Meta-Analysis

High Frequency Repetitive Transcranial Magnetic Stimulation Therapy For Chronic Neuropathic Pain: A Meta-analysis

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Background: Increasing evidence supports an analgesic effect of repetitive transcranial magnetic stimulation (rTMS) for neuropathic pain (NP). However, the optimal parameters of rTMS (stimulation frequency and treatment sessions) for achieving long-term analgesic effects remain unknown. This study analyzed the current findings in the literature.

Objective: The aim of this study was to assess the optimal parameters of rTMS for NP, including the rTMS sessions needed for inducing acute as well as long-term analgesic effects.

Study Design: A meta-analysis of the analgesic effect of high frequency rTMS (HF- rTMS) for neuropathic patients.

Setting: This meta-analysis examined all studies involving the analgesic efficacy of HF-rTMS for NP.

Methods: PubMed, Embase, and the Cochrane library were searched for clinical studies of rTMS treatment on NP published before December 31, 2014. Crude standardized mean differences (SMD) with 95% confidence interval (CI) were calculated for pain intensity after different treatment sessions (from 1 to 10) and follow-up of one or 2 months after rTMS treatment using random effect models.

Results: Twenty-five studies (including 32 trials and 589 patients) were selected for the meta-analysis according to the inclusion and exclusion criteria. All 3 HF-rTMS treatments (5, 10, and 20 Hz) produced pain reduction, while there were no differences between them, with the maximal pain reduction found after one and 5 sessions of rTMS treatment. Further, this significant analgesic effect remained forone month after 5 sessions of rTMS treatment.

Limitations: There are limitations of this meta-analysis. For example, the long-term analgesic effects of different HF-rTMS and low frequency (LF) rTMS sessions, including the single session of rTMS on different NP of varying origins have yet not been evaluated; the full degree of pain relief is still unclear for many rTMS studies.

Conclusions: HF-rTMS stimulation on primary motor cortex is effective in relieving pain in NP patients. Although 5 sessions of rTMS treatment produced a maximal analgesic effect and may be maintained for at least one month, further large-scale and well-controlled trials are needed to determine if this enhanced effect is specific to certain types of NP such as post-stroke related central NP.

Key words: High frequency, repetitive transcranial magnetic stimulation, neuropathic pain, single stimulation, multiple stimulation, meta-analysis

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Neuropathic pain (NP) is a localized sensation of unpleasant discomfort caused by damage or disease in the peripheral (peripheral neuropathic pain) and/or central (central neuropathic pain) nervous system that affects the somatosensory system (1). NP may include abnormal sensations (dysesthesia), and pain from normally non-painful stimuli (allodynia). It may resemble stabbings or electric shocks, burning or coldness, "pins and needles" sensations, numbness, and itching. The International Association for the Study of Pain (IASP) defined NP as follows: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (2). The annual incidence of NP has been reported to be 0.82% (3), and the prevalence of chronic NP has been reported as between 7 and 8% in the general population (4,5). Despite the IASP's recommendation of a 3-line drug treatment for NP (6), these drugs are often ineffective and high doses are required for achieving partial pain relief. In a recent meta-analysis of evidence-based pain studies, Finnerup et al (7) reported that only 30 – 50% of the patients responded to pharmacological treatment and only with 30 – 40% pain reduction (8).

The major characteristic of NP is neuronal over-excitability resulting from a combination of multiple factors that contribute to the diverse features of NP under various medical conditions (6). NP could arise from peripheral sensitization or abnormal central sensitization. After peripheral nerve lesion, aberrant regeneration may lead to abnormal neuronal excitability, and heightened sensitivity to various stimuli (9). The spinal cord dorsal horn neurons of the spinothalamic tract (STT) constitute the major ascending nociceptive pathway. As a consequence of ongoing spontaneous activity arising in the periphery, STT neurons develop increased background activity, enlarged receptive fields, and increased responses to afferent impulses, including normally innocuous tactile stimuli. Changes in impulse processing in the dorsal horns of the spinal cord, due to the release of neurotransmitters after the nerve damage or loss of the balance between the activities of the ascending excitatory systems and the descending inhibitory systems caused by various diseases in central nervous system has been supposed as the pathological mechanism of NP (10).

