Efficacy and tolerability in patients with chronic facial pain of two consecutive treatment periods of rTMS applied over the facial motor cortex, using protocols differing in stimulation frequency, duration, and train pattern

Laura Säisänen, Jukka Huttunen, Jelena Hyppönen, Mette Nissen, Ulla Kotiranta, Esa Mervaala, Mikael von und zu Fraunberg

Department of Applied Physics, Faculty of Forestry and Natural Sciences, University of Eastern Finland, Kuopio, Finland
Department of Clinical Neurophysiology, Clinical Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland
Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland
Department of Neurosurgery, Kuopio University Hospital, Kuopio, Finland
School of Medicine, Institute of Dentistry, University of Eastern Finland, Kuopio, Finland
University of Oulu, Oulu, Finland
Department of Neurosurgery, Oulu University Hospital, Oulu, Finland

Received 29 October 2021; accepted 4 March 2022
Available online 24 March 2022

Abstract
Objective: We conducted an open-label cross-over study assessing the global effect of two high-frequency protocols of electric-field navigated repetitive transcranial magnetic stimulation (rTMS) targeted to functional facial motor cortex and comparing their efficacy and tolerability in patients with chronic facial pain. Outcome predictors were also assessed.

Methods: We randomized twenty consecutive patients with chronic facial pain (post-traumatic trigeminal neuropathic pain, n=14; persistent idiopathic facial pain, n=4; secondary trigeminal neuralgia, n=2) to receive two distinct 5-day rTMS interventions (10Hz, 2400 pulses and 20Hz, 3600 pulses) separated by six weeks. The target area was assessed by mapping of lower face representation. The primary endpoint was the change in weekly mean of pain intensity (numeric rating

KEYWORDS
Chronic pain;
Neuronavigation;
Orofacial pain;
Repetitive transcranial magnetic stimulation

* Corresponding author at: Department of Clinical Neurophysiology, P.O. Box 100, 70029 KYS, Finland
E-mail address: laura.saisanen@kuh.fi (L. Säisänen).

https://doi.org/10.1016/j.neucli.2022.03.001
0987-7053/© 2022 The Author(s). Published by Elsevier Masson SAS. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Introduction

Chronic facial pain is a disabling disease and may have different causes [1]. It can be idiopathic, or it may develop after the injury of the trigeminal nerve branch due to trauma or medical procedures (e.g. dental treatments or surgical procedures such as trigeminal ganglion electrocoagulation or microvascular decompression for trigeminal neuralgia [9]).

When pharmacological pain treatment is inadequate or has unacceptable systemic side effects [4], there is a non-invasive option of neuromodulation with repetitive transcranial magnetic stimulation (rTMS) [19, 10, 24]. High-frequency rTMS targeted to the primary motor cortex (M1) has been shown to exert a considerable beneficial effect in relieving neuropathic pain with the proportion of responders ranging from 20 to 65% [37, 18], although a systematic review and meta-analysis only led to a weak recommendation and Cochrane review pointed to low evidence of a clinical and non-beneficial effect [58]. Female gender, shorter duration of pain and low Beck Anxiety Inventory scores showed a trend towards a better outcome (p=0.052, 0.060 and 0.055, respectively).

Conclusions: High-frequency rTMS targeted to face M1 alleviates treatment resistant chronic facial pain. Repeated treatment improves the analgesic effect. A protocol with higher frequency (above 10Hz), longer session duration (more than 20 minutes) and higher number of pulses (above 2400 pulses/session) did not improve the outcome. The results support early consideration of rTMS.

Methods

Study population

A total of 27 subsequent patients with chronic facial pain, evaluated by a multidisciplinary pain neuromodulation group and referred for rTMS, were screened between November 2015 and October 2017. Inclusion criteria were a diagnosis of unilateral facial pain other than classic trigeminal neuralgia (ICD-10: G50.1, G50.8, or G50.9) and baseline NRS of at least 4. The diagnosis was made by a neurologist specializing in pain. Disorders of dentoalveolar structures were diagnosed and treated by a dentist or oral and maxillofacial surgeon, if necessary. The etiology of pain was further classified according to the recent International Classification of Orofacial Pain (ICOP) [1] (Table 1). All but one patient who had
| Patient # | Age, gender | Painful side of the face | Most affected facial area* | ICOP code | Diagnosis | Etiology | BAI/BDI at baseline | Pain duration | GCPS | NRS baseline | Pain DETECT |
|-----------|-------------|--------------------------|---------------------------|-----------|-----------|----------|---------------------|---------------|------|------------|-------------|
| 1         | 60, F       | L (R)                    | III                       | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | dental root canal therapy | 5/11               | 1              | II          | 7          | 6           |
| 2         | 38, F       | R                        | II                        | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | zygomatic arch fracture at snowmobile accident + repair + coronoidectomy | 14/12             | 5              | IV          | 8          | 30          |
| 3         | 38, F       | L                        | I, II, III                | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | microvascular decompression for trigeminal neuralgia; anaesthesia dolorosa | 1/5               | 3              | IV          | 9          | 28          |
| 4         | 61, M       | mid                      | II                        | 6.2.2.    | Persistent idiopathic facial pain with somatosensory changes | idiopathic; no response to microvascular decompression | 7/10             | 6              | II          | 8          | 10          |
| 5         | 75, M       | L (R)                    | I                         | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | septoplasty + functional endoscopic sinus surgery (FESS) | 19/22             | 4              | III         | 9          | 1           |
| 6         | 36, M       | R                        | I, II, III                | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | tooth extraction | 15/19             | 4              | III         | 4          | 26          |
| 7         | 43, F       | L                        | II, III                   | 6.2.2.    | Persistent idiopathic facial pain with somatosensory changes | idiopathic; no response to microvascular decompression | 11/21             | 4              | IV          | 4          | 18          |
| 8         | 36, M       | L                        | II                        | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | direct blow to upper cheek during fall | 14/24             | 4              | IV          | 7          | 23          |
| 9         | 76, F       | L                        | I, II, III                | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | stereotactic radiosurgery for trigeminal neuralgia; subsequent anaesthesia dolorosa | 14/14             | 9              | II missing  | 14         |
| 10        | 66, F       | L (R)                    | II                        | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | infraorbital basal cell carcinoma excision with rotation flap | 38/33             | 2              | IV          | 10         | 12          |
| 11        | 57, F       | R                        | I, II, III                | 4.1.1.2.  | Secondary trigeminal neuralgia | pontocerebellar meningioma in contact with trigeminal nerve; stereotactic radiosurgery to meningeoma | 8/0 | 1 | I | 5 | 23 | |
| 12        | 56, F       | R (L)                    | II, III                   | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | dental root canal therapy | 0/3 | 6 | III | 7 | 24 | |
| 13        | 46, F       | L (R)                    | I, II, III                | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | tooth extraction | 7/13 | 5 | IV | 10 | 37 | |
| 14        | 50, M       | L, R                     | I                         | 4.1.1.2.  | Secondary trigeminal neuralgia | multiple sclerosis | 22/16 | 10 | IV | 6 | 17 | |
| 15        | 78, F       | L, R (L)                 | I, II, III                | 6.2.1.    | Persistent idiopathic facial pain without somatosensory changes | idiopathic | 30/28 | 1 | II | 7 | 14 | |
| 16        | 74, F       | R                        | II, III                   | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | multiple dental operations | 29/24 | 15 | IV | 9 | 31 | |
| 17        | 79, M       | R                        | II                        | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | maxillary sinus surgery; thermocoagulation of the Gasserian ganglion worsening the pain | 29/27 | 15 | IV | 7 | 26 | |
| 18        | 82, F       | L                        | II, III                   | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | maxillary sinus surgery; thermocoagulation of the Gasserian ganglion x 3 for trigeminal neuralgia with subsequent anaesthesia dolorosa | 8 | 7 | 20 | |
| 19        | 49, F       | L (R)                    | I, II                     | 4.1.2.3.  | Post-traumatic trigeminal neuropathic pain | maxillary sinus surgery | 14/15 | 3 | III | 5 | 12 | |
| 20        | 53, M       | L                        | I                         | 6.2.2.    | Persistent idiopathic facial pain with somatosensory changes | idiopathic; temporary relief from sphenopalatine ganglion block | 4/7 | 17 | II | 5 | 15 | |

