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Review Article

rTMS for Suppressing Neuropathic Pain: A Meta-Analysis

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Abstract: **This pooled individual data (PID)-based meta-analysis collectively assessed the analgesic effect of repetitive transcranial magnetic stimulation (rTMS) on various neuropathic pain states based on their neuroanatomical hierarchy. Available randomized controlled trials (RCTs) were screened. PID was coded for age, gender, pain neuroanatomical origins, pain duration, and treatment parameters analyses. Coded pain neuroanatomical origins consist of peripheral nerve (PN); nerve root (NR); spinal cord (SC); trigeminal nerve or ganglion (TGN); and post-stroke supraspinal related pain (PSP). Raw data of 149 patients were extracted from 5 (1 parallel, 4 cross-over) selected (from 235 articles) RCTs. A significant ($P < .001$) overall analgesic effect (mean percent difference in pain visual analog scale (VAS) score reduction with 95% confidence interval) was detected with greater reduction in VAS with rTMS in comparison to sham. Including the parallel study (Khedr et al), the TGN subgroup was found to have the greatest analgesic effect (28.8%), followed by PSP (16.7%), SC (14.7%), NR (10.0%), and PN (1.5%). The results were similar when we excluded the parallel study with the greatest analgesic effect observed in TGN (33.0%), followed by SC (14.7%), PSP (10.5%), NR (10.0%), and PN (1.5%). In addition, multiple (vs single, $P = .003$) sessions and lower (>1 and ≤10 Hz) treatment frequency range (vs >10 Hz) appears to generate better analgesic outcome. In short, rTMS appears to be more effective in suppressing centrally than peripherally originated neuropathic pain states.**
Perspective: ***This is the first PID-based meta-analysis to assess the differential analgesic effect of rTMS on neuropathic pain based on the neuroanatomical origins of the pain pathophysiology and treatment parameters. The derived information serves as a useful resource in regards to treatment parameters and patient population selection for future rTMS-pain studies.***

Key words: *Transcranial magnetic stimulation, TMS, rTMS, neuropathic pain, neuromodulation, meta-analysis.*

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Neuropathic pain is broadly defined as chronic pain resulting from injury or dysfunction of the nervous system. The underlying pathophysiology is usually associated with plastic changes both functionally and structurally in the nervous system, and depending on the areas of the nervous system being affected, different neuropathic pain states may respond differently to pain interventions.[1-6] Transcranial magnetic stimulation (TMS) offers a noninvasive and nonpainful means of central neuromodulation for both studying and treating neuropathic pain states.[7] The technology uses electromagnetic principles to produce small and localized electrical currents in the cortex. With technological advancement in capacitors that allow rapid electrical charge and discharge, repetitive transcranial magnetic stimulation (rTMS) has been made available as a treatment option for a variety of psychiatric and neurological diseases including various chronic neuropathic pain states.[8-13] Several recent articles have provided a preliminary qualitative and quantitative overview of rTMS in treating various chronic pain states.[13,14] However, definitive and quantitative information is still lacking in the current literature in regard to the relative rTMS efficacy in treating various neuropathic pain conditions, based on their neuroanatomical origins. Similarly, the current literature lacks information regarding combinations of treatment parameters that are likely to provide favorable clinical outcome. Given that the locations of neuronal injury or lesions may significantly affect the underlying pathophysiology that leads to neuropathic pain states and the subsequent response to rTMS, assessing the analgesic effect based on neuroanatomical origins of pain may shed light on the underlying analgesic mechanisms of rTMS. Therefore it will be important to assess whether:

(1) rTMS is effective in suppressing all or only certain types of neuropathic pain conditions;
(2) the neuroanatomical origins of pain pathophysiology and their relative cranio-caudal (top-down) neuroanatomical locations may affect the outcome;
(3) the different combinations of treatment parameters may affect the analgesic benefit.

With these questions in mind and in hopes of better characterizing the effect of rTMS in treating different neuropathic pain states, we conducted a pooled individual data (PID) meta-analysis to specifically address these crucial issues related to the use of rTMS in chronic pain management.

Our main objectives are as follows:

(1) To quantitatively assess the overall analgesic effect of rTMS at the motor cortex for neuropathic pain states;
(2) to assess the overall and the differential analgesic effect of rTMS among individual neuropathic pain states in regard to their corresponding neuroanatomical origins of pain and their relative cranio-caudal (top-down) neuroanatomical order;
(3) to assess the effect of treatment parameters such as pulses, frequency, and number of treatment sessions on the outcome.

Methods

Guidelines for meta-analysis were followed whenever applicable.[15]

Search Strategy

An extensive literature search was conducted in August 2007 in the following databases: PubMed, Psycinfo, Cinahl, Cochrane, and EMBASE, using the following key words: pain, transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS), transcortical electrical stimulation. Studies identified as randomized controlled trials (RTC) in either cross-over or parallel designs were individually screened for analysis, based on the following inclusion and exclusion criteria.

Inclusion criteria:

(1) Human study
(2) Neuropathic pain related
(3) Pain diagnoses of the subjects can be attributed to a neuroanatomical origin
(4) Primary motor cortex (M1) as the treatment site
(5) rTMS was used as treatment intervention
(6) Pain visual analog scale (VAS) score as 1 of the primary outcome measurements

Exclusion Criteria:

(1) Studies published in non-English literature
(2) Studies published in non–peer review journals
(3) Studies used treatment paradigm outside the published safety guidelines[16]

Trial Quality Assessment

Authors of articles that met the above criteria were contacted for providing individual subject level data for the meta-analysis. The articles were further reviewed by 2 independent reviewers (a neurologist with an extensive TMS experience and a pain specialist) for study inclusion.