Because primary motor cortex stimulation (MCS) with surgically implanted epidural electrodes has been found to produce analgesic effects in about half of NP patients (11), and because a non-invasive coil-generated pulsating magnetic field near the cortex could induce electric currents to modulate nerve cell activity in focal brain areas (12), it was proposed that repetitive transcranial magnetic stimulation (rTMS) could be a safe method to modulate cortical excitability and pain threshold (13,14).

As summarized in recent reviews, high frequency rTMS (HF-rTMS) applied over the primary motor cortex (M1) could alleviate NP of various origins, such as spinal cord injury (SCI), post-stroke, amputation, and brachial avulsion pain (15-17). In a randomized, double-blind, sham-controlled crossover multi-center study, Hosomi et al (18) showed that HF-rTMS (5Hz) on M1 caused modest pain reduction in people with NP. However, the optimal number of rTMS sessions and the duration of rTMS-induced analgesic effect have not been reported.

Previous meta-analyses of NP mainly focused on the neuroanatomical origins or the chronic nature of NP (16,17). The aim of this study was to assess the optimal parameters of rTMS for NP, including the rTMS sessions needed for inducing acute as well as long-term analgesic effects. Only HF-rTMS (> 1Hz) studies were included due to the data availability.

Methods

Literature Search

A systematic search of the literature was performed to identify the relevant clinical studies. PubMed, Embase, and the Cochrane Library were searched up to 31 December, 2014. Search terms were selected to link NP and rTMS. Keywords were ("repetitive transcranial magnetic stimulation" or "rTMS" or "TMS") and ("pain" or "neuropathic pain").

Study Selection

The selected studies, based on their title and abstract, had to meet the following criteria:

1. Types of studies: randomized sham-controlled or self-controlled trials; double-blind or single-blind; parallel or cross-over study designs;
2. ≥ 5 patients in a trial;
3. Characteristics of NP patients: all patients must be 18 years of age or older, and clearly diagnosed according to the criteria for NP by the IASP (6,19). If an etiological factor is known, it should be included, e.g., diabetic neuropathic pain, post-herpetic neuropathic pain, central post-stroke pain, or neuropathic pain following SCI. In addition, other types of pain should be taken into account as long as NP was reported as the most disturbing pain (20);

4. Types of intervention: HF-rTMS (> 1Hz) over the M1 by single or multiple rTMS stimulation.
5. Publication limit: articles were human studies and written in English;
6. Types of outcome: Pain level was self-scored by the patient assessed on a 0 – 10 visual analog scale (VAS) or 0 – 10 numerical rating scale (NRS) after each session. The VAS consists of a 15 cm plastic ruler with a slider in the middle, with values from 0 to 10. The 2 sides represented "no pain sensation" (0 on the VAS scale) and "the most intense pain" (10 on the VAS scale) (21). The NRS was used digitally from 0 to 10 to represent pain intensity. The endpoints were set as "no pain sensation" (0 on the NRS) and "the most intense pain sensation imaginable" (10 on the NRS) (22). The analgesic effects of rTMS were estimated by comparing the pain scores obtained before and after the intervention, or by comparing the experimental group with the sham group using VAS or NRS scores, whenever applicable;
7. The article must contain the original data (VAS or NRS score), or data could be extracted and calculated based on the existing materials.

Exclusion criteria:

1. Articles did not meet the above criteria;
2. Studies did not provide pre-treatment score, and/or the score of sham group for NP;
3. The outcomes were not described as a mean ± standard deviation (SD) or mean ± standard errors of the mean (SEM), but as median or inter-quartile range.