*Affected facial area described according to trigeminal nerve branches: I — ophthalmic nerve area, II — maxillary nerve area, III — mandibular nerve area. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; GCPS, Graded Chronic Pain Scale; ICOP, International Classification of Orofacial Pain; NRS, Numeric Rating Scale; F, female; M, male; L, left; R, right.
received 5 days of rTMS 3 months prior to enrollment into the study, were naïve to TMS. Exclusion criteria were active epilepsy, severe acute psychiatric disorders and contraindications to MRI or TMS [53]. Written informed consent was obtained from each participant before inclusion in the study. The protocol was approved by the local Ethical Committee (89/2015).

Study design
The timeline of the crossover study is depicted in Fig. 1. Structural three-dimensional (3D) T1-weighted MR brain images (TR 8.07 ms, TE 3.7 ms, flip angle 8°, 1 × 1 × 1 mm³ resolution) were acquired for neuronavigation with a 3T scanner (Philips Achieva TX, Philips Healthcare, Eindhoven, The Netherlands). At the baseline visit to the Department of Clinical Neurophysiology, the hotspots of hand (m. abductor pollicis brevis) and face (m. mentalis or m. orbicularis oris) representation areas were determined and their resting motor thresholds (rMT) were assessed with navigated TMS (software versions 3.2 and 4.3, Nexstim Plc., Helsinki, Finland) and EMG monitoring. The orientation of the coil was anteroposterior, approximately 45 degrees to midline, however, taking into account the underlying anatomy and sulcal patterns. More detailed description of the face muscle motor mapping is depicted in [55]. The rTMS treatment was targeted at the hotspot of the lower face using a stimulus intensity 90% of the rMT of hand or face, whichever was lower. If treatment of the lower face hotspot was not tolerated, the target was changed to the hand hotspot (n=1).

Before the first rTMS session, patients were randomly allocated to one of two five-day treatment protocols, using

---

**Fig. 1** Timeline of the study. Daily NRS was assessed one week before, during the therapy week, and during the following two weeks, for both rounds of treatment. The questionnaires were administered at baseline, and again after the last treatment session considering the whole study period. There was a phone call during the wash-out period. BAI=Beck Anxiety Inventory, BDI=Beck Depression Inventory, GCPS-DC=graded chronic pain scale, LS=life satisfaction.
also a ten minute pause in the middle of the 20Hz protocol.

1) the pain drawing (head and neck, mouth from inside and at baseline and a few days after the last treatment session: several secondary outcome measures, which were reported in the overall effect of two consequent treatments, we used could be before, after or during the rTMS. This daily assess-

Patients also wrote down the time of the assessment, which could elect to continue with maintenance therapy. The deci-

sion, patients received questionnaires regarding the whole study period, and returned them after two days. After the study protocol described above, the patients
decision about continuation was made during a consultation or phone call with the treating physician 4-6 weeks after the second rTMS session. The standard therapeutic maintenance protocol consisted of one rTMS session per day for five days with 3000 pulses at 10 Hz, train duration 6 s and ITI of 24 s, resulting in 15000 pulses weekly. In the maintenance phase, the protocol was repeated with an interval of approximately 2-3 months between consecutive treatments based on individual need (meaningful analgesic effect for the patient and willingness to continue), which was monitored by the referring physician.

Outcome measures

The primary outcome measure was the weekly mean of the maximum daily pain intensity, using NRS as compared to baseline. However, due to the high variabil-

ity in NRS, we additionally defined response to treatment using a combination with secondary outcomes of PGIC, whether the patients continued with at least two maintenance treatment sessions and the change in area size or intensity of coloring in the pain drawing. Criteria used for the categorization of the patients as having ‘significant pain relief’, ‘clinically non-significant change’, ‘no change’ and ‘worsening’ are presented in the Table 2. In the outcome prediction analysis for gender and medication, the first two categories were defined as a positive outcome and the latter two as a negative outcome (n=20). In the ROC analysis, only patients with ‘significant pain relief’ were considered as a positive outcome, and those with ‘no change’ and ‘worsening’ as a negative outcome (n=16). Patients with ‘clinically non significant change’ were not included in this analysis.

Statistical methods

Firstly, the effect of time on NRS (during the 8 weeks it was assessed) was tested by a linear mixed model with unstructured covariance, allowing correlations between all sequentially numbered envelopes. The two protocols were A) 10Hz (2400 pulses, trains of 6 s, inter-train interval (ITI) 24 s, total duration approximately 20 minutes) resulting in total of 12000 pulses weekly or B) 20Hz (3600 pulses, trains of 4 s, ITI 46 s, total duration of stimulations 37 minutes) resulting in total of 18000 pulses weekly (Fig. 1). There was also a ten minute pause in the middle of the 20Hz protocol.