Data Extraction

The raw data provided by the authors of the final chosen studies were pooled for the meta-analysis. The outcome data collected after the last treatment of the studies were used for the analysis. Percentage changed for the treatment effect was calculated by the following equation:

$$\%\ \text{of pain VAS score change} = (\text{Post-treatment Pain VAS score} - \text{Pretreatment Pain Vas Score})/(\text{Pretreatment Pain VAS Score})$$

The PID was coded for further analysis as follows:

(1) Age;
(2) Gender;

(3) Pain diagnoses based on their neuroanatomical origins in the cranio-caudal (top-down) order: post-stroke supraspinal related pain (PSP); trigeminal nerve or ganglion (TGN); spinal cord (SC); nerve root (NR); and peripheral nerve (PN);
(4) Treatment frequency: high range (>10 and ≤20 Hz) vs low range (>1 and ≤10hz);
(5) Number of pulses given per treatment session: high (>1000) vs low (≤1000); and
(6) Total number of sessions: single (S) vs multiple (M)

Since none of the included studies have systematically reported medication utilization with all the information in regard to the duration, dosage, and class of medications used by subjects at either the baseline or the postintervention level, it was deemed unfeasible to include pain medications in the current analysis.

Statistical Method

In studies with the cross-over design, the same subject was treated with both sham (placebo) and real rTMS. To account for this within-subject correlation, the generalized estimating equations (GEE) were used to estimate the parameters of the model[17]:

$$Y_{ij} = \alpha_1 1\{study_i = 1\} + + \alpha_5 1\{study_i = 5\} + \beta 1\{trt_j = TMS\} + \epsilon_{ij}$$

where Y_{ij} denotes the percent decrease in pain for subject i under treatment (trt_j) with values sham (placebo) or TMS, $study_i$ is a 5-level factor covariate, ϵ_{ij} are errors (correlated within subject), and 1 is the indicator function. The model includes the study indicators, $study_i$, to account for potential study effects. Next, the effect of subject level covariates (gender and diagnosis) and their interaction with treatment was estimated by adding parameters to the above model and fitting again using GEE. We also assessed the effect of study level covariates: number of pulses given per treatment, frequency of rTMS, and number of sessions. Number of pulses and frequency could only be assessed within the rTMS condition because the sham condition had no real number of pulses or frequency directly being delivered to the subjects. These 2 variables turned out to be collinear with the study indicators. Therefore, 2-sample *t* tests (high versus low) were performed. Finally, because the sham condition could be described as having a particular number of sessions, we reasonably modeled the interaction between treatment and sessions and fitted such a model using GEE. All analyses were conducted using R version 2.6.1 (R Development Core Team 2007, http://www.R-project.org). The GEE analysis was conducted using the GEE package [Ported to R by Thomas Lumley (versions 3.13, 4.4) and Brian Ripley (version 4.13), 2007].

Results

Search Result

A total of 235 articles were identified in the initial data base search. Of those articles, 35 were identified as randomized controlled trials (Table1A).

Table 1A. Initial Search Summary

PUBMED	140	21
PSYCHOI	49	1
CINAHL	29	1
COCHRANE	8	8
EMBASE	9	4
Total	235	35

These 35 articles were subsequently individually screened based on the additional inclusion and exclusion criteria listed in the previous section, and 7 articles were selected by 2 independent reviewers.[18-25] The excluded 28 articles and the reasons for exclusion are listed in Table 1B.[27,30-38,40-43] Three of the 7 selected published articles came from the same group of authors.[18-20] However, due to computer data loss, this author was able to provide data from 1 of the articles. This resulted in the final 5 studies to be included in the meta-analysis (Fig 1, search flow sheet).

Overall, raw data of 149 subjects (75 women and 74 men) were extracted from the 5 articles. Summary statistics of demographics and outcomes for the individual studies were demonstrated as follows: (1) Tables 2 and 3 summarize patient gender distribution and neuroanatomically related pain etiology, respectively; (2) Table 4 summarizes the treatment parameters of each of the 5 studies; and (3) Table 5 lists the sham conditions of the studies.

Treatment Effect

Because the study by Khedr et al[22] used a parallel design that was distinct from the other cross-over studies, we conducted initial analyses both with and without this particular study. Overall, we detected a significant treatment effect (Fig 2) with greater reduction in pain VAS associated with rTMS in comparison to sham (mean reduction = 16.7%, $P < .001$ with Khedr et al; 13.7%, $P < 0.001$ without Khedr et al). In the 2 studies that qualified for the analysis but the authors were unable to provide us with the raw data due to computer data loss, 1 of 2 studies consists of 18 subjects with pain related to supraspinal (12 subjects) and nerve root (6 subjects) etiologies. The summarized result of this study indicated a significant post-rTMS pain VAS scores reduction with a single session of 10 Hz rTMS ($P = 0.001$) in comparison to sham and 0.5 Hz rTMS.[18] In the other study with a cross-over design, the authors reported a significant reduction of pain VAS in 14 subjects (7 with PSP and 7 with TGN) with a single session of 10 Hz rTMS M1 treatment in comparison to sham.[20] The single-session treatment effect lasted up to 1 week. Given that these 2 studies consisted of a relatively small number of subjects (less than 18% of the potential PID) and their summary results were similar to the observed overall treatment effect, we estimated the statistical impact of those nonincluded data on the overall analysis was minimal. In the analyzed data, no significant age or gender effect on analgesia between rTMS and sham in the current meta-analysis was found. In addition, duration of pain data was only available from