Trial Quality Appraisal

Two reviewers independently assessed the methodological qualities of the included studies based on a modified checklist from Moher et al (23) that offered the evaluation criteria as shown in Table 1. If there was a disagreement, a third researcher re-assessed the article and discussed it with the 2 reviewers to reach an agreement. If the patients were randomly allocated, it was recorded as 1. In scoring blinding, 0 represented a non-blind or no-mention in the article, and 1 and 2 represented single-blind and double-blind, respectively. Dropouts were recorded as the numbers of patients who had withdrawn before the end of the study. Descriptions of baseline demographic data were recorded as 1 if described. The numbers and types of adverse effects were recorded.

Table 1. *Quality of the included studies.*

	Study	①	②	③	④	⑤	⑥
1	Ahmed 2011	1	0	0	1	1	0
2	André-Obadia 2006	1	2	2	1	1	0
3	André-Obadia 2008	1	2	2	1	1	0
4	André-Obadia 2011	1	1	0	1	1	0
5	Defrin 2007	1	2	0	1	1	0
6	Goto 2008	0	0	0	1	1	0
7	Hirayama 2006	1	1	0	1	1	0
8	Hosomi 2013[1]	0	0	0	1	1	0
9	Hosomi 2013[2]	1	2	3	1	1	12
10	Jetté 2013	1	2	2	1	1	0
11	Kang 2009	1	2	0	1	1	0
12	Khedr 2005	1	0	0	1	1	0
13	Khedr 2014	1	1	0	1	1	0
14	Lefaucheur 20011	1	1	0	1	1	0
15	Lefaucheur 20012	1	2	0	1	1	0
16	Lefaucheur 2006	1	1	0	1	1	0
17	Lefaucheur 2008	1	2	0	1	1	0
18	Lefaucheur 2012	0	0	0	1	1	0
19	Matsumura 2013	1	0	0	1	1	0
20	Ohn 2012	0	0	0	1	1	0
21	Onesti 2013	1	2	2	1	1	0
22	Picarelli 2010	1	2	1	1	1	23
23	Pleger 2004	0	0	0	1	1	0
24	Rollink 2002	1	0	0	1	1	0
25	Saitoh 2007	1	0	0	1	1	0

① random allocation, ② blinding procedure, ③dropout number, ④description of baseline demographic data,⑤ control study, ⑥ description of adverse events.

Data Extraction

A standard form was jointly designed by both evaluators to collect basic information, which contains the following:

1. Patient characteristics: age (mean ± SD), gender, number of participants, primary diagnosis (resulting in NP), and pain type;
2. Study design;
3. The parameters of rTMS: stimulation site, frequency, intensity (including the total pulses), and stimulation sessions (days);
4. Outcome measurement:
    1. Mean and SD of post-stimulation pain score for both the rTMS treatment group and sham group.
    2. If the study did not have a sham group, the pre-intervention data were used.
    3. If the VAS was on a 0 – 100 scale, it was also allowable.
    4. If the outcome was expressed only as a graph, the software GetData Graph Digitizer 2.25 (http://getdata-graph-digitizer.com/) was used to extract the required data.
    5. If the pain reduction was described as the rate relative to pre-intervention baseline of 100% or as the reduced rate, the following equations were used to calculate the post-intervention VAS score:
        a). VAS% = Post-treatment Pain Score / Pre-treatment Pain Score × 100%;
        b). VAS reduction rate (%) = (Post-treatment Pain Score - Pre-treatment Pain Score) / Pre-treatment Pain Score × 100%.

Data Synthesis and Analysis

To evaluate the optimal number of rTMS sessions required for achieving significant pain reduction, the pain scores were extracted at the end of each of the following rTMS treatments: from the first session (one day session or one session) to the tenth session (10 day sessions). To evaluate long-term analgesic effects of rTMS, the follow-up observation was conducted at one and 2 months post rTMS treatment.

Meta-analysis was performed by using a Review Manager Software version 5.2 (Cochrane Collaboration, Oxford, England). The total analgesic effect-size of rTMS treatment, expressed by the standardized mean difference (SMD) with a 95% confidence interval (95% CI), was computed. The heterogeneity was tested using Q-statistics and the I2 index (24). If the I2 index was greater than 50%, the random effect model was used for the analysis. Otherwise a fixed model was used. Finally, a funnel plot was constructed to test potential publication bias. A *P* value deemed statistically significant was set at less than 0.05.