Electroencephalography (EEG) was monitored during the first session of rTMS with a 61-channel TMS-compatible amplifier (Brain Products GmbH, BrainVision Recorder, version 1.20) to monitor for risk of an epileptic seizure [53]. A clinical neurophysiologist reviewed the EEG for the presence or appearance of epileptic discharges during rTMS.

A follow-up phone call was made by the referring physician between treatments about the response to the first week of treatment. If the patient was willing to continue, he/she received another five-day treatment with the alternative protocol after six weeks. After the last treatment session, patients received questionnaires regarding the whole study period, and returned them after two days.

The primary outcome measure was the weekly mean of the maximum daily pain intensity, using NRS (Fig. 1). Patients assessed the NRS daily during the baseline period (the week before rTMS therapy), during the therapy and during the two follow-up weeks. Patients also wrote down the time of the assessment, which could be before, after or during the rTMS. This daily assessment of NRS allowed us to monitor the progress of analgesia with the aim of describing the temporal aspect. To monitor the overall effect of two consequent treatments, we used several secondary outcome measures, which were reported at baseline and a few days after the last treatment session: 1) the pain drawing (head and neck, mouth from inside and whole body), 2) PainDETECT screening questionnaire [16] including pain grading for the last 30 days (NRS30), and assessment of the severity of symptoms, resulting in the likelihood of neuropathic pain (total score from zero to 35, higher than 19 suggests >90% likelihood) and, 3) Graded Chronic Pain Scale (GCPS-DC)[14] to classify disability (low: grade I and II, or high: grade III and IV) in relation to pain intensity. Characteristic pain intensity score is calculated as the mean intensity ratings for reported current, worse and average pain. For the assessment of psychological symptoms, patients filled in the Beck Depression Inventory (BDI) [7], and Beck Anxiety Inventory (BAI)[6] both of which are 21-item self-reported questionnaires with a 4-point response scale (range 0-63), and additionally the Life Satisfaction (LS) questionnaire with a 4-item questionnaire classifying patients as satisfied, slightly unsatisfied or very unsatisfied [34]. Finally, the Patient Global Impression of Change (PGIC) [30] was completed to assess the patients’ overall impression regarding rTMS. Patients were asked to report any adverse effects during the study. Free comments were noted down and protocol adjustments were made if necessary. 

Definition of the treatment response

The definition for a responder was a decrease >30% in the weekly mean of the maximum daily pain intensity, using NRS as compared to baseline. However, due to the high variability in NRS, we additionally defined response to treatment using a combination with secondary outcomes of PGIC, whether the patients continued with at least two maintenance treatment sessions and the change in area size or intensity of coloring in the pain drawing. Criteria used for the categorization of the patients as having ‘significant pain relief’, ‘clinically non-significant change’, ‘no change’ and ‘worsening’ are presented in the Table 2. In the outcome prediction analysis for gender and medication, the first two categories were defined as a positive outcome and the latter two as a negative outcome (n=20). In the ROC analysis, only patients with ‘significant pain relief’ were considered as a positive outcome, and those with ‘no change’ and ‘worsening’ as a negative outcome (n=16). Patients with ‘clinically non significant change’ were not included in this analysis.

| Table 2 | Criteria for combined outcome categories. In the prediction analysis the first two categories were considered as positive (responders), the last two categories as non-responders. |
|---------|----------------------------------------------------------------------------------|
| PGIC    | NRS change                                                                 |
| Maintenance | Treatment                        | Change in pain drawing (area size, intensity) | Number of patients |
| Significant pain relief | >4 decrease of >15% | at least twice | smaller or milder | 8 |
| Clinically non-significant change | 2 or 3 decrease of >15% | no | - | 4 |
| No change | 1 or 2 ±15% | no | - | 4 |
| Worsening | 1 increase | no | larger or intensified | 4 |
timepoints. Secondly, the effect of time (either the first or second 4 week period), frequency and order of the treatment period (first or second) on NRS weekly mean were included in the linear mixed model. Paired t-test was used for the change in PainDETECT score, NRS30 and psychological variables (BDI, BAI, LS). Pearson correlation was calculated for PGIC and BDI, BAI, age, chronicity and opioid dose. Curve estimation was used when assessing the dependence between PGIC and PainDETECT total score. In the outcome prediction analysis, we used ROC for scale variables (NRS30, characteristic pain intensity, BDI, BAI, chronicity, GCPS disability points) and Fisher’s exact test for dichotomized measures (gender and medication). The statistical analyses were performed with SPSS (IBM SPSS Statistics, version 27, Somers, NY, USA).

Results

Twenty eligible patients (13 females, age range 35 to 82 years) were randomized to either of the study protocols (Fig. 2). Four patients declined to participate, one patient was excluded due to metal clips on the head, and two elderly patients (85 years old and 72 years) had cardiovascular comorbidities and proceeded with conventional rTMS. Demographic and pain characteristics including diagnosis and etiology are presented in Table 1. There were 14 patients with post-traumatic trigeminal neuropathic pain, four with persistent idiopathic facial pain (with or without somatosensory changes) and two with secondary trigeminal neuralgia. Medication during the study was collected from patients’ medical records and questionnaires, and divided into categories of anticonvulsants, psychotropics, sedatives and opiates (Table S1). There were several protocol deviations (Fig. 2): one drop-out from the study (after the treatment with 20Hz protocol), one receiving the 20Hz protocol twice, one received a 4-day protocol at 20Hz rTMS due to a midweek holiday, one experienced pain aggravation with the 20Hz protocol as the second treatment and it was altered back to 10 Hz after two days, and one patient dropped out after the first three days of rTMS (with 20Hz protocol) but continued as planned with the second period. For the latter patient, the rTMS stimulation was also targeted to the hand M1 because stimulation of the face M1 was intolerable. As a minor deviation, the first patient received the rTMS treatment at slightly higher stimulus intensity than intended (50% instead of 42% of the maximum stimulator output), which however remained subthreshold to face rMT.