Table 1B. Excluded Studies

	Data Base	Authors (Year)	Abbreviated Publication Name	Subject Population	Main Reasons of Exclusion
1	PubMed	Avery et al (2007)[26]	J Nerv Ment Dis	Chronic pain patients of depression (n = 68)	Left DLPFC as the simulation site and no clear description of neuroanatomical origin of pain
2	PubMed	Borckardt et al (2006)[27]	Anesthesiology	Postop patients (n = 20)	Left prefrontal cortex stimulation. Nonchronic neuropathic pain patients and no clear description of neuroanatomical origin of pain
3	PubMed EMBASE	Brighina et al (2004)[28]	J Neurol Sci	Migraine patients (n = 11)	Left DLPFC stimulation and no clear description of neuroanatomical origin of pain
4	PubMed EMBASE	Clarke et al (2006)[29]	J Headache Pain	Migraine patients (n = 42)	rTMS given over headache area and no clear description neuroanatomical origin of pain
5	Cochrane	Dougall et al (2006)	Cochrane Database of Systematic Reviews	Schizophrenic patients	Non–pain-related review article
6	PubMed Psychoinfo	Fregni et al (2005)[30]	Annuals of Neurology	Patients with visceral pain (n = 5)	No clear description neuroanatomical origin of pain
7	PubMed	Fregni et al (2006)[31]	Pain	Patients with traumatic spinal cord injury (n = 17)	Transcranial direct current stimulation of the motor cortex was used for the study; a non-rTMS study
8	Cochrane Cinahl	Furlan et al (2002)	Cochrane Database of Systematic Reviews	Nonspecific low back pain	Non–rTMS-related review article
9	PubMed	Graff-Guerrero et al (2005)[32]	Brain Res Cogn Brain Res	Healthy subjects	Nonchronic pain study with DLPFC rTMS stimulation
10	Cochrane	Hoare BJ et al (2007)	Cochrane Database of Systematic Reviews	Children with cerebral palsy	Non–pain-related review article
11	PubMed	Inghilleri et al (2004)[33]	Exp Brain Res	Neuropathic pain patients on anticonvulsants (n = 23)	Only change in motor evoked potentials were assessed in the study
12	EMBASE	Iribacher et al (2006)	Nervernarzt	Patients with central (n = 13) and phantom limb (n = 14) pain	Non-English publication
13	PubMed	Kofler et al (1998)[34]	Neurosci Lett	Healthy subjects (n = 5)	Nonchronic pain study
14	PubMed	Lee et al (2005)[35]	Neurosci Lett	Patients with schizophrenia (n = 39)	Non–pain-related studies with rTMS at temporoparietal areas
15	Cochrane	Martin et al (2001)	Cochrane Database of Systematic Reviews	Patients with depression	Non–pain-related review article
16	Cochrane	Martin et al (2003)	Cochrane Database of Systematic Reviews	Patients with obsessive-compulsive disorder	Non–pain-related review article
17	Cochrane	Martinsson L et al (2007)	Cochrane Database of Systematic Reviews	Post-stroke patients	Non–pain-related review article
18	PubMed	Mosimann et al. (2000)[36]	Psychiatry Res.	Healthy subjects (n = 25)	Nonchronic pain subjects
19	PubMed	Padberg et al (2002)[37]	Neuropsycho-pharmacology	Patients with depression (n = 31)	Not a neuropathic pain rTMS study
20	PubMed	Pleger (2004)[23]	Neurosci Lett	Patients with complex regional pain syndrome (n = 10)	No clear description of neuroanatomical origin of pain
21	PubMed	Pope et al (1994)[38]	Spine	Patient with low back pain	A transcutaneous muscular stimulation (TMS) study
22	PubMed	Passard et al (2007)[39]	Brain	Patients with fibromyalgia (n = 30)	No clear description of neuroanatomical origin of pain
23	PubMed	Rosenberg et al (1985)[40]	Ann Emerg Med	Patient with urinary tract infection (n = 52)	An antibiotic study with trimethoprim-sulfamethoxazole (TMS). Non–pain-related study
24	PubMed	Schwenkreis et al (2003)[41]	Neurology	Patients with CRPS (n = 25) and healthy subjects (n = 20) as controls	Main assessment was intracortical motor cortex stimulations

Table 1B. Continued

	Data Base	Authors (Year)	Abbreviated Publication Name	Subject Population	Main Reasons of Exclusion
25	PubMed	Smania et al (2005)[42]	J Neurol	Patients with myofascial pain (n = 56)	A non-rTMS study
26	PubMed EMBASE	Svensson et al (2003)[43]	Eur J Pain	Healthy subjects with experimental pain	Non-neuropathic pain states
27	Cochrane	Tharyan et al (2005)	Cochrane Database of Systematic Reviews	Patients with schizophrenia	Non–pain-related review article
28	Cochrane	Van der Wurff et al (2003)	Cochrane Database of Systematic Reviews	Depressed elderly	Non–pain-related review article

3 studies (Andre-Obadia et al, Hirayama et al, and Khedr et al). The interaction of pain duration and treatment was not significant. None of these studies reported any major side effect such as seizures or any significant neurological deficits related to the rTMS interventions. The pretreatment VAS scores were only available from 3 studies (Hirayama et al, Lefaucheur et al, Khedr et al). The interaction of pretreatment VAS scores and treatment was not significant either including or excluding the Khedr et al study.