Results

Literature Search

Of the total 470 studies found after the initial search, 25 studies were identified (N = 589) by 2 independent reviewers according to the inclusion and exclusion standards (18,25-48). The flow diagram of the selection process is shown in Fig. 1.

Of the 25 studies selected for this meta-analysis, 5 studies were self-controlled (30,32,40,42,45), 6 studies were parallel sham controlled (25,29,35,36,38,44), and 14 studies were crossover sham controlled (18,26-28,31,33,34,37,39,41,43,46-48), respectively. The duration time of NP ranged from 3 months to 122.4 months. The frequencies of rTMS applied were 5Hz, 10Hz, and 20Hz. The stimulation site was the M1 corresponding to a painful region or contralateral to the painful site. For 18 studies, the pain scores of the experimental group were directly compared with those of the sham control group (18,25-29,33-39,43,44,46-48). The other studies compared the pain scores obtained before and after rTMS intervention (30-32,40-42,45).

Thirteen studies involved the use of indirect outcome measures; the data were further extracted using the software of GetData (18,25,29,31,35-38,40,41,44,47,48). The relative data of 6 studies was calculated using the formula described in the above methodology: a). VAS% = Post-treatment Pain score / Pre-treatment Pain Score × 100%; b). VAS reduction rate (%) = (Post-treatment Pain Score - Pre-treatment Pain Score) / Pre-treatment Pain Score × 100% (26-28,30,32,33). The data of the remaining studies were directly extracted from the articles (34,39,42,43,45).

The duration of the rTMS treatment included 10 different sessions: one session (18,25-28,30-33,35-41,44-48), 2 sessions (18,37,44), 3 sessions (18,34,37,44), 4 sessions (18,35,37,44), 5 sessions (18,25,34-37,42-44), 6 sessions (18,37,44), 7 sessions (18,37,44), 8 sessions (18,37,44), 9 sessions (18,37,44), and 10 sessions (18,29,36,37,44). The follow-up analgesic effects were observed at one month (25,34-36,43,44), and 2 months (25,34) after the end of 5 repeated rTMS sessions, respectively. The main characteristic of the included studies is listed in Table 2.

