Systematic Review

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Repetitive transcranial magnetic stimulation of the primary motor cortex in management of chronic neuropathic pain: a systematic review

https://doi.org/10.1515/sjpain-2020-0054
Received April 10, 2020; accepted July 27, 2020; published online September 7, 2020

Abstract

Objectives: Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) with frequencies 5–20 Hz is an expanding non-invasive treatment for chronic neuropathic pain (NP). Outcome data, however, show considerable inhomogeneity with concern to the levels of effect due to the great diversity of treated conditions. The aim of this review was to survey the literature regarding the efficacy and safety of M1 rTMS, and the accuracy to predict a positive response to epidural motor cortex stimulation (MCS) which is supposed to give a more longstanding pain relief.

Methods: A systematic literature search was conducted up to June 2019 in accordance with the PRISMA guidelines. We used the PICO Model to define two specific clinical questions: (1) Does rTMS of M1 relieve NP better than sham treatment? (2) Can the response to rTMS be used to predict the effect of epidural MCS? After article selection, data extraction, and study quality assessment, the certainty of evidence of treatment effect was defined using the GRADE system.

Results: Data on 5–20 Hz (high-frequency) rTMS vs. sham was extracted from 24 blinded randomised controlled trials which were of varying quality, investigated highly heterogeneous pain conditions, and used excessively variable stimulation parameters. The difference in pain relief between active and sham stimulation was statistically significant in 9 of 11 studies using single-session rTMS, and in 9 of 13 studies using multiple sessions. Baseline data could be extracted from 6 single and 12 multiple session trials with a weighted mean pain reduction induced by active rTMS, compared to baseline, of –19% for single sessions, –32% for multiple sessions with follow-up <30 days, and –24% for multiple sessions with follow-up ≥30 days after the last stimulation session. For single sessions the weighted mean difference in pain reduction between active rTMS and sham was 15 percentage points, for multiple sessions the difference was 22 percentage points for follow-ups <30 days, and 15 percentage points for follow-ups ≥30 days. Four studies reported data that could be used to evaluate the accuracy of rTMS to predict response to MCS, showing a specificity of 60–100%, and a positive predictive value of 75–100%. No serious adverse events were reported.

Conclusions: rTMS targeting M1 can result in significant reduction of chronic NP which, however, is transient and shows a great heterogeneity between studies; very low certainty of evidence for single sessions and low for multiple sessions. Multiple sessions of rTMS can maintain a more longstanding effect. rTMS seems to be a fairly good predictor of a positive response to epidural MCS and may be used to select patients for implantation of permanent epidural electrodes. More studies are needed to manifest the use of rTMS for this purpose. Pain relief outcomes in a longer perspective, and outcome variables other than pain reduction need to be addressed more consistently in future studies to consolidate the applicability of rTMS in routine clinical practice.

Keywords: chronic pain; motor cortex stimulation; neuromodulation; repetitive transcranial magnetic stimulation; rTMS; systematic review.

Note: This systematic review is in part based on the results from a Health Technology Assessment accomplished by the same authors during the period 2015-12-07–2017-02-22 at Sahlgrenska University Hospital, Göteborg, Sweden (Regional activity-based HTA-report 2017:94).

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Introduction

Clinical conditions with chronic neuropathic pain (NP) pose a major treatment challenge [1–3]. Symptomatic first line therapies consist of different drug strategies which can be combined with conservative non-pharmacological treatments [4, 5]. Interventional neuromodulation techniques, using modern implantable technology to deliver long-term electric stimulation to the nervous system, can be considered when drug therapies fail due to insufficient effect or intolerable side effects [6, 7]. Patients with chronic, intractable NP caused by lesions in the peripheral nervous system can be treated with spinal cord/peripheral nerve stimulation [6]. The interventional, operative treatments for chronic NP of central origin, which is more difficult to access, include electrical deep brain stimulation (DBS) and epidural motor cortex stimulation (MCS) [7–10]. DBS generally yields poor results in patients with chronic NP and is utilised only in a small subset of pain patients in whom other interventional methods have failed [8, 11, 12]. Although MCS has been demonstrated to produce significant pain reduction in subsets of patients with NP [13, 14], the use of this technique has been hampered by difficulties to select the right patients, and to optimise and standardize stimulation parameters in order to achieve adequate, long-term pain relief [15–17].

Repetitive transcranial magnetic stimulation (rTMS) is an expanding, non-invasive neuromodulation procedure for treatment of pain through transcranial stimulation of the cerebral cortex [18–20]. It can induce immediate and lasting changes in cortical excitability via electrical currents generated by a transcranial magnetic field [21]. In the majority of trials investigating rTMS for treatment of NP, M1 has been the primary target of stimulation [8, 22–24]. The precise mechanisms of action remain incompletely elucidated [15]. Recent studies using 3D-positron emission tomography have shown that rTMS applied to M1 for pain relief activates the endogenous opioid system in a wide brain network associated with processing of pain and other salient stimuli [25, 26]. The stimulation frequency and type and orientation of the stimulating coil are considered as the most crucial variables to achieve a good response [22, 27]. The procedure has been reported to be safe and the most common side effect is transient headache.

High frequency rTMS using stimulus rates of 5–20 Hz has proven to give best analgesic effect [28]. Studies investigating this stimulation mode were initially based on a single stimulation session which induced a short analgesic effect for up to one week [22, 28]. Prolonged effects (weeks to months), probably related to processes that modulate long-term synaptic plasticity, can be obtained by repeated rTMS sessions daily for several weeks [22, 29]. rTMS has also been used to select patients with chronic NP who may be suitable for invasive epidural MCS, which is considered to induce a larger and more longstanding pain relief than non-invasive techniques for stimulation of M1 [17, 30]. Even though guidelines have been presented on the therapeutic use of rTMS in pain treatment, there are still substantial knowledge gaps and inconsistencies considering treatment effect due to the large variety of treated NP conditions [8, 22]. The purpose of this systematic review is (i) to critically evaluate the effects of high frequency (5–20 Hz) rTMS of M1 in the treatment of chronic NP based on the magnitude of relative pain reduction (active vs. sham stimulation); (ii) to investigate the applicability of rTMS as a predictive test to proceed with epidural MCS.