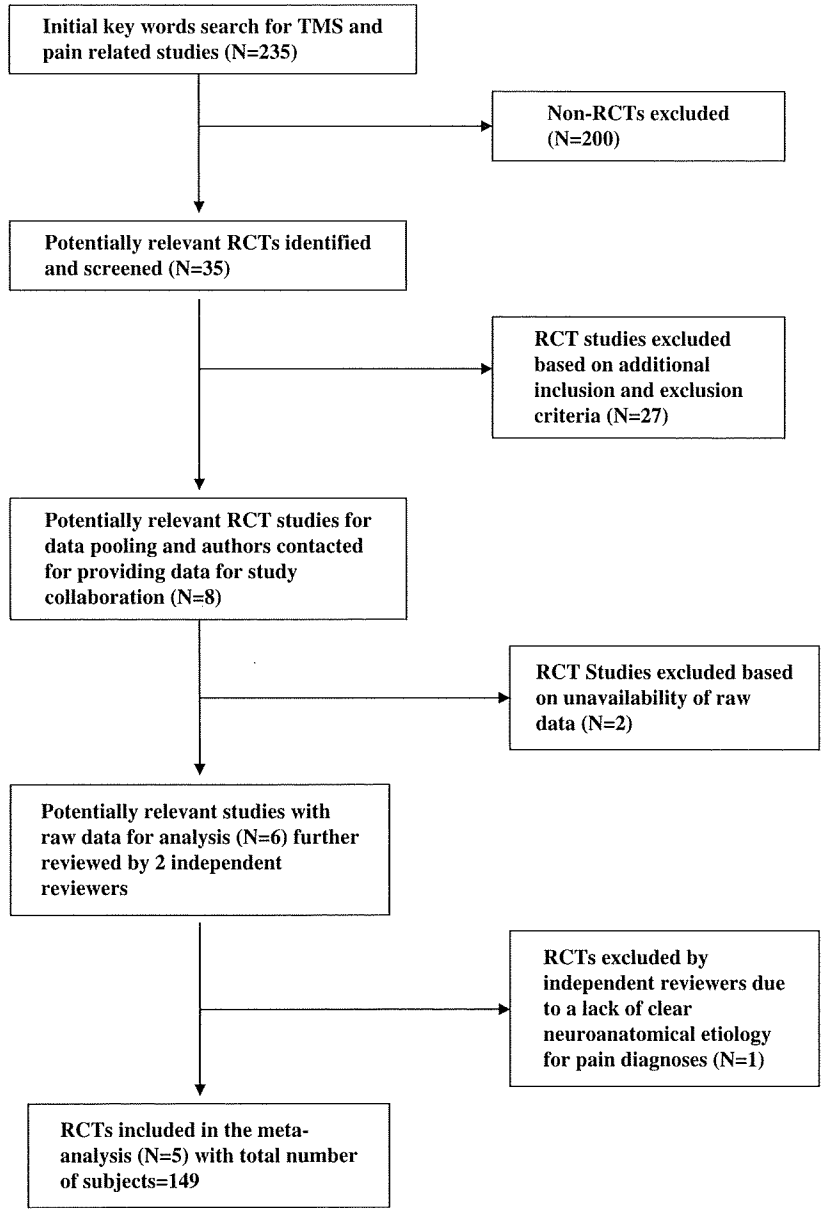

Figure 1. Search flow sheet. RCT, randomized controlled trials; TMS, transcranial magnetic stimulation.

Table 2. Summary of Studies and Gender Distribution

Gender	Female		Total
Khedr et al (2005)[22]	26	53.1%	49
Rollnik et al (2002)[24]	6	50.0%	12
Lefaucheur et al (2004)[19]	32	53.3%	60
Andre-Obadia et al (2006)[25]	4	33.3%	12
Hirayama et al (2006)[21]	7	43.8%	16
Total	75	50.3%	149

Neuroanatomical Origins of Pain and Treatment Effect

The effect of diagnosis (Fig 3) by treatment interaction was marginally significant (Wald test $P = .053$). We found the TGN subgroup (Fig 3) to have the greatest treatment effect (28.8% mean difference in VAS reduction), followed by PSP (16.7%), SC (14.7%), NR (10.0%), and PN (1.5%). In addition, the results were similar when we excluded the Khedr study, with the greatest treatment effect observed in TGN (33.0%), followed by SC (14.7%), PSP (10.5%), NR (10.0%), and PN (1.5%).

Treatment Parameters

Because of the statistical concern of colinearity, we performed the expected analyses for outcome related to treatment parameters by reducing the analytical approach to simple 2-sample *t* tests (low number of pulses vs high and low range frequency versus high) in which we pooled all experimental arms. The effects of the number of pulses (low: ≤1000 vs high) and frequency (low: >1 and ≤ 10 Hz vs high: >10 and <20 Hz) were sensitive to the inclusion of the Khedr et al study. When we excluded Khedr (a high-pulse, high-frequency study), low pulse ($P = .038$), and frequency in the range of ≤10 and >1 Hz ($P < .001$) are more efficacious compared with frequency above 10 Hz. However, including the Khedr et al study, more pulses given per session of treatment appeared to be more effective (2-sample *t* test, $P = .043$) and there was no significant difference between high frequency (>10 and ≤20 Hz) and low frequency (≤10 and >1 Hz). This paradox might be explained by the multiple (n = 5) therapy sessions being used by Khedr et al, whereas the other studies used single therapy session. Comparing the results of Khedr et al with the other studies, we found that the reduction in VAS with TMS compared with sham was 20.4% ($P = .003$) greater with 5 sessions compared with the single session studies. Of note, Rollnik's study used a nonfocal circular coil, whereas all the other 4 studies adopted a figure-of-8 coil. This difference in TMS coil design may attribute to the less robust effect reported in Rollnik's study as compared with the other studies included in the analysis.

Discussion

Statistical Concern

Previous reviews have provided the readers with useful qualitative overviews about the analgesic effect of rTMS and its potential usage in clinical pain management.[14,44-46] However, to the best knowledge of the authors, this is the first PID-based meta-analysis conducted to qualitatively assess the efficacy of rTMS in treating different neuropathic pain states related to their neuroanatomical origins. Although using summary statistics extracted from the literature is a common means to conduct a meta-analysis, PID is by far the preferred method for this type of analysis.[47,48] Stewart et al[47]suggest that PID should be used for meta-analysis whenever possible because this "provides the least biased and most reliable means of addressing questions that have not been satisfactorily resolved by individual clinical trials." Therefore, to address the clinically and mechanistically relevant issues being raised in the current study, a PID-based meta-analysis with the appropriate selection criteria serves as the most effective analytical approach for the task. Given that 1 of our main objectives was to specifically assess whether neuroanatomical origins of pain could affect rTMS analgesic effect, it was necessary for the analysis to strictly exclude studies in which neuroanatomical origins of pain were not clearly indicated. Despite these stringently designed selection criteria, 2 of the available articles that consisted of the highest number of subjects for RCTs in this field were included in the analysis.[19,22] Therefore, the analysis was equipped with the adequate statistical power to address the specific questions being raised, especially when we were able to obtain and combine individual raw data (n = 149) from studies containing the highest number of subjects.