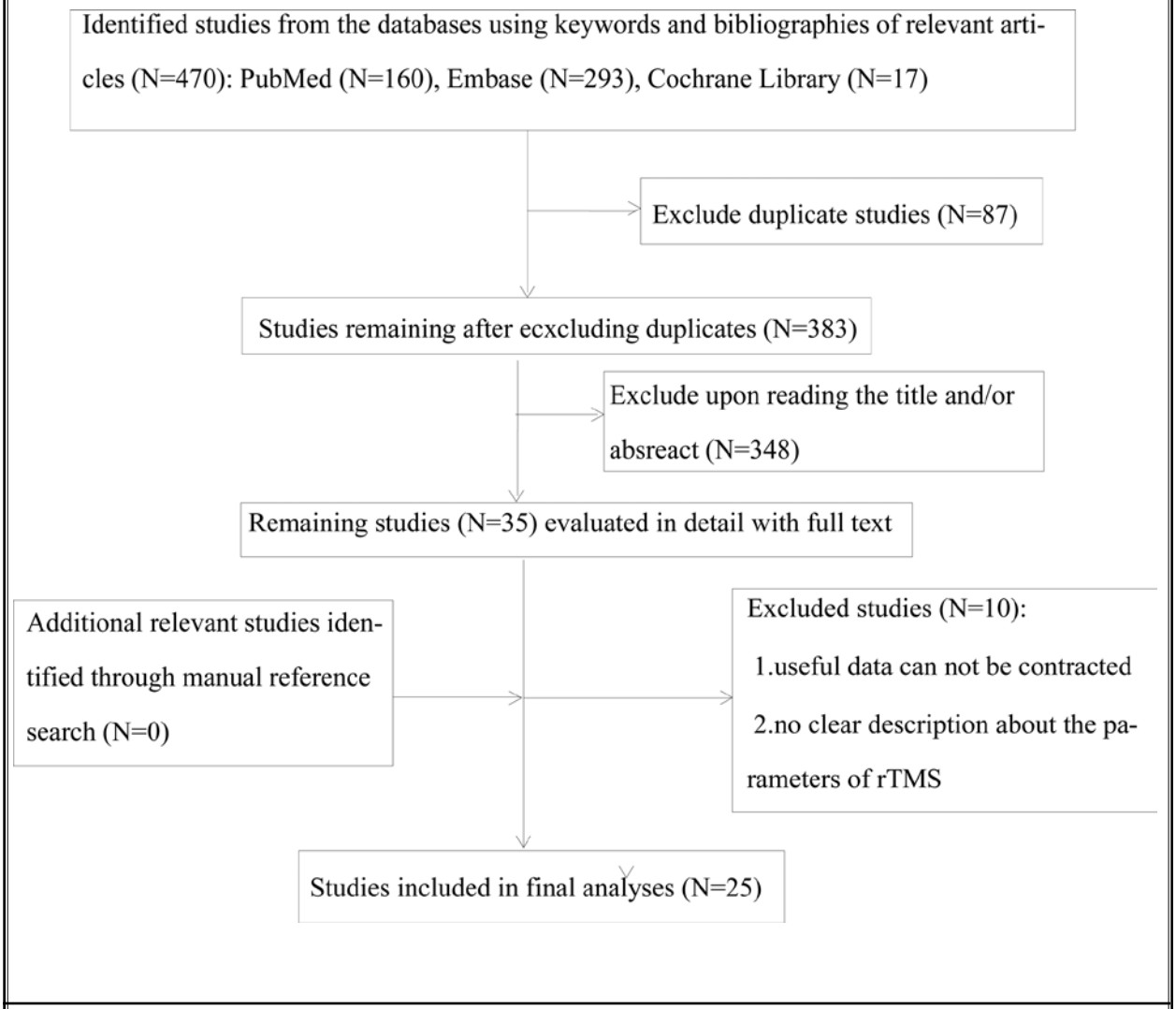

Fig. 1. *Flow diagram of literature search.*

Quality Appraisal

The results of quality appraisal are shown in Table 1. Apart from the self-controlled studies (30,32,40-42,45), randomized allocation of the patients was applied in all other trials. Most of these studies were also double-blind or single-blind. Six studies described the dropout rate (18,26,27,33,43,44). All studies contained the demographic data and were controlled. Two studies (18,44) mentioned the adverse events, such as headache, dizziness, anxiety, etc. However, no study reported serious adverse events related to rTMS treatment.

Meta-analysis

Primary Outcome

A total of 32 trials from 25 articles were extracted. This meta-analysis of the pooled analgesic outcome data showed a statistically significant effect size of -0.86 (95% CI, -1.15 to -0.56; $P < 0.05$), suggesting that rTMS was effective in reducing the pain intensity of NP of varying origins as shown in the forest plot of this analysis (Fig. 2). As the associated funnel plot was symmetrical, no publication bias was assumed. However,