Methods

Data sources and search strategies

This systematic review was conducted in line with the preferred reporting items for systematic reviews (PRISMA) guidelines [31]. Two authors performed systematic searches in PubMed, Embase, the Cochrane Library and PsycInfo of articles published from 1990. Last update of searches was made in June 2019. Searches were conducted using controlled vocabulary and title/abstract words, combining variations of “Transcranial direct current stimulation”, “Transcranial magnetic stimulation”, “Direct current stimulation”, “Motor cortex stimulation” with “Pain” or “Pain management”. The web-sites of the Swedish Council on Health Technology Assessment (SBU), and the corresponding national centres of health technology assessment in Norway (Kunnskapssenteret) and Denmark (Sundhedsstyrelsen) were also searched.

We used the PICO Model (P=patients, I=intervention/index test, C=comparison, O=outcome variable) to define two specific clinical questions at issue, and to develop literature search strategies [32]. The questions were:

(1) Does rTMS of M1 relieve pain better than placebo (sham treatment) in patients with chronic NP?
(2) Can the response to rTMS be used as a predictor of the effect of epidural MCS in these patients? The questions were structured into the four components as PICO 1 and PICO 2 (Table 1).

Study selection

Eligible articles were published in English, French, Swedish, Norwegian or Danish and included randomised controlled trials (RCTs), and non-randomised controlled studies and case series with more than 10 patients over the age of 18 with pain of 3 months duration or more. Reference lists of relevant articles were also scrutinised for additional references.

Table 1: The structured approach to the questions at issue.

PICO 1
P = Patients with therapy-resistant NP originating from lesions in the central or peripheral nervous systems
I = Active high frequency (5–20 Hz) rTMS targeting the primary motor cortex
C = Sham/placebo treatment
O = *Critical for decision making*
Pain relief estimated by validated numeric scales
Important for decision making
HRQoL according to validated scales
Medication use

PICO 2
P = Patients with therapy-resistant NP originating from lesions in the central or peripheral nervous systems
I = rTMS (clinically relevant pain reduction: yes/no)
C = Epidural MCS (clinically relevant pain reduction: yes/no)
O = *Critical for decision making*
Sensitivity and specificity[a]
Important for decision making
Positive and negative prediction value of rTMS for MCS in pain treatment[a]

[a]Based on a clinically relevant pain reduction defined as a reduction of 30% or more from baseline [59–61]. The severity of pain was estimated by validated numeric scales.
NP, neuropathic pain; rTMS, repetitive transcranial magnetic stimulation; HRQoL, health-related quality of life; MCS, motor cortex stimulation.

The authors that conducted the initial literature searches and selection of studies then assessed the obtained abstracts and independently of one another made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors who read the articles independently of one another. It was finally decided in a consensus meeting which articles should be included in the systematic assessment. A graphic presentation of the selection process is presented in a flow chart (Figure 1).

Data extraction and quality assessment

Data extraction was performed independently by two authors (KG, OS). The following information was extracted from each study: the last name of the first author, year of publication, patient characteristics, study design, number of treatment sessions, length of follow-up, and the effects on pain according to validated 0–10 numeric rating scales (visual analogue scale [VAS]; numeric rating scale [NRS]; brief pain inventory [BPI]). If a publication did not present the mean and standard deviation of the baseline and follow-up pain score derived from the numeric scales in tabulated form, the average values were estimated from the graph and figure presentations.

The quality of the included studies was critically appraised using checklists from the SBU with assessment of directness (patient selection), risk of bias (randomisation, blinding), and precision (www.sbu.se/sv/var-metod/). The grading of recommendations, assessment, development and evaluation (GRADE) classification was used for evaluating certainty of evidence of outcomes [33].

Statistical analysis

Based on available baseline data a weighted mean (taking into account study size) was calculated for both the baseline and the follow-up pain score for studies of a single rTMS session and sham stimulation, and for studies of multiple sessions of rTMS and sham stimulation. The mean change in pain score in percent was calculated as the difference between the weighted means for follow-up and baseline divided by the weighted mean at baseline.

Sensitivity and specificity for the accuracy to predict a pain-relieving response to MCS were calculated using VassarStats Clinical Calculator 1 statistical software (Poughkeepsie, NY, USA) (www.vassarstats.net/clin1.html).

Results

Search results

The initial literature search identified 2,469 articles after removal of duplicates (Figure 1). After reading the abstracts 2,323 articles were excluded. Another 88 articles were excluded after reading the full text by three authors. The remaining 58 articles were sent to all participants of the project group. After reading these articles in full text, 32 of them (24 RCTs and eight case series) which all investigated high frequency rTMS were selected for final assessment (Figure 1). Reasons for exclusion of articles read in full text are given in Figure 1.

Characteristics of included studies

Only RCTs with blinding were included in the analysis. The main characteristics of trials comparing a single session of rTMS and sham stimulation, and trials comparing multiple sessions of rTMS and sham stimulation are presented in Tables 2 and 3.