Treatment Efficacy

The result of this PID-based meta-analysis indicates that rTMS can provide significant pain reduction in patients with various neuropathic pain conditions. The analysis also suggests that rTMS treatment may be

Table 3. Summary of Studies and Neuroanatomical Etiologies for Pain

	NR	PN	PSP	SC	TGN	Total
Khedr et al (2005)[22]	None	None	25 (51.0%)	None	24 (49.0%)	49
Rollnik et al (2002)[24]	3 (25.0%)	7 (58.3%)	None	2 (16.7%)	None	12
Lefaucheur et al (2004)[19]	12 (20.0%)	None	24 (40.0%)	12 (20.0%)	12 (20.0%)	60
Andre-Obadia et al (2006)[25]	1 (8.3%)	1 (8.3%)	9 (75.0%)	1 (8.3%)	None	12
Hirayama et al (2006)[21]	1 (6.2%)	1 (6.2%)	8 (50.0%)	3 (18.8%)	3 (18.8%)	16
Total	17 (11.4%)	9 (6.0%)	66 (44.3%)	18 (12.1%)	39 (26.2%)	149

Abbreviations: NR, nerve root; PN, peripheral nerve; PSP, post-stroke supraspinal related pain; TGN, trigeminal nerve or ganglion.

Table 4. Summary of Treatment Parameters

Study	Design	Pulses/Session	Coding for Pulses	Frequency	Coding for Frequency	Sessions	Coding for Sessions
Khedr et al (2005)[22]	Parallel	2000	High	20 Hz	High	5	Multiple
Rollnik et al (2002)[24]	Cross-over	800	Low	20 Hz	High	1	Single
Lefaucheur et al (2004)[19]	Cross-over	1000	Low	10 Hz	Low	1	Single
Andre-Obadia et al (2006)[25]	Cross-over	1600	High	20 Hz	High	1	Single
Hirayama et al (2006)[21]	Cross-over	500	Low	5 Hz	Low	1	Single

particularly effective in alleviating pain in patients with TGN-related pain. Since our estimate of treatment effect for TGN subjects both with and without the Khedr et al study was similar and consistently the highest among all coded pain origins (33.0% and 28.8%, respectively), we discerned that this observation was due to the fact that the Khedr et al study was the only study that used multiple treatment sessions and 61.5% of the TGN data were extracted from this study (49.0% of the subjects in Khedr et al study were TGN). Instead, we postulated that this observed analgesic effect was largely due to the neuroanatomical origins of pain and the underlying analgesic mechanisms of rTMS.

Neuroanatomical Origins of Pain and Treatment Outcome

Although statistically marginally significant, the overall trend of efficacy related to the pain origins as observed in the current analysis suggests that rTMS study may have a differential analgesic effect based on neuroanatomical origins of the neuropathic pain pathophysiology with more effective treatment response observed in neuropathic pain states originating from the "top" (supraspinal, cranial or spinal) than the "bottom" (nerve root or peripheral nerve) locations in the overall cranio-caudal neuroanatomical scheme. This observed differential trend is unlikely simply due to sample size or treatment session differences because overall there were more subjects with PSP (44.3%) than TGN (26.2%) related pain etiologies, and a similar differential effect was observed with or without the Khedr et al study, in which multiple treatment sessions were used. In addition, 1 of the important distinctions among the pain pathophysiology originating from the "top" locations is that subjects with pain related to PSP usually consist of lesions that may directly impact centrally mediated pain modulatory pathways, whereas in TGN-related neuropathic pain conditions, these pathways are usually uninterrupted. Therefore, this observed differential response pattern alludes to the underlying mechanisms of rTMS induced analgesic mechanisms further discussed in the "Potential Analgesic Mechanisms of rTMS" section of the report.

In addition, outside the scope of the current analysis are neuropathic pain states that may involve both peripheral and central nervous systems as in the case of complex regional pain syndrome (CRPS Type I). A single session of rTMS in patients with CRPS Type I has demonstrated significant short-term analgesic benefit with rTMS in comparison to sham.[23] Similarly, due to the absence of clearly defined neuroanatomically correlated etiology, not included in the analyses were also RCTs that have demonstrated the analgesic effect of rTMS for fibromyalgia and migraine headache.[28,29,39] Although some may consider these chronic pain conditions consist of a more centrally than peripherally originated pathophysiology, the exact neuroanatomical correlation and the underlying pain pathophysiology of these conditions have not been well defined in current literature. In addition, 2 of these studies also used stimulation sites other than the motor cortex.[28,29] Therefore, considering the objectives of the current analysis, to include these studies in the current analysis would undoubtedly cloud the interpretation of the analyzed result. With these concerns, these studies were reasonably excluded.

Table 5. Sham Conditions

Study	Sham Conditions
Khedr et al (2005)[22]	Coil elevated from the skull with a nonspecified angle
Rollnik et al (2002)[24]	Coil elevated with a 45° angle from the skull
Lefaucheur et al (2004)[19]	Placebo coil
Andre-Obadia et al (2006)[25]	Sham coil on top of active coil at a 90° angle
Hirayama et al (2006)[21]	Coil elevated with a 45° angle from the skull

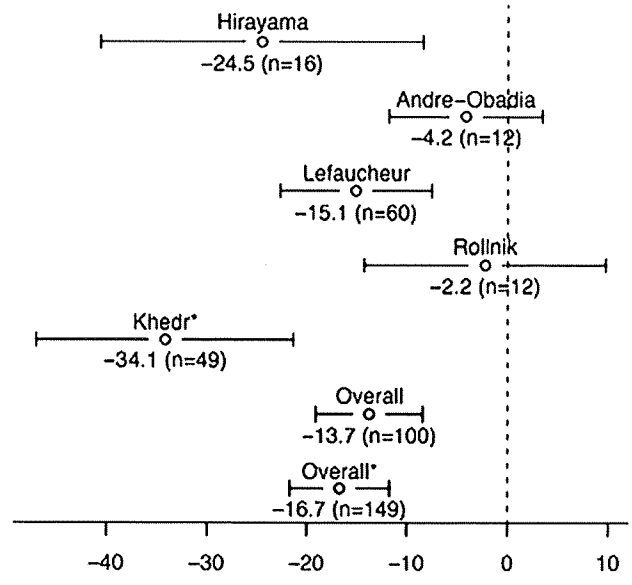

Figure 2. Treatment effect analysis. Mean difference (95% confidence interval) in percent of pain visual analog scale (VAS) score change. *$P < .05$.

