Repetitive Transcranial Magnetic Stimulation for the Treatment of Chronic Pain – A Pilot Study

Jens D. Rollnik\textsuperscript{a} Stefanie Wüstefeld\textsuperscript{a} Jan Däuper\textsuperscript{a} Matthias Karst\textsuperscript{b} Matthias Fink\textsuperscript{c} Andon Kossev\textsuperscript{d} Reinhard Dengler\textsuperscript{a}

Departments of \textsuperscript{a}Neurology and Clinical Neurophysiology, \textsuperscript{b}Anesthesiology, Pain Clinic, and \textsuperscript{c}Physical Medicine and Rehabilitation, Medical School of Hannover, Germany; \textsuperscript{d}Department of Biophysics, Bulgarian Academy of Sciences, Sofia, Bulgaria

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Repetitive transcranial magnetic stimulation - rTMS treatment - Chronic pain, treatment

Abstract
Invasive electrical stimulation of the motor cortex has been reported to be of therapeutic value in pain control. We were interested whether noninvasive repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex might also act beneficially. Twelve patients with therapy-resistant chronic pain syndromes (mean age 51.3 \pm 12.6, 6 males) were included in a pilot study. They were treated with rTMS of the corresponding motor cortex area for 20 min (20 Hz, 20 \times 2 s trains, intensity 80\% of motor threshold) and sham stimulation (sequence-controlled cross-over design). Some of the patients (6/6) had an analgesic effect, but for the whole group, the difference between active and sham stimulation did not reach a level of significance (active rTMS: mean VAS reduction -4.0 \pm 15.6\%; sham rTMS: -2.3 \pm 8.8\%). Further studies using different rTMS stimulation parameters (duration and frequency of rTMS) or stimulation sites (e.g. anterior cingulate gyrus) are strongly encouraged.

Introduction
There is increasing evidence from the literature that electrical stimulation of the central nervous system might contribute to pain reduction. Gerhart et al. \cite{1} demonstrated that stimulation of the ventral posterior lateral thalamic nucleus inhibits primate spinothalamic tract neurons. In addition, stimulation of central motor fibers may inhibit dorsal horn afferents leading to analgesic effects \cite{2, 3}. Tsubokawa et al. \cite{4} demonstrated an amelioration of central post-stroke pain by means of chronic motor cortex stimulation (MCS). It has to be mentioned that MCS offers a better risk-benefit ratio than the more invasive stimulation of deeper structures such as the thalamus \cite{4}. Further studies proved the efficacy of MCS in trigeminal neuropathic pain and central pain in Wallenberg syndrome \cite{5, 6}.

The precise pain-inhibiting mechanism of MCS is still a matter of discussion. Positron emission tomography (PET) studies indicate that MCS leads to an increase of cerebral blood flow in the ipsilateral thalamus, orbitofrontal and cingulate gyri, and in the upper brainstem \cite{7}. These results were reproduced and expanded by Garcia-Larrea et al. \cite{8}. The authors hypothesize that thalamic nuclei connected with motor and premotor cortices are
### Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Patient (initials)</th>
<th>Sex (m/f)</th>
<th>Age (years)</th>
<th>Pain site</th>
<th>Pain etiology</th>
<th>VAS change active rTMS, %</th>
<th>VAS change sham rTMS, %</th>
<th>Motor threshold, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.K. m</td>
<td>51</td>
<td>Left arm</td>
<td>Brachial plexus injury</td>
<td>-2.0</td>
<td>-2.3</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>B.M. m</td>
<td>67</td>
<td>Left arm</td>
<td>Neuromas of the brachial plexus</td>
<td>-4.7</td>
<td>+12.8</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>M.M. f</td>
<td>41</td>
<td>Right foot</td>
<td>Radiculopathy</td>
<td>+4.0</td>
<td>+2.8</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>W.N. m</td>
<td>58</td>
<td>Right hand</td>
<td>Sympathetic dystrophy</td>
<td>-17.9</td>
<td>-</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>H.R. m</td>
<td>64</td>
<td>Both forearms and chest</td>
<td>Cervical myelopathy</td>
<td>-25.3</td>
<td>-7.4</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>W.R. f</td>
<td>67</td>
<td>Both feet</td>
<td>Polyneurathy</td>
<td>-32.6</td>
<td>-1.1</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>P.R. m</td>
<td>39</td>
<td>Left foot</td>
<td>Osteomyelitis</td>
<td>+0.4</td>
<td>+2.3</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>B.K. f</td>
<td>63</td>
<td>Right leg</td>
<td>Phantom limb</td>
<td>+16.1</td>
<td>-3.9</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>D.V. m</td>
<td>48</td>
<td>Both legs</td>
<td>Myelopathy</td>
<td>-15.1</td>
<td>-</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>G.K. f</td>
<td>51</td>
<td>Right foot</td>
<td>Sympathetic dystrophy</td>
<td>+4.8</td>
<td>-</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>B.Z. f</td>
<td>33</td>
<td>Left hand</td>
<td>Peripheral nerve lesion</td>
<td>+10.2</td>
<td>-4.0</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>A.H. f</td>
<td>34</td>
<td>Right face</td>
<td>Post-herpetic neuralgia</td>
<td>+14.3</td>
<td>-20.1</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Mean or sum¹</td>
<td>6/6</td>
<td>51.3 ± 12.6</td>
<td>-</td>
<td>-</td>
<td>-4.0 ± 15.6</td>
<td>-2.3 ± 8.8</td>
<td>64.5 ± 12.1</td>
</tr>
</tbody>
</table>