Table 2. *Characteristics of the included studies.*

	Study	Mean Age (Year)	Mean Continue Time of NP (Month)	N(E/C)	Study Design	Coil/ Stimulation Site	Parameters and Dosage	Outcome measure
1	Ahmed 2011	52.7	33.4	27(17/10)	Parallel sham control	Figure8/M1	20Hz, 80%RMT, 200 pulses × 10 train/ session, five sessions days, ITI = 50s	VAS
2	André-Obadia 2006	53	82.8	12(12/12)	Cross-over sham control	Figure8/M1&	20Hz, 90 %RMT, 80 pulses × 20 trains, ITI = 84s	VAS
3	André-Obadia 2008	54.2	60	28(28/28)	Cross-over sham control	Figure8/M1&	20Hz, 90% RMT, 80 pulses × 20 trains, ITI = 84s	NRS
4	André-Obadia 2011	55	>6	45(45/45)	Cross-over sham control	Figure8/M1&	20Hz, 90% RMT, 80 pulses × 20 trains, ITI = 84s	NRS
5	Defrin 2007	52.0	12	11(6/5)	Parallel sham control	Figure8/M1&	5Hz, 115% RMT, 500 pulses × 1train/session, 10 sessions days	VAS
6	Goto 2008	63.1	61.2	17(17/17)	Self control	Figure8/M1&	5Hz, 90% RMT, 50 pulses × 10 trains, ITI = 50s	NRS
7	Hirayama 2006	56.8	76.8	20(20/20)	Cross-over sham control	Figure8/M1&	5Hz, 90% RMT, 50 pulses × 10 trains, ITI = 50s	VAS
8	Hosomi 2013[2]a	61.2	56.4	29(29/29)	Cross-over sham control	Figure 8/M1	5Hz, 90% RMT, 50 pulses × 10 trains/session, 10 sessions days. ITI = 50s,	VAS
	Hosomi 2013[2]b	60.1	59.5	35(35/35)	Cross-over sham control	Figure 8/M1	5Hz, 90% RMT, 50 pulses × 10 trains/session, 10 sessions days, ITI = 50s,	VAS
9	Hosomi 2013[1]	59.6	48.1	21(21/21)	Self control	Figure 8/M1	5Hz, 90% RMT, 50 pulses × 10 trains/session, ITI = 50s	VAS
10	Jetté 2013a	50	93.6	16(16/16)	Cross-over sham control(arm)	Figure8/M1*	10 Hz, 90% RMT, 50 pulses × 40 trains/session, ITI = 25s	NRS
	Jetté 2013b	50	93.6	16(16/16)	Cross-over sham control(leg)	Figure8/M1*	10Hz, 110% RMT, 50 pulses × 40 trains/session, ITI = 25s	NRS
11	Kang 2009	54.8	60.5	11(11/11)	Cross-over sham control	Figure8/M1#	10Hz, 80% RMT, 50 pulses × 20 trains/session, 5 sessions days, ITI = 55s	NRS
12	Khedr 2005a	51.5	36	24(14,10)	Parallel sham control(TGN)	Figure 8/M1	20Hz, 80% RMT, 200 pulses × 1 train/session, 5 sessions days	VAS
	Khedr 2005b	52.3	18	24(14,10)	Parallel sham control(PSP)	Figure 8/M1	20Hz, 80% RMT, 200 pulses × 1 train/session, 5 sessions days	VAS
13	Khedr 2014	47.5	16.1	30(15/15)	Parallel sham control	Figure 8/M1	20Hz, 80% RMT, 200 pulses × 10 trains/session, ten session days, ITI = 30s	VAS
14	Lefaucheur 2001[1]	57.2	…	14(14/14)	Cross-over sham control	Figure 8/M1	10Hz, 80% RMT, 50 pulses × 20 trains/session, 12 sessions days, ITI = 55s	VAS
15	Lefaucheur 2001[2]	54.7	…	18(18/18)	Cross-over sham control	Figure 8/M1	10Hz, 80% RMT, 50 pulses × 20 trains/session, ITI = 55s	VAS