Eleven RCTs evaluated a single treatment session (Table 2) [19, 27, 28, 34–41]. All had a cross-over design. A total of 290 patients were included. The majority of the patients suffered from post-stroke pain or pain from a spinal cord injury/lesion. The time of follow-up after stimulation varied between 5 min and 12 days. The quality of the studies according to the SBU checklist was low to moderate with some study limitations in most of them. There was some uncertainty with regard to the directness since the selection of patients was not adequately

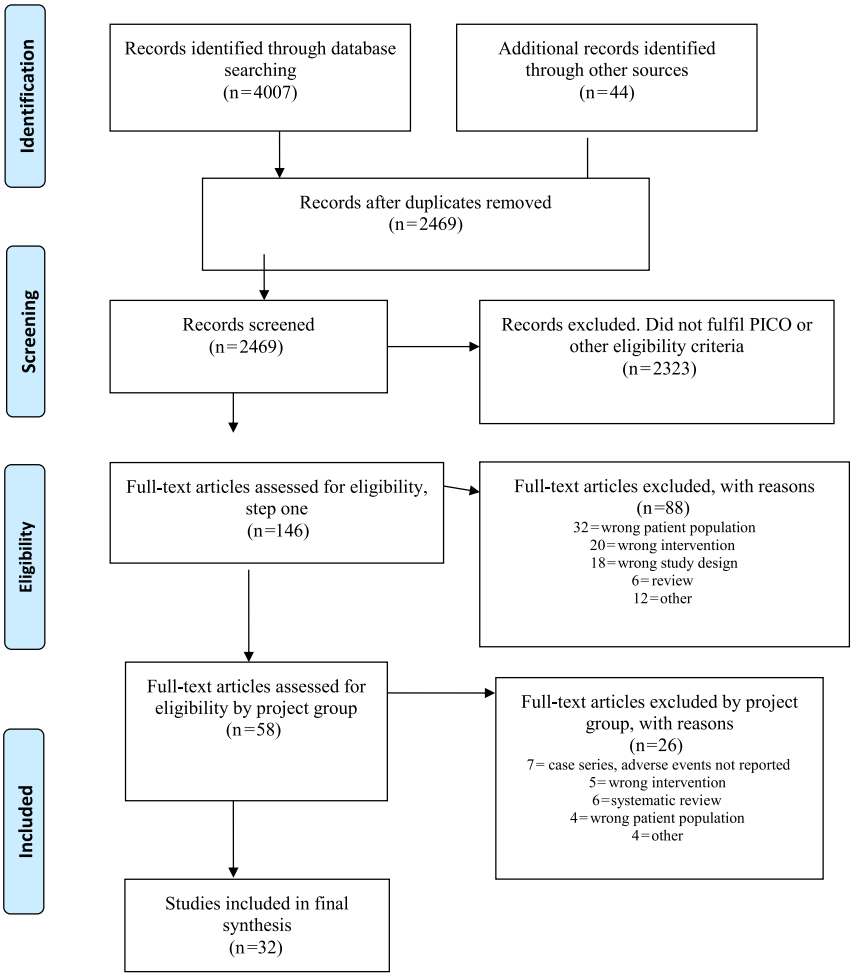

Figure 1: Study selection process – PRISMA flow diagram.

described in most of the trials. The randomisation procedure was not clearly presented in some studies, while in other the stimulation procedure (active or sham) seemed only to be blinded to the patients and not to the investigator(s) that did the outcome assessment after the treatment (Table 2).

Thirteen RCTs with a total of 392 patients utilising multiple treatment sessions (from 3 to 20 sessions) were included in the analysis (Table 3) [42–54]. Five of the RCTs had a cross-over design and eight a parallel group design. In contrast to single-session trials, a mixture of conditions with pain of various origin emanating from both the peripheral and the central nervous system were investigated using highly variable stimulation parameters. The longest follow-up of the stimulation effect was 6 months. Seven of the RCTs were assessed being of high quality, and six of moderate quality (Table 3). There were some inconsistencies of various magnitudes of both the absolute and the relative reduction in pain after treatment, as well as of the difference between active and sham stimulation.

Six studies reported the effects of rTMS followed by MCS in the same patients [30, 39, 55–58]. However, only four studies including a total of 101 patients presented data that could be used to calculate sensitivity and specificity of rTMS to predict a good response to MCS [30, 55, 56, 58]. Of these studies only two had a blinded assessment of the outcome. There was also some uncertainty with regard to directness since the selection of patients was not adequately described, and due to small sample sizes in two studies there was also uncertainty with regard to precision.

Main analysis

Effect of a single session of rTMS on pain

Data from each study are presented in Table 4. In 9 of the 11 RCTs the difference between active and sham M1 rTMS was statistically significant [19, 27, 34, 35, 37–41]. Baseline data could be extracted from six of the RCTs. The weighted mean pain score at baseline was 6.8 for active rTMS and 6.7 for

Table 2: Characteristics of included studies using a single session of rTMS.

Study	Number of patients	Dropout/Withdrawal rate (n)	Type of patients	rTMS vs. Sham	Study design	Age, (years)	Male sex	Outcome	Follow-up	Study quality
André-Obadia et al. 2006 [28]	14	2	CPSP	20 Hz	RCT, Cross-over, DB	53	71%	VAS	1 week	Medium
André-Obadia et al. 2008 [27]	30	2	CPSP Spinal lesion	20 Hz	RCT, Cross-over, DB	55	77%	VAS	5 days	Medium
André-Obadia et al. 2011 [34]	45	0	CPSP Spinal/brain stem lesion	20 Hz	RCT, Cross-over, DB	55	62%	VAS	5 days	Low
Hirayama et al. 2006 [35]	20	0	CPSP Spinal/brain stem lesion	5 Hz	RCT, Cross-over, SB	57	65%	VAS	3 h	Low
Jetté et al. 2013 [36]	18	2	SCI	10 Hz	RCT, Cross-over, DB	50	69%	NRS	5-6 days	Low
Lefaucheur et al. 2001b [37]	18	0	CPSP Brain stem lesion	10 Hz	RCT, Cross-over, DB	55	61%	VAS	5-10 min	Low
Lefaucheur et al. 2001a [19]	14	0	CPSP	10 Hz	RCT, Cross-over, SB	57	43%	VAS	12 days	Medium
Lefaucheur et al. 2004 [39]	60	0	Mixed NP	10 Hz	RCT, Cross-over, SB	55	47%	VAS	5 min	Medium
Lefaucheur et al. 2008 [38]	48	2	CPSP Spinal lesion	10 Hz	RCT, Cross-over, DB	54	50%	VAS	15 min	Medium
Pleger et al. 2004 [40]	10	0	CRPS	10 Hz	RCT, Cross-over, SB	51	30%	VAS	1.5 h	Low
Saitoh et al. 2007 [41]	13	0	CPSP SCI	10 Hz	RCT, Cross-over, SB	59	54%	VAS	3 h	Low

CPSP, central post stroke pain; CRPS, complex regional pain syndrome; DB, double-blind; NP, neuropathic pain; NRS, numeric rating scale; RCT, randomised controlled trial; SB, single-blind; SCI, spinal cord injury; VAS, visual analogue scale.

sham rTMS with a weighted mean difference following treatment of –1.3 and –0.3, respectively. The calculated average pain reduction was –19% for active rTMS, and –4% for sham (Table 6).