Primary outcome NRS - global effect of two rTMS protocols combined as one therapy

Linear mixed model analysis showed an overall effect of time on NRS (F=2.852, p=0.037), which decreased from 7.4 at baseline to 6.1 assessed two weeks after the second rTMS protocol (Fig. 3). The NRS change correlated with PGIC (r = -0.599, p=0.011). The NRS decreased significantly during the first therapy week (p=0.010) and nearly significantly during after the first post treatment week (p=0.052), and it was significantly lower at two weeks post treatment (p=0.022). Thereafter, the NRS increased and although it was lower (7.0), it was not significantly different from the baseline prior to the first rTMS (7.4) (p=0.271). After the second rTMS treatment with the alternative protocol, a significant NRS decrease was found during the rTMS week (p=0.035). All the NRS scores after second rTMS protocol were lower than the baseline prior to first rTMS (p=0.001, p=0.016 and p=0.033). Repetition of the treatment had a significant effect.

---

**Fig. 2** Consort diagram of the study.
indicating that the NRS scores were lower during the second four week period.

Post-hoc, we looked at the evolution of analgesia from the daily scores of NRS during the therapy week. A decline was usually seen on the second day (especially in responders), but in several patients the pain intensified after this (Fig. 4). In one patient (#12), the pain relief began later, two weeks after first rTMS session.

Comparison of the 10Hz and 20Hz protocols

There was an effect of frequency on NRS, with the 10Hz protocol resulting in lower overall NRS values (6.3) compared to 20Hz (6.8) (F=8.360, p=0.009) (Fig. 5). There was a trend towards an interaction effect of frequency and time (F=2.725, p=0.077). Although it did not reach statistical significance level, we observed lower NRS using the 10Hz protocol at time points during the therapy (p=0.024) and in the first post treatment week (p=0.001). By visual evaluation of NRS separated according to iteration and frequency, the 10Hz protocol administered after 20 Hz protocol caused a larger drop in NRS, but the variation was high. Subjectively, two patients considered higher stimulation frequency as more beneficial.

Secondary outcomes

NRS30 assessing pain intensity during the preceding month decreased from 7.1 at baseline to 5.8 at the end of the study (p=0.017). The PainDETECT total score declined from 20.2 to 18.2 at the group level (p=0.015). Considering separate symptoms, the feeling of cold and warmth as a painful sensation decreased (p=0.007), and all symptoms showed a non-significant trend towards improvement, except electric-like shocks, which were aggravated. The symptomatic area in pain drawings decreased in eight patients, and the intensity of coloring was lighter afterwards in two patients (Table 3). In four patients, pain decreased in the upper part of the face, but in two of them, pain intensified in the lower face, which was the target area of rTMS. Spontaneous individual comments on the pain relief were: pain attacks milder, shorter, fewer or away (n=4), subjective feeling of higher sensory threshold (n=1), more active (n=1), less need for medication (n=2), better situation (n=1), severe pain no longer present (n=1).

There were trends towards a decrease in BDI and BAI (18 to 15, p=0.082 and 15 to 11, p=0.061, respectively), LS did not change (p=0.838) (Table 4). The BDI change correlated with NRS change (r=0.581, p=0.048). There were no changes in overall GCPS grade, disability points or disability scores. Two patients’ disability grades due to pain decreased, but in contrast, the grade increased in two patients. One patient was able to start working part-time again.
Tolerability and side-effects

Spontaneously reported side-effects were tiredness (n=3, of which two related to 20 Hz protocol), headache (n=1, related to 20 Hz protocol), dizziness (n=2), pain in the head (eye, ear, cheek bone, lower jaw, temporal, parietal regions)(n=6), nausea (n=1), poor sleep (n=1), ophthalmic branch tickling (n=1), twitching of hand (n=1), tingling in hand (n=1), and tightness in the chest / crushing chest pain (n=1).

During the baseline TMS measurements, bilateral frontal spike-and-wave discharges were seen in one patient without a previous history of epilepsy or suspected epileptic events. No alterations in the frequency or morphology of epileptiform activity were found in the EEG monitored during the 10Hz and 20Hz rTMS, and the patient continued according to the study protocol.

Combined scale as outcome measure

Eight patients (40%) experienced significant pain relief. Four patients had a slight, clinically non-significant benefit, four patients had no change, and the pain was aggravated in four patients (Table 3). The pain aggravation was considered different to a transient, few days' worsening of pain, and

Table 3

| Patient # | Change in NRS (%) | PGIC | Change in Pain DETECT | Change in the pain drawing * | Maintenance therapy** | Outcome*** |
|-----------|-------------------|------|------------------------|-----------------------------|----------------------|------------|
| 1         | -22.4             | 3    | missing                | smaller area                | no                   | Clinically non-significant change |
| 2         | missing           | 5    | -5                     | missing data                | 22 / 98              | Significant pain relief [1]       |
| 3         | -16.9             | 6    | -6                     | smaller area (I), more intense (II,III) | 10 / 50 | Significant pain relief [1] |
| 4         | +12.5             | 2    | 0                      | no difference               | no                   | No change [0]                       |
| 5         | -83.3             | 3    | -1                     | lighter intensity           | no                   | Clinically non-significant change |
| 6         | +107.3            | 1    | -6                     | smaller area (I,II)         | no                   | Worsening [0]                       |
| 7         | -34.9             | 3    | +3                     | smaller area (I), more intense (II,III) | no                   | Clinically non-significant change |
| 8         | -56.3             | 6    | -2                     | clearer (trigger), radiation post | 4 / 20 | Significant pain relief [1] |
| 9         | -9.6              | 1    | +11                    | clearer (branches)          | no                   | Worsening [0]                       |
| 10        | -30.0             | 2    | -2                     | lighter intensity           | 28 / 135             | Significant pain relief [1] |
| 11        | -10.8             | 1    | -11                    | smaller area, clearer branches, radiating pain disappeared | no                   | No change [0]                       |
| 12        | -100              | 7    | 0                      | smaller area (I)            | 16 / 89              | Significant pain relief [1]       |
| 13        | 0                 | 6    | -3                     | smaller area (I)            | 31 / 149             | Significant pain relief [1]       |
| 14        | +1.3              | 1    | -8                     | no difference              | no                   | No change [0]                       |
| 15        | -18.9             | 2    | -1                     | new areas (I, back of the head) | no                   | Clinically non-significant change |
| 16        | missing           | 1    | -1                     | larger area (inside the mouth, other side) | no | Worsening [0]                       |
| 17        | missing           | 1    | +1                     | more intense               | 1 / 5                | No change [0]                       |
| 18        | -36.1             | 5    | -4                     | smaller area, tooth more intense | 4 / 20 | Significant pain relief [1] |
| 19        | -40.7             | 5    | +2                     | no difference              | 10 / 48              | Significant pain relief [1]       |
| 20        | +28.8             | 1    | -1                     | more intense               | no                   | Worsening [0]                       |

# number; NRS, numeric rating scale; PGIC, Patient Global Impression of Change. * The area, color intensity, precision and radiation are evaluated. I, II, III – correspond to the branches of the trigeminal nerve. **Continuation with the maintenance therapy: no, if patient did not continue with rTMS maintenance; numbers presented show how many times and total rTMS therapy days patients has received during the maintenance period. ***The number in the square brackets indicates the categorization of benefit which was used in the prediction of the effect analyses.
depicted as more troubling, greater or protracted pain. Increased consumption of on-demand medication was noted (n=1). Two patients reported aggravation of pain related to the 20 Hz protocol. This aggravation occurred later, during the weeks after the treatment.

