			4.72	4.23	4.02	3.73	3.73	
SD			2.58	2.68	2.78	2.89	2.88	
SE			0.77	0.8	0.83	0.87	0.87	

Using a computerized random generator, five patients were first assigned to the placebo group (sham rTMS), while the others were treated using verum rTMS. On the next day the groups were reversed.

Patients were comfortably seated and the CRPS-affected limb was laid on the armrest in a relaxed position. The evaluation of motor thresholds (MT) as well as the application of rTMS was performed with a Magstim Super Rapid (Magstim, Whitland, Deyfed, UK) and a figure-of-eight shaped TMS-coil. Using single-pulse TMS, we determined individual resting MT of the first dorsal interosseus muscle (FDI). The scalp position for the rTMS application was considered to be located over the hand area of the motor cortex where single-pulse TMS elicited the highest amplitudes. MT was defined as the minimum intensity which produced five MEPs >50 μV out of ten trials. Pulse intensity was adjusted to 110% of MT. The frequency was set to 10 Hz. A series of ten rTMS applications, each lasting 1.2 s in length, were applied. Between each series, rTMS was interrupted for 10 s. During rTMS EMG response of the FDI and Biceps brachii muscle were continuously monitored to exclude a spread of excitation. Sham rTMS was applied to the same position over the motor cortex using identical stimulation parameters. However in this case the coil was angled at 45° with only the edge of the coil resting on the scalp. Patients' impression during sham rTMS was similar to verum rTMS.

Patients determined current pain intensity 30 s, 15 min, 45 min and 90 min after rTMS application using a visual analogue scale (VAS) ranging from 0 (= no pain) to 10 (= most extreme pain). VAS data was statistically analyzed using ANOVA for repeated measurement and Student's paired *t*-test for post-hoc analysis.

Mean MT of the M. interosseus dorsalis 1 (FDI) was found at 51% (±12.5%, SD). The initial pain intensities (VAS) were similar prior to verum and sham rTMS (Student's paired *t*-test, $P = 0.47$). The level of intensity was also independent of whether the patients were first subjected to sham or verum rTMS ($P > 0.05$).

Seven out of ten patients responded to verum rTMS and showed decreased pain levels after rTMS ($n = 10$; ANOVA: df = 4, $F = 4.035$, $P = 0.008$; Fig. 1a; for individual data, clinical features and side effects see Table 1). This effect occurred 30 s after stimulation (post-hoc Student's paired *t*-test: pre-rTMS vs. post-30 s, $P = 0.03$), whereas maximum analgesic effect was observed 15 min later (pre-rTMS vs. post-15 min, $P = 0.009$). After 45 min pain re-intensified increasingly (pre-rTMS vs. 45 min, $P = 0.02$; pre-rTMS vs. 90 min, $P = 0.03$; Fig. 1a).

Sham rTMS caused no changes in individual pain intensity (ANOVA: df = 4, $F = 0.286$, $P = 0.885$; 30 s ($P = 0.34$), post-hoc Student's paired *t*-test, 15 min ($P = 0.46$), 45 min ($P = 0.63$) and 90 min ($P = 0.63$); Fig. 1b).

We additionally compared the effect of verum and sham rTMS intra-individually using Student's paired *t*-test. We calculated differences between initial pain intensity and pain intensities experienced in the following four successive evaluations and compared both conditions statistically (pre – 30 s: $P = 0.01$; pre – 15 min: $P = 0.006$; pre – 45 min: $P = 0.02$; pre – 90 min: $P = 0.02$; Fig. 2).

In order to provide a subject-by-subject comparison, we extended statistic analyzes by calculating ANOVA for repeated-measurements using the within-subject factor time (pre-rTMS, after-rTMS: 30 s, 15 min, 45 min, 90 min) and condition (verum, sham). The findings corroborated significantly decreased individual pain intensity after verum rTMS (ANOVA: df = 4, $F = 3.665$, $P = 0.013$).

In summary, seven out of ten patients experienced decreased pain intensity after rTMS was applied to the motor cortex contralateral to the CRPS-affected limb.

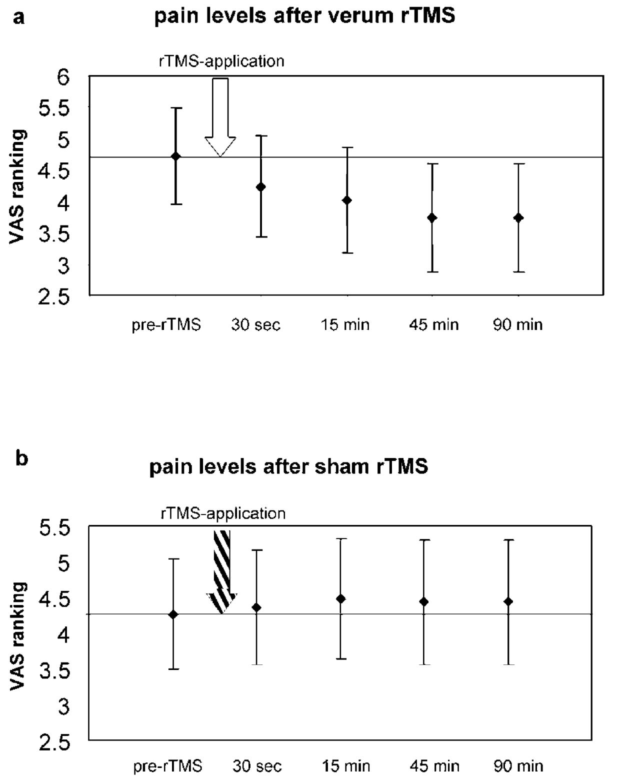

Fig. 1. The figure demonstrates the mean pain intensities and the standard errors after verum rTMS (a); and sham rTMS (b). After verum rTMS we found a decrease in pain intensity, whereas sham rTMS caused no changes in pain perception. This effect was provable directly after stimulation, whereas the maximum pain reduction was found 15 min after verum rTMS. Afterwards, pain re-intensified increasingly.