¹ Standard deviation is indicated (±).

activated by MCS. This thalamic activation would entail a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the medial thalamus, anterior cingulate and upper brainstem [8]. In addition, MCS might influence the affective-emotional component of chronic pain by means of cingulate and orbitofrontal activation, and lead to descending inhibition of pain impulses by activation of the upper brainstem [8].

Transcranial magnetic stimulation (TMS) allows a noninvasive stimulation of the motor cortex and enables the evaluation of motor-evoked potentials [9]. Repetitive TMS (rTMS) means that more than two stimuli at constant inter-stimulus intervals are applied with a higher frequency than 1 Hz [10]. High stimulation frequencies (e.g. 20 Hz) are able to activate cortical areas, whereas lower frequencies have an inhibiting influence [11]. rTMS has been tried therapeutically in psychiatric disorders associated with a frontal hypometabolism, e.g. major depression or schizophrenia [12–15]. In addition, rTMS of the motor cortex has been tried to ameliorate dystonic symptoms [16].

Since rTMS allows a noninvasive stimulation of the motor cortex, we were interested whether rTMS might have pain-reducing effects comparable to those of electrical MCS [8]. The benefit of such a therapy is obvious: In contrast to conventional MCS, no neurosurgical intervention would be necessary. Therefore, we carried out a study including 12 patients with different intractable pain syndromes being treated with rTMS of the motor cortex. The major goal of the study was to reduce – at least temporarily – subjectively reported pain in chronic pain sufferers.

### Material and Methods

We included 12 patients (6 males) with intractable chronic pain syndromes from our Pain Clinic (table 1), aged 33–67 years (mean 51.3, SD 12.6). Mean duration of chronic pain was 2.7 years (SD 2.3). Patients showed moderate depressive symptoms with a mean Beck Depression Inventory (BDI) [17] value of 14.5 (SD 10.2). Five of them were suffering from chronic pain at the upper, and 6 at the lower extremities, 1 patient had facial pain. The pain etiologies were brachial plexus impairment (n = 2), peripheral nerve lesion (n = 1), radiculopathy (n = 1), sympathetic dystrophy (n = 2), polyneuropathy (n = 1), myelopathy (n = 2), post-herpetic neuralgia (n = 1), phantom limb (n = 1), and osteomyelitis (n = 1) (table 1). After description of the study to the patients, written informed consent was obtained through a protocol approved by the local ethics committee. Patients with a history of seizures or a pacemaker were excluded.

rTMS was performed with a MagstimRapid (Magstim Co., Whitland, UK). On the initial visit the motor threshold (MT) of a muscle close to the pain region (for upper extremity: abductor digiti quinti muscle; for lower extremity: tibialis anterior muscle) was determined. In order to determine MT at rest we usually started with 40% of maximum stimulator output, increasing stepwise in 5% intervals [18, 19]. When MEPs could be evoked, stimulus intensity was reduced in steps of 1–2% until MT could be identified (lowest intensity which produced three responses with an amplitude of at least
Fig. 1. VAS monitoring of patient H.R. (male, 64 years). The patient was suffering from intractable pain in both arms and chest because of a cervical myelopathy for 6 months. After active stimulation, VAS markedly decreased and remained on a relatively low level for several days. Sham stimulation did not change the situation.

50 µV in four trials). Mean MT in our sample was 64.5% (± 7.8) of maximum stimulator output. Stimulation site was the motor cortex contralateral to the pain site. A double-cone coil was used to stimulate the corresponding leg area (current in the coil was directed anteriorly) and a circular coil (current direction in the coil was anti-clockwise when viewed from above) over vertebrae for the arm area. We performed twenty 2-second, 20-Hz stimulations with 80% of MT intensity over 20 min (800 pulses per session) as active treatment once (paradigm of George et al. [13]). Sham stimulation occurred in the same manner as active rTMS, except that the angle of the coil, rather than being tangential to the skull was at 45° off the skull. In a sequence-controlled cross-over design, sham and active treatment were given in random order (on different days), 6 subjects started with placebo and 6 with active rTMS.