Since baseline data could be extracted only from 6 of the 11 studies that were included in the single session analysis, we also calculated a weighted mean for active rTMS and sham based on change in percent in the pain score after one stimulation session. This data could be obtained from 10 studies (Table 4). The change in pain score relative to baseline varied from ±0% to –24% for active rTMS, and from +27% to –9% for sham. The calculated average pain reduction in the 10 included studies based on weighted percentage values was –16% for active rTMS, and –3% for sham.

According to the GRADE classification, taking into account the overall quality of the evidence, it is uncertain whether one single session of high frequency rTMS results in little or no reduction of pain in patients with chronic NP. Very low certainty of evidence (GRADE ⊕OOO).

Effect of multiple sessions of rTMS on pain

Data from each study are presented in Table 5. In 9 of the 13 RCTs the difference between active and sham rTMS was statistically significant [42–46, 50–53], in four trials no significant difference was observed [47–49, 54]. In one study [48] the change in pain score before and after an intervention was expressed as mean VAS reduction rates of 10 averaged sessions without specifying a baseline value

Table 3: Characteristics of included studies using multiple sessions of rTMS.

Study	Number of patients	Dropout/Withdrawal rate (n)	Type of patients	rTMS vs. Sham	Study design, duration	Age, (years)	Male sex	Outcome variable	Last follow-up	Study quality
Ahmed et al. 2011 [42]	27	0	Phantom pain	20 Hz, 5 sessions	Quasi-RCT, Parallel groups, DB	52	70%	VAS	2 months	Medium
Attal et al. 2016 [43]	51	16	Radiculopathy	10 Hz, 3 sessions	RCT, cross-over, DB	51	49%	BPI	5 days	Medium
Cervigni et al. 2018 [44]	15	2	Urinary bladder pain syndrome	20 Hz, 10 sessions	RCT, cross-over, DB	53	0%	VAS	6 weeks	High
Choi et al. 2018 [45]	12	0	Traumatic brain injury	10 Hz, 10 sessions	RCT, Parallel groups, DB	42	50%	NRS	4 weeks	High
Choi & Chang 2018 [46]	24	0	CPSP	10 Hz, 10 sessions	RCT, Parallel groups, DB	59	54%	NRS	4 weeks	High
Defrin et al. 2007 [47]	12	1	SCI	5 Hz, 10 sessions	RCT, Parallel groups, DB	54	64%	VAS	After 10th session	Medium
Hosomi et al. 2013 [48]	70	9	CPSP Spinal lesion	5 Hz, 10 sessions	RCT, cross-over, DB	61	62%	VAS	60 min	High
Kang et al. 2009 [49]	13	2	SCI	10 Hz, 5 sessions	RCT, Cross-over, DB	55	55%	NRS	7 weeks	Medium
Khedr et al. 2015 [50]	34	4	NP due to malignancy	20 Hz, 10 sessions	RCT, Parallel groups, DB	48	10%	VAS	1 month	High
Malavera et al. 2016 [51]	54	0	Phantom pain	10 Hz, 20 sessions	RCT, Parallel groups, DB	34	93%	VAS	30 days	High
Nurmikko et al. 2016 [52]	40	13	Mixed NP	10 Hz, 5 sessions	RCT, cross-over, SB	53	57%	NRS	3 weeks	Medium
Picarelli et al. 2010 [53]	23	1	CRPS	10 Hz, 10 sessions	RCT, Parallel groups, DB	42	39%	VAS	3 months	High
Yilmaz et al. 2014 [54]	17	1	SCI	10 Hz, 10 sessions	RCT, Parallel groups, DB	39	100%	VAS	6 Months	Medium

BPI, brief pain inventory; CPSP, central post stroke pain; CRPS, complex regional pain syndrome; DB, double blind; NP, neuropathic pain; NRS, numeric rating scale; RCT, randomised controlled trial; SB, single blind; SCI, spinal cord injury; VAS, visual analogue scale.

prior to the start of the first stimulation session. This study could accordingly not be used to calculate the change in pain score relative to baseline. In the remaining 12 studies which all presented baseline data the change in pain score in percent varied from ±0% to −57% after active rTMS, and +7% to −32% after sham. The weighted mean pain score at

Table 4: Pain score means measured by validated numeric scales (0=no pain, 10=worst pain) after one single session of rTMS.