**Prediction of the treatment effect**

rTMS was applied with stimulation intensities of 21–50% of maximum stimulator output. These correspond to 73–156 V/m at the surface of the cortex. The stimulus intensity did not correlate with the outcome. No individual with only I-branch (pain located near the eye) involvement (n=3) benefited from rTMS. All patients with significant pain relief had post-traumatic trigeminal neuropathic pain.

Analysis of the correlation between PainDETECT questionnaire and PGIC, revealed a U-shaped curve \((F=5.164, p=0.018)\) (Fig. 6). Thus, a high score in PainDETECT was correlated to a good response to rTMS, but the patients with pain aggravation could also have a clear neuropathic component.

PGIC showed trends towards a correlation with chronicity \((r = -0.427, p=0.060)\) and BAI at baseline \((r = -0.447, p=0.055)\), suggesting that patients with a shorter duration of pain, and those with less anxiety were more content. BDI or life satisfaction at baseline did not correlate with PGIC.

The proportion of responders to treatment was greater in females \((10 \text{ out of } 13, 77\%)\) than males \((2 \text{ out of } 7, 29\%)\) \((p=0.052)\). The use of selective serotonin reuptake inhibitor (SSRI) or selective noradrenaline reuptake inhibitor (SNRI) showed a trend towards an association with a positive outcome \((p=0.055)\). All five patients taking SSRI/SNRI medication had a positive outcome.

The ROC analysis with all tested variables is shown in Fig. 7. Higher disability points predicted positive outcome \((AUC=0.845, p=0.043)\). Considering different pain intensity measures, the characteristic pain intensity assessed in the GCPS questionnaire \((AUC=0.847, p=0.045)\) was predictive of outcome compared to the NRS30 \((AUC=0.764, p=0.128)\) or the weekly mean NRS \((AUC 0.653, p=0.378)\). Psychological measures did not predict the outcome.

**Maintenance therapy**

Eleven patients did not continue with rTMS after the second period in this study, and one patient received it on one further occasion, but did not experience sufficient benefit. Of the remaining eight patients, those that experienced significant pain relief using the combined scale as an outcome measure, underwent the maintenance treatment between 4 and 31 times, corresponding to 20 to 179 rTMS therapy days (Table 3). Some patients had a few pain-free days, but due to the short-lasting decrease in pain intensity, they did not consider it worthwhile continuing with maintenance treatment. The duration of the analgesic effect was individually variable. An effect of greater than one month duration was found in two patients.

**Discussion**

This clinical trial showed a sustained decrease in pain intensity NRS with two high-frequency rTMS protocols in chronic facial pain. An effect of repetition of the treatment was found, with the second treatment after an interval of six weeks causing a more pronounced decrease in NRS. The 10 Hz protocol resulted in overall lower NRS scores, with some indications that it was also slightly better tolerated. However, in two patients, higher frequency stimulation seemed to yield a better effect. Using a combined scale, significant pain relief was observed in eight of twenty \((40\%)\) patients, who also continued with maintenance treatment. This is similar to an earlier study of unilateral central pain, where 40% of the patients were responders \([51]\). Predictive factors for response were a strong neuropathic pain component, high disability and female gender.

At the group level, pain relief lasted about two weeks, after which pain recurred, and was almost back to baseline level at six weeks, before the second treatment period. However, in two patients, the treatment effect lasted up to three months, observed as a more infrequent need for maintenance treatment. The analgesic effect appeared during the first three days, in line with previous studies, with peak analgesia on day 3 \([41, 35, 28]\).

**Comparison of efficacy of 10Hz and 20Hz protocols**

In contrast to an earlier study \([17]\), we did not find the higher frequency protocol to be superior in terms of better or longer lasting analgesia. The 10Hz protocol was more effective when given after the 20Hz protocol (Fig. 5A). This finding is consistent with a previous study where the effects of 10Hz stimulation were enhanced by priming with intermittent and prolonged continuous theta-burst-stimulation (TBS) \([38]\), and with a proposal to start with a higher pulse frequency and decrease over time \([21]\). One study found a frequency-dependent increase in cortical excitability, and emphasized that each individual seemed to have his/her frequency tuning curve with substantial inter-individual variability \([42]\). We also observed this in one patient for whom 20Hz was somewhat pro-algesic, but 10Hz was analgesic.
Since the 10Hz protocol containing fewer pulses was superior to 20Hz containing more pulses, our results suggest that an increase in stimulation frequency or the number of pulses may not yield more beneficial results. However, both protocols contained a higher number of pulses than are conventionally used [35, 21, 56], which together with the longer stimulation duration, has been suggested to produce cumulative and longer-lasting pain modulation [25]. Moreover, pulses up to 5050 per session have been applied [48]. Halawa and co-workers (2018) provided some evidence that ITIs longer than 20 s are superior to shorter duration ITIs. They suggested that 50 s between trains would be the most effective for pain and depression, and that conduction failure may be a reason for treatment failure. In a recent study on post-stroke pain this ITI was used [48], but the effect of M1 stimulation was not superior to sham stimulation. Conversely, in healthy volunteers, no influence of ITI was found between ITIs 4 to 32 s, but short ITIs caused greater disinhibitory effects [8]. A study on train duration showed opposite effects of 5 s trains (inhibitory) compared to those of 1.5 s (excitatory) [31]. Theoretically, the longer train duration could be a possible factor causing pain aggravation. Session breaks may turn a facilitatory effect into an inhibitory one, which is stronger but develops more slowly. This may be crucial in determining the direction of the induced neuroplastic changes [54]. Stimulation intensity was set to subthreshold to the lower of APB or lower face muscle, for safety reasons. Nonetheless, the depth of facial motor cortex exhibits high variance [11], which means that the stimulation may be unnecessarily high in some individuals.