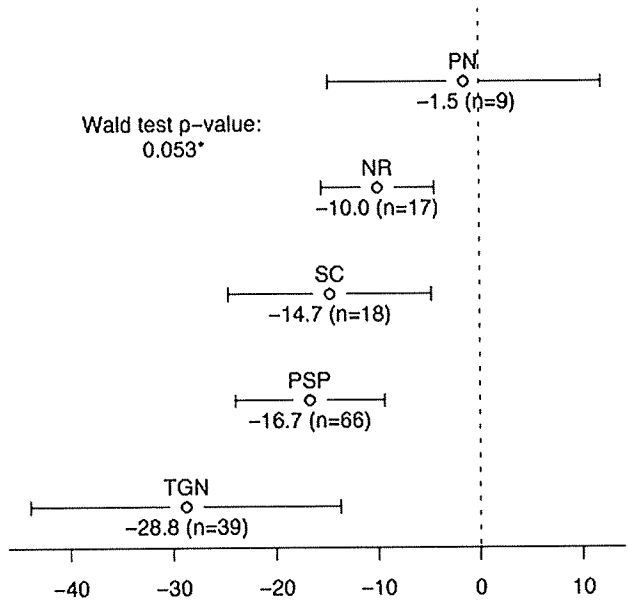

Figure 3. Diagnosis and treatment effect. Mean difference (95% confidence interval) in percent of pain visual analog scale (VAS) score change.*P value is from Wald test for the interaction effect of diagnosis and treatment on the percent decrease in VAS score. This P value increases to 0.140 when we exclude the Khedr study. NR, nerve root; PN, peripheral nerve; PSP, post-stroke supraspinal related pain; TGN, trigeminal nerve or ganglion.

Site of Treatment

To minimize confounding factors such as stimulation location difference in the analysis and considering most RCTs in pain with rTMS were conducted with motor cortex stimulation, we selectively included studies with motor cortex (M1) stimulation in the analysis. Of the excluded chronic pain RCTs, which used rTMS stimulation at locations other than the motor cortex, other selection criteria such as "no clear description of neuroanatomical origin of pain" also attributed to their exclusion (Table 1B).[26,28,29] Therefore it would not be feasible to include those studies in the site-related treatment effect analysis. Of note, the favorable analgesic effect of M1 in comparison to other cortical areas (premotor, primary somatosensory, and supplemental motor association cortex), except the prefrontal cortical areas, was nicely demonstrated by Hirayama et al[21] in a previous study. However, considering the small number of RCTS that used prefrontal cortical rTMS for pain and other aforementioned confounding factors, to further compare the analgesic effect of motor verses specific prefrontal cortical rTMS stimulations would be beyond the scope of the current analytical power.

Treatment Parameters

Previous studies with measurement of motor-evoked potentials have demonstrated that the effect of TMS in cortical excitability was frequency and intensity dependent. Traditionally, stimulation below or equal to 1 Hz is considered low frequency rTMS, which has been shown to decrease cortical excitability, whereas high frequency (>1 Hz) rTMS can increase cortical excitability.[49,50] There is evidence to suggest that treatment frequency above 1 Hz provides better analgesic effect than low frequency (≤1 Hz) for pain.[51] In the current analysis, all the studies (except 1 group from André-Obadia) used high stimulation frequency in the range of 5 to 20 Hz. When we assessed the treatment effect within the high frequency stimulation at either above (higher range) or below (lower range) 10 Hz with a single treatment session, we established that the treatment effect at the lower range were more effective in comparison to higher range frequency stimulation. However, adding the Khedr et al study with multiple sessions at 20 Hz, we found that stimulation given at the higher range to have a better analgesic effect as compared with the lower range frequency stimulation. This paradoxical observation suggests that the number of treatment sessions rendered may have a more profound impact on the overall analgesic effect than the treatment frequency itself. However, considering other variables involved in the analysis, further controlled studies are required to assess how these specific treatment parameters may differ in analgesic efficacy in specific neuropathic pain conditions.

Furthermore, as noticed in the result difference between Rollnik's study and other included studies, TMS coils such as the figure-of-8 coil that can deliver more focal stimulation may generate a more favorable clinical outcome in comparison to coils that deliver less focal stimulation. The importance of the coil design in regard to stimulation precision and the corresponding clinical outcome may be largely due to the fact that M1 consists of a clear somatopical boundary as demonstrated in previous studies with either noninvasive or invasive M1 stimulation.[7,52] Therefore, information derived from the current analysis can serve as a useful reference in considering coil selection and the choice of frequency, pulse, and number of session rendered per treatment protocol.

Potential Analgesic Mechanisms of rTMS

It is now well known that chronic pain states are associated with plastic changes in the nervous system and that the development of neuropathic pain states may involve functional changes in supraspinal components involved in pain perception.[53-75] Therefore, 1 of the hypothesized mechanisms for the observed analgesic effect of rTMS is that the noninvasive stimulation can induce plastic changes in the brain, which in turn corrects or modulates plastic changes associated with chronic pain. Initial evidence suggests that TMS affect central neurotransmitters activity in other neurological diseases.[76-78] However, how these TMS-related neurochemical changes may functionally affect supraspinal pain processing is largely unknown. Studies from direct motor cortex stimulation (MCS) suggest that motor cortex stimulation may result in direct inhibition of regions of brain involved in emotional response of pain and/or induce mechanisms that will trigger descending inhibitory pathway to act at the dorsal horn level. The former consists of brain region such as the anterior cingulate cortex (ACC), and the later consists of brain areas such as the brainstem periaqueductal grey matter (PAG).[79-85]

Other studies also indicate the possible role of endogenous opioid secretions triggered by long-term MCS.[86,87] Although whether similar analgesic mechanisms may occur with rTMS or not has yet to be defined, the observed neuroanatomically based differential order of clinical efficacy in the current analysis is in line with these hypothesized analgesic mechanisms of rTMS. The current analysis also suggests the importance of the proximity of pain origin to the central nervous system and the overall intactness of the pain modulatory pathways in affecting the potential analgesic effect of rTMS.