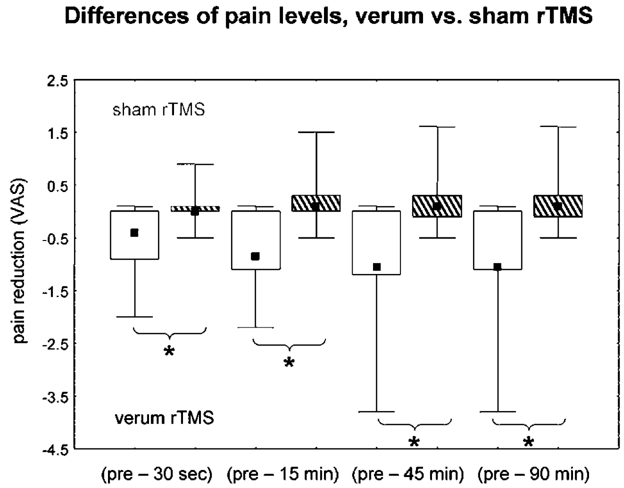

Fig. 2. The box-whisker-plot shows the benefit of verum rTMS when compared to sham rTMS. We calculated the pain-level (VAS) differences between pre-rTMS and the four successive evaluations over 90 min post-rTMS (the black point within the box gives the median of data. The top and bottom of the box gives the 25 and 75 percentiles, respectively. The top and bottom of the whisker gives the maximum and the minimum, respectively). To elucidate the difference between both conditions we used Student's paired *t*-test (*$P < 0.05$).

Whereas, placebo rTMS (sham rTMS) caused no changes in pain perception.

After placing electrodes epidurally repetitive stimulation of M1 elicited analgesic effect in patients with previously intractable neurogenic pain [12]. The non-invasive stimulation of the precentral gyrus by means of transcranial rTMS proved a similar efficiency in the treatment of neurogenic pain [10,11,16,22] with less complications [24]. Lefaucheur et al. investigated eighteen patients with definite neuropathic pain syndromes due to peripheral nerve injury and central nervous lesions. After 10 Hz rTMS patients experienced significantly decreased mean pain intensities, whereas 0.5 Hz and placebo rTMS did not interfere with pain perception [10]. The presented findings provide first evidence for a pain-relieving effect of precentral rTMS in a homologous group of patients suffering from CRPS I. In spite of these encouraging results, the pathophysiological origin remains elusive [5].

A number of functional imaging studies reported bilateral thalamic response in healthy subjects during pain stimulation, probably reflecting generalized arousal in reaction to pain (for a review see ref. [14]). In patients suffering from CRPS [3,4] as well as in patients with other chronic neuropathic pain syndromes [7] altered thalamic blood flow was found contralateral to the pain affected limb. In CRPS, changes in thalamic activity are therefore discussed as the crucial neurophysiological mechanism mediating neuropathic pain [4].

Garcia-Larrea et al. previously studied regional changes in cerebral blood flow (rCBF) in ten patients undergoing precentral stimulation for pain control. Using positron emission tomography (PET), they found the most significant increase in rCBF from ventral-lateral thalamus. This highlighted the thalamus as the key structure mediating the analgesic effect [5].

We propose that an influence on thalamic activity might therefore represent a possible mechanism allowing the pain-relieving effect of repetitive motor cortex stimulation in CRPS I. rTMS applied contralateral to the CRPS affected limb may trigger attenuated thalamic activity [3,4] directly via cortico-thalamic projections [13,15]. This in turn might intercede with ascending nociceptive pathways, like the spinothalamic tract as the main 'pain' pathway, that project from the spinal cord to the brainstem as far rostral as the thalamus (for a review see ref. [6]). Alternatively, the influence of rTMS on pain processing at the level of brainstem or spinal cord and a possible interference with the central efferent sympathetic outflow which in turn might interrupt the positive feedback circuit of pain might be considered [8].

In summary, the neurophysiological mechanism underlying analgesic effect of precentral rTMS remains speculative and is beyond the scope of this study. However, our findings provide evidence that pain perception can be modulated by repetitive motor cortex stimulation also in CRPS I, a subtype of neuropathic pain syndromes. Studies combining modern functional imaging methods and rTMS are necessary to provide deeper insight into the complex neurophysiological mechanism underlying the observed analgesic effect of precentral rTMS.

Acknowledgements

This research was supported by a grant from the BMBF (NR. 01EM0102) and by a grant of the Scientific Research Council of BG-Kliniken Bergmannsheil, Bochum (to C.M. and P.S.). We thank Steve Langan for skilful editing of the manuscript.

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