Study	rTMS	Sham	Mean change in pain score compared to baseline (%)		Between-group difference; p-Value
			rTMS	Sham	
André-Obadia et al. 2006 [28]	Baseline: NR	Baseline: NR			
	After 1 week: NR	After 1 week: NR	−11%	−8%	NS
André-Obadia et al. 2008 [27]	Baseline: NR	Baseline: NR			
	After 5 days: NR	After 5 days: NR	Between group difference: −5%[a]		<0.05
André-Obadia et al. 2011 [34]	Baseline: NR	Baseline: NR			
	After 5 days: NR	After 5 days: NR	−10%	−1%	<0.001
Hirayama et al. 2006 [35]	Baseline: 8.2[a]	Baseline: 8.1[a]			
	After 1 session: 7.7[a]	After 1 session: 8.2[a]	−6%	+1%	<0.05
Jetté et al. 2013 [36]	Baseline: NR	Baseline: NR			
	After 5–6 days: NR	After 5–6 days: NR	−5%	−5%	NS
Lefaucheur et al. 2001b [37]	Baseline: 7.0 (sd 0.4)	Baseline: 6.7 (sd 0.5)			
	After 1 session: 5.6 (sd 0.6)	After 1 session: 6.2(sd 0.5)	−20%	−7%	<0.001
Lefaucheur et al. 2001a [19]	Baseline: 6.7[a]	Baseline: 6.4[a]			
	After 1 week: 5.5[a]	After 1 week: 7.8[a]	−18%	+22%	<0.05 at 1 week
	After 12 days: 6.7[a]	After 12 days: 8.1[a]	±0%	+27%	NS
Lefaucheur et al. 2004 [39]	Baseline: 6.8 (sd 0.2)	Baseline: 6.8 (sd 0.2)			
	After 1 session: 5.4 (sd 0.3)	After 1 session: 6.2 (sd 0.3)	−21%	−9%	<0.001
Lefaucheur et al. 2008 [38]	Baseline: 6.6 (sd 0.3)	Baseline: 6.4 (sd 0.2)			
	After 1 session: 5.0 (sd 0.4)	After 1 session: 5.8 (sd 0.3)	−24%	−9%	<0.05
Pleger et al. 2004 [40]	Baseline: 4.7 (sd 2.6)	Baseline: 4.4[a]			
	After 1 session: 3.7 (sd 2.9)	After 1 session: 4.5[a]	−21%	+2%	<0.05
Saitoh et al., 2007 [41]	Baseline: NR	Baseline: NR			
	After 3 h: NR	After 3 h: NR	−10%	+2%	<0.05

[a]Estimated from a figure-illustration in the publication.
NR, data not reported; NS, not significant.

baseline was 6.5 for active rTMS and 6.2 for sham rTMS with a weighted mean difference following treatment of −1.4 and −0.5, respectively, at the last follow-up. The calculated average pain reduction was −22% for active rTMS and −8% for sham.

In order to investigate the effect of multiple rTMS sessions over time, we performed a sub-analysis of follow-up assessments that were performed <30 days, and ≥30 days after the last stimulation session, respectively. For assessments performed <30 days (12 studies, mean follow-up 12 days), the weighted mean difference in pain score compared to baseline was −2.1 following active rTMS, and −0.6 after sham stimulation (Table 6). The calculated mean reduction in the pain score relative to baseline was −32% for active rTMS and −10% for sham (Table 6). Data from follow-up ≥30 days could be extracted from seven studies (mean follow-up 67 days). The weighted mean difference in pain score compared to baseline was −1.6 for active rTMS, and −0.6 for sham. The calculated mean reduction in pain score was −24% for active rTMS, and −9% for sham (Table 6).

Based on the overall quality of the evidence, the GRADE classification indicates that multiple sessions of high frequency rTMS may result in pain reduction in patients with chronic NP. Low certainty of evidence (GRADE ⊕⊕◯◯).

The findings of the effect of single and multiple session treatments with active vs. sham rTMS on NP are summarised in Table 6. Only three studies reported effects on HRQoL using validated tools, with significant improvement in some sub-scores after active rTMS compared to sham [44, 46, 53]. No study reported changes of analgesic drug use in the long term.

No serious or life-threatening adverse events were observed when rTMS was used. The reported side effects mainly included mild headaches and an uncomfortable sensation of the magnetic pulse.

Table 5: Pain score means measured by validated numeric scales (0=no pain, 10=worst pain) after multiple sessions of rTMS.

Study	rTMS	Sham	Mean change in pain score compared to baseline (%)		Between-group difference; p-Value
			rTMS	Sham	
Ahmed et al. 2011 [42]	Baseline: 7.4 (sd 1.3)	Baseline: 7.6 (sd 0.8)			
	After 5 sessions: 3.4 (sd 1.2)	After 5 sessions: 7.4 (sd 0.8)	−54%	−3%	
	After 2 months: 4.5 (sd 2.2)	After 2 months: 7.6 (sd 1.0)	−39%	±0%	<0.05
Attal et al. 2016 [43]	Baseline: 5.9[a]	Baseline: 6.2[a]			
	After 5 days: 4.5[a]	After 5 days: 6.0[a]	−24%	−3%	<0.05
Cervigni et al. 2018 [44]	Baseline: 7.8[a]	Baseline: 6.7[a]			
	After 3 weeks: 6.3[a]	After 3 weeks: 7.1[a]	−19%	+6%	
	After 6 weeks: 6.7[a]	After 6 weeks: 7.2[a]	−14%	+7%	<0.05
Choi et al. 2018a [45]	Baseline: 5.8 (sd 0.8)	Baseline: 5.8 (sd 0.8)			
	After 4 weeks: 3.2[a]	After 4 weeks: 5.8[a]	−45%	±0%	<0.05
Choi et al. 2018b [46]	Baseline: 6.3 (sd 1.3)	Baseline: 5.8 (sd 1.5)			
	After 4 weeks: 4.7 (sd 1.7)	After 4 weeks: 5.8 (sd 1.4)	−25%	±0%	<0.05
Defrin et al. 2007 [47]	Baseline: 4.6[a]	Baseline: 3.4[a]			
	After 10 sessions: 3.3[a]	After 10 sessions 2.3[a]	−28%	−32%	NS
Hosomi et al. 2013 [48]	Baseline: NR	Baseline: NR			
	After 10 sessions: NR	After 10 sessions: NR	(−3.4%)	(+0.7%)	NS
Kang et al. 2009 [49]	Baseline: 6.5 (sd 2.2)	Baseline: 6.2 (sd 1.8)			
	After 1 week: 5.5 (sd 1.8)	After 1 week: 5.9 (sd 2.0)	−15%	−5%	
	After 7 weeks: 5.7 (sd 2.1)	After 7 weeks: 5.9 (sd 2.1)	−12%	−4%	NS
Khedr et al. 2015 [50]	Baseline: 6.3 (sd 0.5)	Baseline: 6.1 (sd 0.6)			
	After 15 days: 4.0[a]	After 15 days: 5.0[a]	−37%	−18%	<0.05 at 15 days
	After 1 month: 4.8[a]	After 1 month: 5.1[a]	−24%	−16%	NS at 1 month
Malavera et al. 2016 [51]	Baseline: 4.9 (sd 1.8)	Baseline: 4.8 (sd 1.8)			
	After 15 days: 2.3 (sd 2.5)	After 15 days: 3.7 (sd 3.0)	−53%	−23%	< 0.05 at 15 days
	After 30 days: 3.0 (sd 2.6)	After 30 days: 3.9 (sd 2.7)	−39%	−19%	NS at 30 days
Nurmikko et al. 2016 [52]	Baseline: 6.8 (sd 1.7)	Baseline: 6.5 (sd 1.8)			
	Δ after 1 week: −0.6 (sd 1.0)	Δ after 1 week: −0.01(sd 0.8)	−9%	±0%	<0.05 at 1 week
	Δ after 3 weeks: −0.5 (sd 1.1)	Δ after 3 weeks: −0.2 (sd 0.9)	−7%	−3%	<0.05 at 3 weeks
Picarelli et al. 2010 [53]	Baseline: 9.3 (sd 0.9)	Baseline: 8.8 (sd 1.0)			
	After 1 week: 3.9	After 1 week: 6.4	−57%	−27%	<0.05 at 1 week
	After 3 months: 8.0	After 3 months: 6.9	−14%	−22%	NS at 3 months
Yilmaz et al. 2014 [54]	Baseline: 7.0	Baseline: 7.0			
	After 10 days: 5.0	After 10 days: 6.0	−29%	−14%	
	After 6 weeks: 5.0	After 6 weeks: 7.0	−28%	±0%	NS
	After 6 months: 7.0	After 6 months: 7.0	±0%	±0%	