Study Limitations

Potential limitation of the analysis is unequal and unbalanced number of subjects per diagnosis with respect to the parameters of the treatment (eg, number of treatment sessions). In particular, this imbalance made it impossible to control for diagnosis while assessing the effect of the number of treatment session.

In short, this is the first PID-based meta-analysis that quantitatively and collectively demonstrates the overall treatment effect of rTMS in various neuropathic pain conditions. This analysis further suggests the effect of rTMS on neuropathic pain may consist of a differential "top-down" pattern based on the neuroanatomical origins of the neuropathic pain pathophysiology and the intactness of the intrinsic pain modulatory pathways. On the other hand, treatment parameters may also affect the outcome. A multiple session and/or low range, high frequency rTMS treatment protocol may generate better analgesic effect for neuropathic pain conditions compared to a single session protocol with higher frequency range stimulation. However, the authors cautioned that a definitive conclusion should and could not be solely derived from a single analysis. Further studies are required to thoroughly assess the effect of treatment parameters and/or duration on analgesia in patients with presumably centrally originated neuropathic pain. In addition, long-term cost analysis comparing rTMS with other pain management modalities should be conducted if repetitive/maintenance treatments are to be considered as a routine ongoing pain intervention option.

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難治性神経因性疼痛に対する反復経頭蓋磁気刺激療法（rTMS）

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Repetitive transcranial magnetic stimulation for intractable neuropathic pain

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Abstract: The aim of this retrospective study was to confirm the pain relief with repetitive transcranial magnetic stimulation (rTMS) in neuropathic pain. The subject was 86 patients with neuropathic pain who underwent 5Hz-rTMS of the primary motor cortex and evaluation of that efficacy with visual analogue scale (VAS). Among the 43 patients who underwent both real and sham rTMS, the pain reduction of real rTMS was greater than that of sham (mean reduction rates of VAS; 30.3%, 14.4%, p=0.0003), and 21 patients (48.8%) showed ≥30% pain reduction in VAS after real rTMS, while six patients (14.0%) after sham (p=0.0005). Regarding real rTMS in all 86 patients, the mean reduction rate in VAS was 23.3% and 28 patients (32.6%) showed ≥30% pain reduction in VAS. These results confirmed that 5Hz-rTMS of the primary motor cortex could provide pain relief in patients with neuropathic pain.

Keywords: **repetitive transcranial magnetic stimulation, neuropathic pain, fiber tracking**

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機能的脳神経外科 48(2009)4–5

はじめに

難治性神経因性疼痛に対する運動野電気刺激術（motor cortex stimulation; MCS）の経験をもとに，非侵襲的に神経系を刺激できる反復経頭蓋磁気刺激（repetitive transcranial magnetic stimulation; rTMS）が臨床に応用されるようになってきた。我々も対側一次運動野（M1）の刺激や5 Hz以上の高頻度刺激が，難治性神経因性疼痛に有効であることを報告してきた[2,5]。しかし，その治療報告症例はまだ世界的にも少なく，現時点では十分確立した治療法とは言えない。本研究では，過去の報告例も含め自験例全てを解析することで，難治性神経因性疼痛に対するrTMSの有効性とそれに影響を与える因子，ならびにMCSの除痛効果との関係を後方視的に検討した。

対象と方法

当科では2002年以降，111例の神経因性疼痛に対しrTMSを施行しており，そのうち5 HzでM1を刺激し疼痛スコアによる評価がなされた症例86例を解析対象とした。全例，発症後6ヵ月以上経過し，通常の薬物治療やブロックなどで十分な疼痛コントロールが得られなかった難治症例であった。原因病変は脳卒中48例，脊髄障害15例，切断肢（幻肢痛）7例，神経根引き抜き損傷7例，末梢神経障害6例，三叉神経障害3例であり，男性56例，女性30例，平均年齢57.4歳（28～78歳），疼痛発症後から治療までの平均期間66.3ヵ月（6～292ヵ月）であった。治療疼痛部位は顔面4例，上肢40例，体幹1例，下肢41例であった。

rTMSは以前に報告しているようにナビゲーションガイド下に，8の字コイル（MC B-70; Medtronic）とMagPro magnetic stimulator（Medtronic）で疼痛部位に相当するM1（疼痛側の対側中心前回）を反復刺激（5 Hz，計500回または1500回）した[2,5]。86例中，43例には本刺激のほかシャム刺激（偽刺激）も行われており，16例はrTMSの後，MCSを受けていた。最近の脳卒中後疼痛17例では，diffusion tensor imageを撮影しFiber tracking（FT）で病側の皮質脊髄路および視床皮質路の描出量を健側と比較した。rTMSの前後でvisual analogue scale（VAS）とマギル疼痛質問票（SF-MPQ）で疼痛を評価し，30%以上の低下を有効と判定した。VASの低下率と各患者背景，FTの描出量，MCSの除痛率との関係を解析した。疼痛スコアの低下率はmean±SEMで表記した。

結　果

本刺激とシャム刺激の両者が施行された43例では，除痛率（VASの低下率）は本刺激で30.3±3.9%，シャム刺激で14.4±3.5%であり，30%以上VASが低下した有効症例は本刺激で48.8%（21/43例），シャム刺激で14.0%（6/43例）であった。本刺激が除痛率，有効率ともに勝っていた（p=0.0003, p=0.0005）（Fig. 1）。