Table 2 (cont.). *Characteristics of the included studies.*

	Study	Mean Age (Year)	Mean Continue Time of NP (Month)	N(E/C)	Study Design	Coil/ Stimulation Site	Parameters and Dosage	Outcome measure
16	Lefaucheur 2006	55.5	64.8	44(22/22)	Parallel sham control	Figure 8/M1	10Hz, 90%RMT, 60 pulses × 20 trains/session, ITI = 54s	VAS
17	Lefaucheur 2008	54.2	>12	46(46/46)	Cross-over sham control	Figure 8/M1	10Hz, 90%RMT, 60 pulses × 20 trains/session, ITI = 54s	VAS
18	Lefaucheur 2012a	53.8	49.2	14(14/14)	Self control-rTMS	Figure8/M1*	10Hz, 90% AMT, 100 pulses × 20 trains/session, ITI = 30s	VAS
	Lefaucheur 2012b	53.8	49.2	14(14/14)	Self control-iTBS-rTMS	Figure8/M1*	10Hz, 90% AMT, 100 pulses × 20trains/session, ITI = 30s	VAS
	Lefaucheur 2012c	53.8	49.2	14(14/14)	Self control-cTBS-rTMS	Figure8/M1*	10Hz, 90% AMT, 100 pulses × 20trains/session, ITI = 30s	VAS
19	Matsumura 2013	63.6	>3	20(20/20)	Cross-over sham control	Figure 8/M1	5 Hz, 100% RMT, 50 pulses × 10 trains/session, ITI = 25s	VAS
20	Ohn 2012	50.9	21.9	14(14/14)	Self control	Figure 8/M1	10Hz, 90% RMT, 50 pulses × 20 trains/session, 5sessions days, ITI = 55s	VAS
21	Onesti 2013a	70.6	…	11(11/11)	Cross-over sham control	Figure H/M1	20Hz, 100% RMT, 50 pulses × 30 trains/session, 5 sessions days, ITI = 30s	VAS
	Onesti 2013b	70.6	…	12(12/12)	Cross-over sham control	Figure H/M1	20Hz, 100% RMT, 50 pulses × 30 trains/session, 5 sessions days, ITI = 30s	VAS
22	Picarelli 2010	42.1	80.1	22(11,11)	Parallel sham control	Figure 8/M1	10 Hz, 100%RMT, 100 pulses × 25 trains/session, 10 sessions days, ITI = 58 s.	VAS
23	Pleger 2004	51.0	35.0	10(10/10)	Self control	Figure8/M1*	10 Hz, 110%RMT, 12 pulses × 10 trains/session, ITI = 10 s.	VAS
24	Rollink 2002	51.3	32.4	12(12/12)	Cross-over sham sequence-control	Figure8/M1*	20 Hz, 80%RMT, 40 pulses × 20 trains/session, ITI = 58s	VAS
25	Saitoh 2007a	59.4	122.4	13(13/13)	Cross-over sham control	Figure 8/M1	5Hz, 90% RMT, 50 pulses × 10 trains/session, ITI = 50s	VAS
	Saitoh 2007b	59.4	122.4	13(13/13)	Cross-over sham control	Figure 8/M1	10Hz, 90%RMT,100 pulses × 5 trains/session, ITI = 50s	VAS

M1: Primary motor cortex corresponding to a painful region; M1*: Primary motor cortex contralateral to the painful site or to the dominant-hand site; M1#: the right primary motor cortex; M1&: no mention the specific site of coil; Figure 8: figure-of-8 coil; Figure H: figure-of-H coil; N: no. of patients; E: experimental group; C: control group; RMT: the resting motor threshold; AMT: the active motor threshold; ITI: inter-train interval; VAS: visual analgesic scale; NRS: numerical rating scales; VAS (%) = Post-treatment Pain Score / Pre-treatment Pain Score; VAS reduction rate (%) = (Post-treatment Pain Score - Pre-treatment Pain Score) / Pre-treatment Pain Score; …: no available data could be extracted from that article.

because of the substantial heterogeneity (I2 = 81%), further subgroup analysis, stratified by rTMS stimulation frequency, the number of treatment sessions, and the follow-up observation were conducted.

Stratified analysis by rTMS stimulation frequency (5Hz, 10Hz, and 20Hz) did not reduce the heterogeneity, suggesting similar efficacy of pain reduction induced by these HF-rTMS treatments (Fig. 3).