[a]Estimated from a figure-illustration in the publication. In Hosomi et al. [48] change in pain score is expressed as mean VAS reduction rates of 10 averaged sessions of real rTMS and sham immediately before and 60 min after each intervention without presenting any baseline data. This study was accordingly not included in the calculation of change in pain score compared to baseline.
NR, not reported; NS, not significant.

Accuracy of rTMS to predict the response of epidural motor cortex stimulation

The calculated specificity of rTMS to predict a positive clinical response to MCS varied between 60 and 100% in the four studies that were included in the analysis depending on the definition of the magnitude of the response (Table 7) [30, 55, 56, 58]. The 95% confidence interval of the estimates of specificity was of large width in three of the studies which all were based on a small number of patients (Table 7). The positive predictive value in the four studies was in the range of 75–100% (Table 7).

According to the GRADE classification the response to rTMS may be a useful predictor of the response to epidural MCS in patients with chronic NP. Low certainty of evidence (GRADE ⊕⊕◯◯).

Table 6: Summary of results of active rTMS vs. sham from studies presenting baseline data.

Outcome variable	Study design number of studies	Absolute effect VAS/NRS/BPI (0–10)[a]		Pain reduction (%)[b]	Certainty of evidence GRADE*
Pain Validated scales	RCT				
Single session rTMS	6	*Active* Baseline: (weighted mean): 6.8 Mean difference (Post-Pre): −1.3	*Sham* Baseline: (weighted mean): 6.7 Mean difference (Post-Pre): −0.3	−19% vs. −4%	⊕OOO Very low[c]
Multiple sessions rTMS[d] Follow-up: <30 days	12	*Active* Baseline: (weighted mean): 6.5 Mean difference (Post-Pre): −2.1	*Sham* Baseline: (weighted mean): 6.2 Mean difference (Post-Pre): −0.6	−32% vs. −10%	⊕⊕OO Low[e]
Multiple sessions rTMS Follow-up: ≥30 days	7	*Active* Baseline: (weighted mean): 6.7 Mean difference (Post-Pre): −1.6	*Sham* Baseline: (weighted mean): 6.4 Mean difference (Post-Pre): −0.6	−24% vs. −9%	⊕⊕OO Low[e]

[a]Calculated average of the weighted mean VAS/NRS/BPI values from six single session (Table 4) and 12 multiple session trials (Table 5).
[b]Calculated average of the weighted mean reduction in pain score (%) for active vs. sham rTMS.
[c]Serious inconsistency due to the variability in the size of effect, serious study limitations, and some uncertainty with regard to directness and with regard to precision.
[d]One RCT [48] did not report baseline data during the first month of follow-up (Table 5).
[e]Some inconsistency due to the variability in the size of effect, and some uncertainty with regard to precision.
*Certainty of evidence: High certainty ⊕⊕⊕⊕, We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty ⊕⊕⊕O, We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty ⊕⊕OO, Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low certainty ⊕OOO, We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
BPI, brief pain inventory; NRS, numeric rating scale; RCT, randomised controlled trial; VAS, visual analogue scale.

Discussion

The present systematic review shows that 5–20 Hz, high frequency rTMS of M1, both given as single and multiple sessions, usually results in statistically significant reduction of NP compared to sham stimulation. The effect is, however, transient and the difference in pain reduction between active rTMS and sham is moderate at a group level, with inconsistencies in outcome between studies. Based on calculations of baseline data there was a 15 percentage point difference in pain reducing effect between single sessions of active and sham rTMS. For multiple session trials the percentage point difference between active rTMS and sham was 22 if assessment was performed <30 days after the last stimulation session, and 15 at follow-up ≥30 days.