86例全例の平均除痛率はVASでは23.3±2.5%，SF-MPQでは33.1±3.5%であり，有効率はVASでは32.6%（28/86例），SF-MPQでは45.6%（26/57例）であった（Fig. 2）。FTを施行した症例においては，無効症例に比べ有効症例における病側の皮質脊髄路と視床皮質路の描出量が多く（p=0.02,

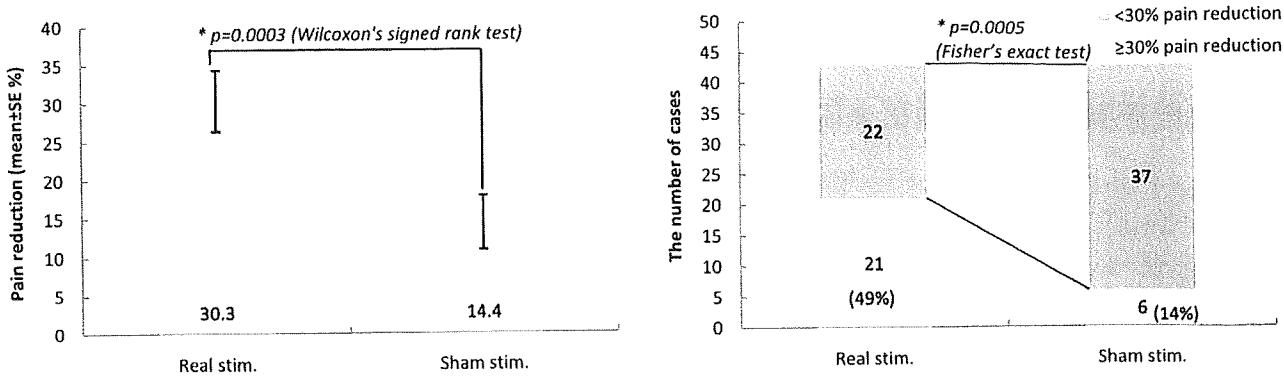

Fig. 1 Among the 43 patients who underwent both real and sham rTMS, the pain reduction of real rTMS was greater than that of sham (p=0.0003), and 21 patients showed ≥30% pain reduction in VAS after real rTMS, while six patients after sham (p=0.0005).

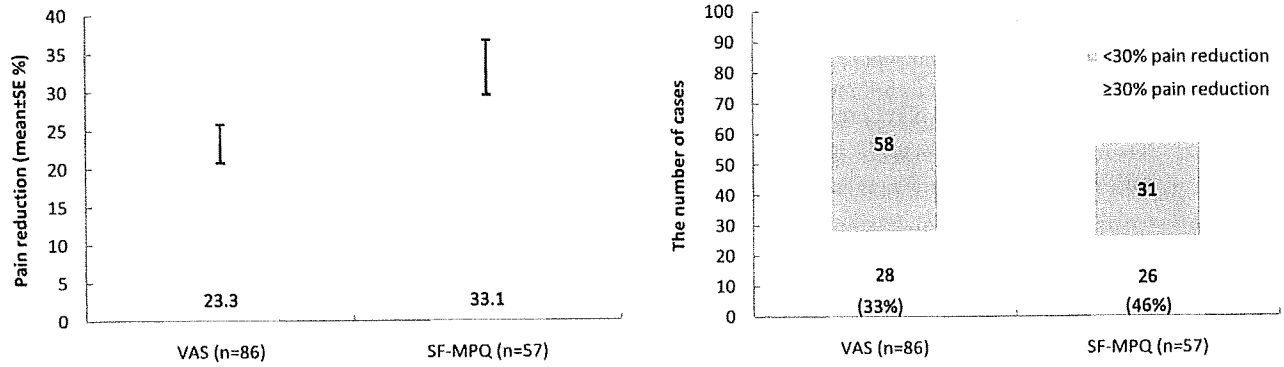

Fig. 2 Among all 86 patients who underwent real rTMS, the mean reduction rate in VAS was 23.3% and 28 patients showed ≥30% pain reduction in VAS.

p=0.005)，比較的保たれていた[1]。以前に報告しているように[3]，今回の16例の解析でも，rTMSの除痛率とMCSの短期の除痛率が相関していた（p=0.003)。疼痛側が左の患者で除痛率が高かったが（p=0.048)，その他の患者背景（年齢，性別，治療までの期間，疼痛の原因疾患など）で有意な除痛率の差や相関傾向は認めなかった。

86例全例で，てんかんなど重篤な副作用や永続的な副作用は認めなかった。

考　察

難治性神経因性疼痛に対する対側M1を刺激部位とした5Hz-rTMSは，シャム刺激より除痛率，有効率ともに勝っており，重篤な副作用も認められなかった。

神経因性疼痛に対する高頻度rTMS（刺激部位：M1，刺激頻度：5～20 Hz）の過去の報告は10編程度である。それらの報告症例の平均除痛率（VAS低下率）と平均有効率（VASが30%以上低下した症例の割合）は本研究の結果と似通っており26.5%，38.1%であった。報告によって結果に差があるが，刺激条件や原因疾患，評価方法の違いなどが影響しているものと思われる。連続5日rTMSを施行した研究では，有効率75%，除痛率45%と良好な結果で，通常1回の刺激では効果持続時間が数時間～数日であるのに対して，2週間以上効果が持続したと報告している[4]。

疼痛認知には多面的な要素があるため，単一の仮説だけで全てを説明できないが，rTMSの除痛機序として，rTMSが刺激部位の皮質興奮性を修飾し，それと同時にM1からの神経回路を通じて，脳内の情動に関与する部位や下行性抑制系など遠隔部に作用し，包括的に除痛が得られるといった機序が推察されている。我々のFTの結果から，rTMSによる除痛に白質下の神経回路が保たれていることが重要であることが示唆される。

結　論

rTMSは難治性神経因性疼痛に対する非侵襲的で副作用の少ない治療法になる可能性がある。皮質下の運動感覚線維が保たれていることが，rTMSの除痛効果に重要であることが示唆された。rTMSがMCSの適応決定の際の参考になると思われた。

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