NRS, PGIC and PainDETECT as treatment response measures

NRS has obvious limitations although it is a straightforward and quantitative measure. Day-to-day variation due to environmental factors has been previously described [50, 43]. The weekly mean is usually better than a random momentary assessment but may give a misleading result due to the varying pain profile. In this study, one patient described an excellent but short-lasting effect (NRS change 11%). Conversely, one patient with a 30% NRS decrease reported ‘slightly better, but no noticeable change’ in PGIC. In addition to pain intensity, pain interference could be worth assessing [48]. The characteristic pain intensity was found to be the best at predicting the effect of treatment. Pain attacks disappeared in some patients, which is considered successful analgesia [25]. In some patients even a small reduction in pain could lead to greatly increased enjoyment of life [22]. Two patients emphasized that eating had provoked pain leading to an inability to enjoy meals, but rTMS improved this. Specific symptom scores in PainDETECT showed statistically non-significant improvements suggesting that rTMS targeted to M1 influenced these neuropathic symptoms. However, a trend towards aggravation in electric like shocks, typical of trigeminal neuralgia, was observed. Although the PainDETECT questionnaire was originally validated for back pain, it was found suitable, easy to assess and cost-effective in this patient population.

Psychological measures of depression and anxiety

Depression and anxiety improved slightly but non-significantly after rTMS; a similar trend to that reported in some, but not all, previous studies [20]. We found a moderate correlation between the decrease in pain intensity and alleviation of depressive symptoms, similar to previous studies [29, 13]. Depression, anxiety and pain most likely share common pathophysiological pathways; mood and anxiety disorders increase the odds of disabling and severely limiting pain [12]. rTMS may act similarly to novel anticonvulsants which not only reduce pain, but also improve sleep and reduce anxiety and depression [3]. In some patients, the enjoyment of being free of pain may have been hindered by fear of
recurring pain or a pain attack. On the other hand, in this study all patients using SNRI or SSRI medication (n=5) benefited from the rTMS treatment. It has been previously shown that serotonergic enhancement modulates neuroplasticity of motor cortex and effects of transcranial direct current stimulation (tDCS) [44]. The possible synergistic effects of SSRI/SNRI drugs and rTMS treatment in chronic pain have not been previously studied.

Tolerance, side effects and aggravating of pain

Both protocols were safe; side effects were usually mild, as reported earlier [47, 28, 46, 48]. Several patients reported tiredness, which could last for several days. Occasionally somnolence was manifested as a need to have a nap and considered positive. The positive effect on sleep of rTMS targeted to the sensorimotor cortex has been previously reported [40]. We had some indication of poorer tolerability of the 20Hz protocol i.e. tiredness seemed to be more pronounced. In three of four patients in whom rTMS aggravated pain, the starting frequency was 20Hz. Transient increase in pain and hyperalgesia have been reported with rTMS [39, 46]. No common denominator for worsening of pain could be identified. Electric fields induced at the cortex were quite similar or slightly higher than recently reported [48]. In one patient, the target was changed from face M1 to hand M1 due to poor tolerability. In the literature, the hand motor area, which is also easier to target, yielded better results than the face motor area [2, 28]. Other targets such as dorsolateral prefrontal cortex could be better tolerated when simultaneously treating somatic pain and depressive mood disorders [49]. It may be worth monitoring the daily NRS—should pain intensify, the rTMS treatment could be paused to avoid harmful effects.

Predicting the rTMS effect

Pain relief that appeared soon after initiating the treatment predicted positive long-term response, whereas aggravation or no change suggested a poor outcome, in line with [51]. In our study, the mean duration of symptoms was 6 years, range 1 to 17 years. Those with a shorter pain duration showed a trend towards a positive outcome, and chronicity negatively correlated with PGIC, favoring an early rTMS intervention. None of the patients scoring less than 10 points in PainDETECT benefited from the treatment. Similarly, a high characteristic pain intensity and high disability were predictors of a beneficial response. Moreover, our data suggest that the etiology and the somatotopic localization of pain may play a significant role. In our cohort patients having post-traumatic trigeminal neuropathic pain were most likely to benefit. On the other hand, patients having pain localized to the area of the I trigeminal branch had the least favorable outcome. However, the study population is too small to draw stronger conclusions.

Females seemed to respond better to rTMS, as has been observed in depression [32] and in a recent neural network analysis in which predictive variables of implantable motor cortex stimulation in various pain conditions were examined [23]. The trend detected in our study of more satisfaction with treatment in patients with less anxiety at baseline is in line with a previous study in which patients with severe anxio-depressive symptoms had a less favorable response to rTMS [26].

Maintenance treatment

Eight patients (40%) were willing to continue with maintenance treatment. Due to the lack of clear maintenance therapy guidance at the time of the trial, our center opted for continuation using a complete 5-day 10Hz protocol repeated every 2-3 months. Although this was best suited to our patient population, taking into account factors such as distance to the hospital, it is likely that in the long run the maintenance protocol needs to be reviewed. Quesada et al have reported that after at least 4-5 consecutive single rTMS sessions, scheduled according to the individual need, an overall analgesic effect might be sufficient for long-term analgesia [52]. There is also an increasing body of evidence that the gradual down-titration of rTMS sessions and continuation weekly or bi-monthly over 5 months after the induction phase is beneficial for significant pain reduction [25, 26, 45]. Moreover, the economic aspects and, currently, the limited availability of rTMS equipment must be taken into account.

Strengths and limitations

This study is representative of the typical clinical setting, which includes patients with chronic orofacial pain with multiple distinct causes, and a highly variable psychological load. The results are thus well generalizable. Validated patient-reported outcomes were used in this study, although most assessed endpoints were of subjective nature. Navigated rTMS was used for accurate targeting of the stimulation. The participants were highly motivated to participate and completed the questionnaires carefully.