The included RCTs typically involved a limited number of patients (10–70) with highly heterogeneous pain conditions, and used excessively variable stimulation parameters. Many trials had study limitations with regard to the randomisation procedures and blinding. There was also some uncertainty with regard to the directness since the selection of patients was not adequately described in many studies. The timing of sham stimulation relative to active rTMS in studies with a cross-over design was usually not taken into account, although it has been demonstrated that placebo effects seem to be enhanced if being preceded by a previous real rTMS session due to unconscious conditioned learning [34]. Thus, a prior positive experience of active rTMS may act as a conditioning procedure inducing an increased analgesic effect of subsequent sham stimulation, not related to the maximal remnant post-stimulation effect (carryover effect) of the active stimulation [34]. Based on GRADE the certainty of evidence of the effect of rTMS on chronic NP can be classified as very low for single sessions, and low for multiple sessions targeting M1. No serious adverse events were reported in association with the rTMS procedures.

A statistically significant reduction in the pain score must be interpreted in view of the clinical context since a statistical significance at a group level does not necessarily translate into a clinically meaningful reduction in pain at the individual level [59]. The term “clinically important/meaningful/relevant” also provides a foundation to

Table 7: Diagnostic performance of rTMS to predict a response to motor cortex stimulation in patients with chronic neuropathic pain.

Study	Number of patients	Sensitivity	Specificity	Predictive value		Comment
				Positive	Negative	
André-Obadia 2014 [55]	19	60% (95% CI: 33–83%)	75% (95% CI: 22–99%)	90% (95% CI: 54–99%)	67% (95% CI: 31–91%)	Positive response to rTMS: a positive score on CPA[a] Positive response to MCS: a positive score on CPA[1]
Hosomi 2008 [56]	11	89% (95% CI: 51–99%)	100% (95% CI: 18–100%)	100% (95% CI: 60–100%)	67% (95% CI: 13–98%)	Positive response to rTMS: ≥30% pain reduction on VAS (pre-post) Positive response to MCS: ≥30% pain reduction on VAS (pre-post)
		100% (95% CI: 51–100%)	60% (95% CI: 17–92%)	75% (95% CI: 36–96%)	100% (95% CI: 31–100%)	Positive response to rTMS: ≥30% pain reduction on VAS (pre-post) Positive response to MCS: ≥50% pain reduction on VAS (pre-post)
Lefaucheur 2011 [30]	59	74% (95% CI: 56–87%)	71% (95% CI: 48–87%)	79% (95% CI: 61–91%)	65% (95% CI: 44–82%)	Positive response to rTMS: ≥30% pain reduction on VAS (Δ active – sham) Positive response to MCS: ≥50% pain reduction on VAS (pre-post)
Pommier 2019 [58]	12	71% (95% CI: 30–94%)	80% (95% CI: 30–99%)	83% (95% CI: 36–99%)	67% (95% CI: 24–94%)	Positive response to rTMS: ≥30% pain reduction on VAS (after 4 sessions rTMS pre-post) Positive response to MCS: ≥30% pain reduction on VAS (after 6 months pre-post)

[a]CPA, Combined Pain Assessement (score −3 to +3).
CI, confidence interval; MCS, motor cortex stimulation; VAS, Visual Analogous Scale.

evaluate and compare the impact of treatments on symptoms, functioning and overall HRQoL by patients, clinicians and health care providers [59]. A reduction in the pain score at the individual level by a validated numerical scale of 30% or more from the baseline is considered a useful threshold for identifying a clinically important or meaningful improvement based on international consensus statements [59–61].

After a single session of active rTMS the weighted mean pain reduction compared to baseline was calculated to be 19% at the group level in our analysis of the six studies which presented baseline data. Most patients that were included in the overall single-session analysis did not experience a pain relief greater than 30% relative to baseline, and did consequently not fulfil the criteria for a responder defined by a clinically meaningful improvement. The pain reduction at the individual level was, however, often within the limits for minimally important changes of 10–20% according to the IMMPACT recommendations for outcome measures in chronic pain trials [59]. The effect usually faded away within one week. In this context it is important to point out that in three of the included studies in the analysis of single session rTMS follow-up assessment was performed 5–15 min after conclusion of the stimulation session [37–39]. These studies, which showed among the best results with a pain reduction of 21–24% (Table 4), accounted for 44% of the 290 patients from the 11 trials in the overall single session analysis, and 74% of the 168 patients from the six trials which were used to calculate the weighted pain score means for active and sham rTMS based on baseline data (Table 6). Since we did not set a lower time limit for evaluation of treatment effect after a stimulation session in the PICO, these three studies, which fulfilled the criteria for sham/placebo-controlled RCTs, were included in the systematic analysis. In retrospect, given the uncertain clinical relevance of a follow-up time of only 5–15 min for estimation of changes in pain score, setting a lower time limit for assessment of treatment effect may have been advisable. Due to the considerable impact of the three studies on the results, we made an additional calculation based on the difference in percent between follow-up and baseline for active rTMS and sham, respectively, where data could be obtained from 10 of 11 studies (Table 4). This analysis (254 instead of 168 patients) showed that the weighted mean reduction in pain score decreased from 19 to 16% after active rTMS, with a resulting 13 percentage point difference instead of a difference of 15 points, as

obtained in the analysis of the six studies presenting baseline data. The between group difference, active rTMS vs. sham, expressed in percent could be extracted from all 11 studies (284 patients, Table 4) with a calculated weighted mean difference of 12 percentage points. The reduction from 15 to 13 to 12 percentage points based on the increasing number of patients illustrates the relative weight of the three studies with follow-up assessment of 5–15 min on the outcomes.

Multiple sessions of rTMS yield greater pain reduction with a more longstanding effect. Our analysis, which was based on all 12 studies from which baseline data could be extracted, showed that if assessment was performed less than 30 days after the last treatment session, the weighted mean pain reduction, compared to baseline, was 32% with active rTMS at the group level. Compared to single-session rTMS, more patients experienced a pain relief exceeding the arbitrarily defined threshold of 30% for a clinically important reduction in pain. The effect faded, however, with time if the stimulation sessions were not repeated regularly. In addition, in the multiple-session group sham stimulation also resulted in some pain relief, thereby reducing the difference in treatment effect between active and sham stimulation.