Before (baseline) and after (0, 5, 10, and 20 min) active or sham treatment, pain intensity was monitored using a conventional visual analog scale (VAS), ranging from 0 to 100 mm (0 = ‘no pain at all’, 100 = ‘unbearable pain’) [20]. Patients were required to give three consecutive VAS ratings before and at each follow-up examination in order to compute a mean of these three measurements. Patients were well instructed to use the VAS correctly before entering the study. However, most of the patients already knew this instrument due to several years of experience in our Pain Clinic.

Statistics

VAS was the primary outcome parameter. VAS changes following rTMS treatment were compared using t-tests. Differences were regarded as significant with p < 0.05. Results are reported as mean ± SD.

Results

Under active treatment, 6 out of 12 patients reported an improvement of their symptoms. Mean pain reduction under active treatment was –4.0% (± 14.1, range –32.6 to +16.0%). Under sham rTMS, VAS also decreased (mean –2.3 ± 8.8, range –20.1 to +12.8%). For the whole group of patients, the difference between both conditions did not reach a level of significance (p > 0.05).

Patients W.N. (sympathetic dystrophy), H.R. (cervical myelopathy) and W.R. (polyneuropathy) benefited most from the treatment with a VAS reduction of 17.9, 25.3 and 32.6%. Subject H.R. (male, 64 years) profited the longest (for several days) from only one treatment. He was suffering from intractable pain in both arms and chest because of a cervical myelopathy. After active stimulation (left motor cortex), VAS markedly decreased and remained on a relatively low level for several days (fig. 1). Sham stimulation did not change the situation. Before treatment, patient H.R. suffered from strongest pain when moving his hands or fingers; after the treatment he was able to use his hands normally again. The effect was so impressive that the patient wanted to repeat the treatment as soon as possible.

For most patients with a benefit from the treatment, effects of active rTMS were limited to a few minutes, immediately after the stimulation (fig. 2). After 5 min, the values returned to baseline.

No severe side effects could be observed. However, 1 patient reported the temporary occurrence of headaches at the stimulation site and did not want to participate in the study any longer.

Discussion

Invasive electrical MCS may ameliorate symptoms in intractable chronic pain sufferers. It has been shown that MCS leads to a reduction in pain of central and peripheral origin [8]. The mechanisms contributing to this effect are
still unknown. Nevertheless, several authors have observed an increase of cerebral blood flow in the ipsilateral thalamus, orbitofrontal and cingulate gyri, and in the upper brainstem [7, 8]. It may be hypothesized that thalamic nuclei connected with motor and premotor cortices are activated by MCS entailing a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the medial thalamus, anterior cingulate and upper brainstem [8]. Another explanation of pain-reducing effects might be that MCS influences the affective-emotional component of chronic pain by means of cingulate and orbitofrontal activation, and leads to descending inhibition of pain impulses by activation of the upper brainstem [8].

rTMS is a noninvasive and effective tool to stimulate and activate cortical areas [11]. rTMS has been tried therapeutically in depressed and psychotic patients stimulating the dorsolateral prefrontal cortex [12–15]. In addition, rTMS of the motor cortex has been used to ameliorate dystonic symptoms [16].

We examined whether rTMS of the motor cortex might be a useful tool in the therapy of chronic intractable pain syndromes. In a pilot study with 12 patients, we could not demonstrate significant differences between active and sham treatment, although some patients had a remarkable benefit from the treatment. One patient with cervical myelopathy reported a persistent pain relief for several days. For the whole group, however, there was no statistically significant treatment effect. One of the mechanisms for positive and/or negative results might be placebo/nocebo effects. In a previous study focussing on local injections of botulinum toxin vs. placebo into pericranial muscles of tension-type headache sufferers, we reported placebo effects between 15.3 and 17.9% (VAS reduction, compared to baseline) [20]. It may be concluded that the procedure of rTMS per se is acting as a placebo, explaining some of the beneficial effects (in selected patients).

The results of this pilot study defy ready summary, but rTMS of the motor cortex did not show a significant pain-reducing effect in this study. There are, however, some limitations to this study: other stimulation sites or stimulation parameters have not been investigated. Taking into account that MCS techniques employ a chronic stimulation, longer rTMS stimulation periods should be considered. In addition, the sample size is quite small and pain syndromes were heterogeneous. Further studies are encouraged, employing larger sample sizes and using different stimulation techniques, in order to decide whether rTMS might be a noninvasive alternative to MCR in the treatment of therapy-resistant chronic pain syndromes.

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References