As limitations, this was a single-center study, of open-label study nature without a sham arm, and therefore it was not controlled for a placebo effect that may be strong [48]. Power calculations indicated 30 subjects as a sufficient number to detect differences between protocols. Since we were not able to reach this, the study may be inadequately powered, and the results need to be considered as preliminary. However, we continued with 10 more study patients with conventional 3000 pulse 10Hz protocol, which strengthened the overall findings in this study. There were several deviations from the protocol, which may have led to bias in the results. According to current guidelines, outcomes should be monitored for at least 3 months [33] and appropriate multidimensional pain-related quality-of-life measures were not applied. Furthermore, our study did not adequately address psychological health, considered as the most impaired dimension [57]. Larger data sets examining the relationship between symptom duration, related disability and treatment outcomes are needed.

Conclusions

Our study indicated that navigated high frequency rTMS targeted on the functional primary face motor area may be effective and safe for chronic facial pain with a 40% response rate. We have observed a clear cumulative effect of
repeated 5-days rTMS treatments separated by 6 weeks. The first treatment was able to potentiate the effect of the second treatment. The 10Hz protocol was more effective when administered after the 20Hz treatment, as if the 20Hz has a priming effect. However, although subtle differences between protocols were found regarding efficacy, the protocol with higher 20Hz frequency, longer duration and higher number of pulses did not improve the outcome compared with the conventional 10Hz protocol. Its tolerability was also somewhat poorer based on protocol deviations and side effects. We cannot unambiguously support somatotopic targeting, and further studies are needed. In general, a strong neuropathic component, female gender and high disability predicted good treatment response, but occasionally patients with a high PainDETECT score experienced an aggravation of pain. Our results suggest that rTMS has a clinically significant role in multidisciplinary pain management, but patient selection is crucial for improving the response rate.

Conflicts of Interest

LS has received travel support from Nexstim Ltd not related to this study. There are no competing interests to declare.

Acknowledgments

This work was funded by grants from following foundations: Alfred Kordelin, Maud Kuistilan muistos and Minerva säätiö. L.S. is supported by Academy of Finland (project 322423) and Business Finland grant no 2956/31/2018. We would like to acknowledge Eeva Hallikainen-Pirskanen at the Pain Clinic for her major contribution during this study, and in treating the patients with chronic pain. Dr Tuomas Selander is acknowledged for the help with statistical analysis. Tiina-Mari Ikäheimo is acknowledged for coordinating the study. Finally, we warmly thank the patients who were willing to participate in the study despite their demanding situation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.neucli.2022.03.001.

References

[1] International classification of orofacial pain, 1st edition (ICOP). Cephalalgia 2020;40(2):129-221.
[2] Andre-Obadia N, Magnin M, Simon E, Garcia-Larrea L. Somatotopic effects of rTMS in neuropathic pain? A comparison between stimulation over hand and face motor areas. Eur J Pain 2018;22(4):707-15.
[3] Argoft CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. Clin J Pain 2007;23(1):15-22.
[4] Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17(9):1113-e88.
[5] Ballantyne JC, Sullivan MD. Intensity of chronic pain—the wrong metric? N Engl J Med 2015;373(22):2098-9.
[6] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56(6):893-7.
[7] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
[8] Cash RFH, Dar A, Hui J, De Ruiter L, Baarbe J, Fettes P, et al. Influence of inter-train interval on the plastic effects of rTMS. Brain Stimul 2017;10(3):630-6.
[9] Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P, et al. Trigeminal neuralgia: New classification and diagnostic grading for practice and research. Neurology 2016;87(2):220-8.
[10] Cruccu G, Garcia-Larrea L, Hansson P, Reindl M, Lefaucheur JP, Paulus W, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. Eur J Neurol 2016;23(10):1489-99.
[11] Davis NJ. Variance in cortical depth across the brain surface: implications for transcranial stimulation of the brain. Eur J Neurosci 2021;53(4):996-1007.
[12] de Heer EW, Gerrits MM, Beekman AT, Dekker J, van Marwijk HW, de Waal MW, et al. The association of depression and anxiety with pain: a study from NESDA. PloS one 2014;9(10):e106907.
[13] de Oliveira RA, de Andrade DC, Mendonca A, Barros R, Luvisoto T, Myczkowski ML, et al. Repetitive transcranial magnetic stimulation of the left prefrontal and dorsolateral prefrontal cortex does not have anxiogenic effect on central poststroke pain. J Pain 2014;15(12):1271-81.
[14] Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6(4):301-55.
[15] Forssell H, Sipilä K, Teerijoki-Oksa T, Vartiainen P, Kautianen H, Sintonen H, et al. The impact of chronic orofacial pain on health-related quality of life. Scand J Pain 2019;20(2):329-38.
[16] Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22(10):1910-20.
[17] Fricova J, Klírova M, Masopust V, Novak T, Verebova K, Rokyta R. Repetitive transcranial magnetic stimulation in the treatment of chronic orofacial pain. Physiological Research /Academia Scientiarum Bohemoslova 2013;62(1):512-34 Suppl.
[18] Galhardoni R, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziyama HH, et al. Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. Arch Phys Med Rehab 2015;96(4):5156-572.
[19] Gatzinsky K, Bergh C, Liljegren A, Silander H, Samuelsson J, Svanberg T, et al. Repetitive transcranial magnetic stimulation of the primary motor cortex in management of chronic neuropathic pain: a systematic review. Scand J Pain 2021;21(1):8-21.
[20] Hagelberg N, Hanno H, Saajonkari M, Isojarvi J, Mäkelä M, Silvio S, et al. Transkraanialinen magneettistimulaatio neuropaatisen kivun hoidossa (HALO-katsaus). Suomen Lääkärilehti 2017;4(214).
[21] Halawa I, Goldental A, Shirato Y, Kanter I, Paulus W. Less might be more: conduction failure as a factor possibly limiting the efficacy of higher frequencies in rTMS protocols. Front Neurosci 2018;12:358.
[22] Henssen D, Scheepers N, Kurt E, Arnts I, Steegers M, Vissers K, et al. Patients’ expectations on spinal cord stimulation for failed back surgery syndrome: a qualitative exploration. Pain Pract 2018;18(4):452-62.
[23] Henssen D, Wittkam RL, Dao J, Comes DJ, Van Cappellen van Walsum AM, Kozic T, et al. Systematic review and neural network analysis to define predictive variables in implantable
motor cortex stimulation to treat chronic intractable pain. J Pain 2019;20(9):1015-26.

Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. J Pain Res 2018;11:1445-57.

Hodaj H, Alibeau JP, Payen JF, Lefaucheur JP. Treatment of chronic facial pain including cluster headache by repetitive transcranial magnetic stimulation of the motor cortex with maintenance sessions: a naturalistic study. Brain Stimul 2015;8(4):801-7.