In a previous review by Lefaucheur et al. from 2014, with a recent update 2020, outlining evidence-based guidelines on the therapeutic use of rTMS, a level A (definite efficacy) recommendation was proposed for high frequency rTMS of M1 for treatment of NP, despite inhomogeneities in outcomes between studies [22, 62]. In contrast to the analyses by Lefaucheur et al. and most prior guidelines and systematic reviews on the use of neuromodulation techniques in pain treatment, our assessment of the level of evidence of effects was based on the GRADE system [33, 63]. If the level of evidence of a positive effect is of high or moderate certainty it most probably qualifies to be used in routine medical care. If the level of evidence is of low certainty the use of the technology may be motivated provided that there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Due to this structured and informative approach GRADE is increasingly being adopted by organisations worldwide and has also been utilised in several recent evaluations of neuromodulation techniques for pain treatment [8, 24].

In 2014 O'Connell et al. published an updated version based on GRADE of their first Cochrane review from 2011 investigating non-invasive brain stimulation techniques for chronic pain [24]. Their literature search was not restricted only to NP but included trials of all types of chronic pain. The authors found that single doses of high-frequency rTMS of M1 resulted in statistically significant but small short-term effects on chronic pain which did not meet the predetermined threshold of minimal clinically important difference of 15%. The evidence for multiple-dose studies of rTMS was heterogeneous and did not demonstrate a significant effect. However, in a subsequent subgroup analysis that specifically included patients with chronic NP it was found that active rTMS reduced pain by 20% (95% confidence interval of the relative risk reduction was −0.27 to −0.12) in comparison to sham treatment. The authors concluded that available studies had not consistently demonstrated effectiveness, and stated in accordance with other reviews and meta-analyses that there was a need for larger, rigorously designed studies, particularly of longer courses of stimulation [64–66]. The broad conclusions did not change substantially in the last Cochrane update from the authors published in 2018, although several new studies of high quality using multiple-session rTMS with longer follow-up were added. Our systematic review included three additional studies of high quality with a total of 51 patients [44–46]. We classified the overall certainty of evidence of outcomes for multiple sessions of rTMS based on GRADE as low, instead of very low as evaluated by O'Connell et al. Furthermore, in contrast to the Cochrane review, our analysis focused solely on the use of rTMS for treatment of chronic NP, and also took into account the timing aspect for follow-up, i.e. how long after the last stimulation session that assessment was done, which is important to consider due to the fading of effect with time.

In 2016 The European Academy of Neurology updated the guidelines of the European Federation of Neurological Societies on central neurostimulation therapy in chronic pain [8]. Using the GRADE classification it was concluded that there is a weak recommendation for multiple sessions of high frequency rTMS of M1 in treatment of chronic NP. In accordance with our analysis these guidelines indicate that rTMS may be used to predict the response to epidural MCS. A significant pain reduction as a response to a preoperative non-invasive rTMS test increases the probability of a good MCS therapeutic result [67]. However, since the available data is based on a limited number of patients, additional placebo-controlled, prospective clinical trials using neuronavigated rTMS are needed to manifest this relationship [13, 68, 69].

Even though previous studies, meta-analyses and systematic reviews have indicated that there is good clinical evidence for rTMS of M1 for certain types of chronic NP, such as trigeminal neuropathic facial pain and central post-stroke pain, the treatment is not for all types of NP [22, 39, 66]. Most of the included RCTs in our systematic

analysis using single-session rTMS investigated patients suffering from post-stroke pain or pain due to a spinal cord injury/lesion. The RCTs investigating multiple sessions of rTMS included a large variety of different NP conditions of both central and peripheral origin (Table 3). We attempted to perform a sub-analysis of outcomes based on distinction in the origin of the pain but could not, due to the relatively small numbers of patients for each individual pain type, discern any significant differences or draw any firm conclusions considering treatment response between the investigated conditions (data not shown). Additional data is required to bring more clarity in this context.

Since rTMS, like MCS, may be relevant only to some patients, predictive factors for the efficacy on different types of NP must be defined in greater detail in future research [65, 66, 70]. In addition, standardised protocols identifying optimal stimulation parameters for achieving best long-term maintenance of treatment effect need to be designed and evaluated [52, 64, 71, 72]. Better data on health economics, as well as evaluation of the effect on HRQoL, ADL and changes in analgesic drug use also are needed to provide a more solid basis for the application of rTMS in pain management in the long term [73].

Conclusions

Use of rTMS as therapy for chronic NP has increased in popularity due to the non-invasive mode of this technique. Both single and multiple sessions of high-frequency rTMS targeting M1 result in statistically significant pain reduction. The effect compared to sham stimulation is, however, moderate and highly variable. Multiple, consecutive sessions of rTMS give a better and more longstanding pain relief and are therefore mainly utilised clinically today [58, 74]. Single-session rTMS may be suitable as a test to predict a positive pain-relieving response of epidural MCS which can facilitate the selection of appropriate patients for implantation of epidural electrodes [8, 17, 22, 67]. Somatotopic, navigated rTMS for appropriate electrode placement has the potential to further improve the outcomes in this respect [15, 52, 75]. Additional critical appraisal of the efficacy of rTMS for different types of NP is needed. There are still major knowledge gaps concerning the long-term effects of rTMS on HRQoL and analgesic medication use, as well as lack of data on the cost-effectiveness of this therapy in pain treatment. These important outcome variables need to be addressed more consistently in future studies to consolidate a routine use of rTMS in chronic pain management.

Acknowledgements: We would like to thank Magnus Pettersson, biostatistician (PStat®), Statistikkonsulterna for help with the statistical analysis.
Research funding: Authors state no funding involved.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Conflict of interest: Authors state no conflict of interest.

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