Hodaj H, Payen JF, Hodaj E, Dumolard A, Maindet C, Cracowski JL, et al. Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex. Clin Neurophysiol 2020;131(7):1423-32.

Hodaj H, Payen JF, Lefaucheur JP. Therapeutic impact of motor cortex rTMS in patients with chronic neuropathic pain even in the absence of an analgesic response. A case report. Neurophysiol Clin 2018;48(5):303-8.

Hosomi K, Shimokawa T, Ikoma K, Nakamura Y, Sugiyama K, Ugawa Y, et al. Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. Pain 2013;154(7):1065-72.

Hsu JH, Daskalakis ZJ, Blumberger DM. An update on repetitive transcranial magnetic stimulation for the treatment of co-morbid pain and depressive symptoms. Curr Pain Headache Rep 2018;22(7):51.

Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27(1):26-35.

Jung SH, Shin JE, Jeong YS, Shin HI. Changes in motor cortical excitability induced by high-frequency repetitive transcranial magnetic stimulation of different stimulation durations. Clin Neurophysiol 2008;119(1):71-9.

Kedzior KK, Azorina V, Reitz SK. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997-2013. Neuropsychiatr Dis Treat 2014;10:727-56.

Klein MM, Treister R, Raji T, Pascual-Leone A, Park L, Nurminikko T, et al. Transcranial magnetic stimulation of the brain: guidelines for pain treatment research. Pain 2015;156(9):1601-14.

Kolivumaa-Honkanen HT, Viinamaki H, Honkanen R, Tanskanen A, Antikainen R, Niskanen L, et al. Correlates of life satisfaction among psychiatric patients. Acta Psychiatr Scand 1996;94(5):372-8.

Kumru H, Albu S, Vidal J, Tormos JM. Effectiveness of repetitive transcranial or peripheral magnetic stimulation in neuropathic pain. Disabil Rehabil 2017;39(9):836-66.

Kurt E, Henssen D, Steegers M, Staal M, Beese U, Maarrawi J, et al. Motor cortex stimulation in patients suffering from chronic neuropathic pain: summary of expert meeting and pre-meeting questionnaire, combined with literature review. World Neurosurg 2017;108:254-63.

Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benningh DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125(11):2150-206.

Lefaucheur JP, Ayache SS, Sorel M, Farhat WH, Zouari HG, Ciampi de Andrade D, et al. Analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex in neuropathic pain: influence of theta burst stimulation priming. Eur J Pain 2012;16(10):1403-13.

Lindholm P, Lamusuo S, Taiminen T, Pesonen U, Lahti A, Virtanen A, et al. Right secondary somatosensory cortex-a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation. Pain 2015;156(7):1276-83.

Lindholm P, Lamusuo S, Taiminen T, Virtanen A, Pertovaara A, Forsell H, et al. The analgesic effect of therapeutic rTMS is not mediated or predicted by comorbid psychiatric or sleep disorders. Medicine 2016;95(44):e5231.

Ma SM, Ni JX, Li XY, Yang LQ, Guo YN, Tang YZ. High-frequency repetitive transcranial magnetic stimulation reduces pain in postherpetic neuralgia. Pain Med 2015;16(11):2162-70.

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 2000;133(4):425-30.

Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, et al. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: a case-control study. Arch Phys Med Rehabil 2011;92(11):1820-6.

Melo L, Mosayebi-Samani M, Ghanaati E, Nitsche MA, Kuo MF. Dosage-dependent impact of acute serotonin enhancement on transcranial direct current stimulation effects. Int J Neuropsychopharmacol 2021;24(10):787-97.

Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, et al. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain 2011;152(7):1478-85.

Nurminikko T, Maclver K, Bresnahan R, Hird E, Nelson A, Sacco P. Motor cortex reorganization and repetitive transcranial magnetic stimulation for pain-a methodological study. Neuromodulation 2016;19(7):669-78.

O’Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018;3:CD008208.

Ojala J, Vanhanen J, Harno H, Lioumis P, Vaalto S, Kaunisto MA, Randomized A, et al. Sham-controlled trial of repetitive transcranial magnetic stimulation targeting M1 and S2 in central poststroke pain: a pilot trial. Neuromodulation 2021 in press. doi: 10.1111/ner.13496.

Phillips AL, Burr RL, Dunner DL. rTMS effects in patients with co-morbid somatic pain and depressive mood disorders. J Affect Disord 2018;241:411-6.

Pico-Espinosa OJ, Cote P, Hogg-Johnson S, Jensen I, Axen I, Holm LW, et al. Trajectories of pain intensity over 1 year in adults with disabling subacute or chronic neck pain. Clin J Pain 2019;35(8):678-85.

Pomnier B, Creach C, Beavieux V, Nuti C, Vassal F, Peyron R. Robot-guided neuro-navigation rTMS as an alternative therapy for central (neuropathic) pain: clinical experience and long-term follow-up. Eur J Pain 2016;20(6):907-16.

Quesada C, Pommier B, Fauchon C, Bradley C, Creach C, Vassal F, et al. Robot-guided neuro-navigation repetitive transcranial magnetic stimulation (rTMS) in central neuropathic pain. Arch Phys Med Rehabil 2018;99(11):2203-15 e1.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS/CG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008-39.

Rothkegel H, Sommer M, Paulus W. Breaks during 5Hz rTMS are essential for facilitatory after effects. Clin Neurophysiol 2010;121(3):426-30.

Saisanen L, Jukkunen P, Kemppainen S, Danner N, Immonen A, Mervaala E, et al. Locating and outlining the cortical motor

107 Neurophysiologie Clinique 52 (2022) 95–108
representation areas of facial muscles with navigated transcranial magnetic stimulation. Neurosurgery 2015;77:394-405.

[56] Umezaki Y, Badran BW, DeVries WH, Moss J, Gonzales T, George MS. The efficacy of daily prefrontal repetitive transcranial magnetic stimulation (rTMS) for burning mouth syndrome (BMS): a randomized controlled single-blind Study. Brain Stimul 2016;9(2):234-42.

[57] Vartiainen P. Health-related quality of life in patients with chronic pain. Anaesthesiology, intensive care and pain medicine. University of Helsinki; 2018.

[58] Vartiainen P, Heiskanen T, Sintonen H, Roine RP, Kalso E. Health-related quality of life and burden of disease in chronic pain measured with the 15D instrument. Pain 2016;157 (10):2269-76.