Fig. 4 shows that one session of rTMS treatment was significantly effective in reducing the pain intensity of NP (the pooled SMD = -0.94 [95%CI, -1.28 to -0.61; $P < 0.001$]). After excluding the single rTMS data in Fig. 4, the effective size of one session of rTMS treatment was 0.54, 95% CI -1.01 to -0.08, $P < 0.01$. The relative symmetrical funnel plot suggested little publication bias. Increasing the treatment session from 2 to 10 also

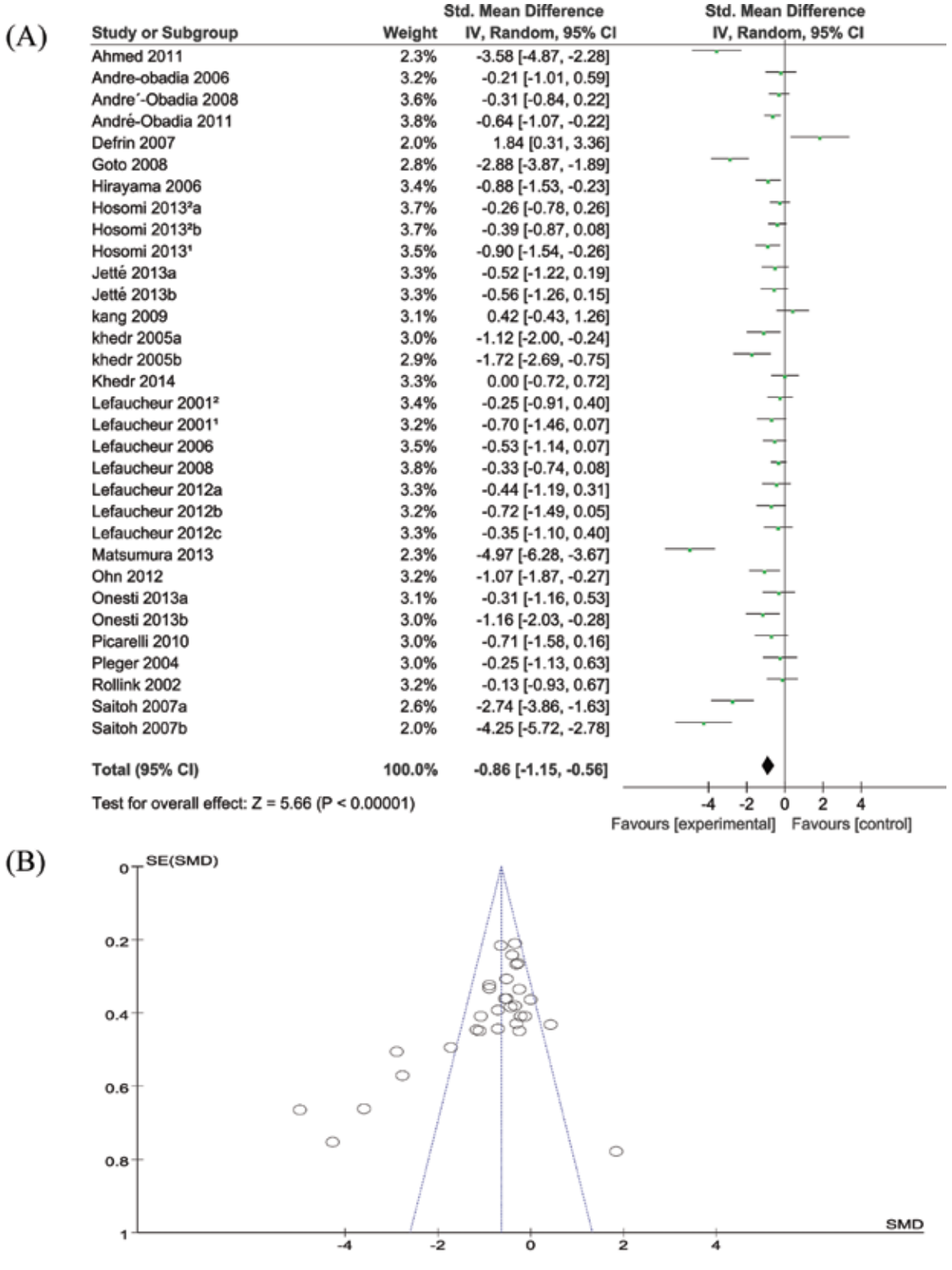

Fig. 2. *The forest plot and funnel plot of an overall analgesic effect size of rTMS for NP of various orgins.*

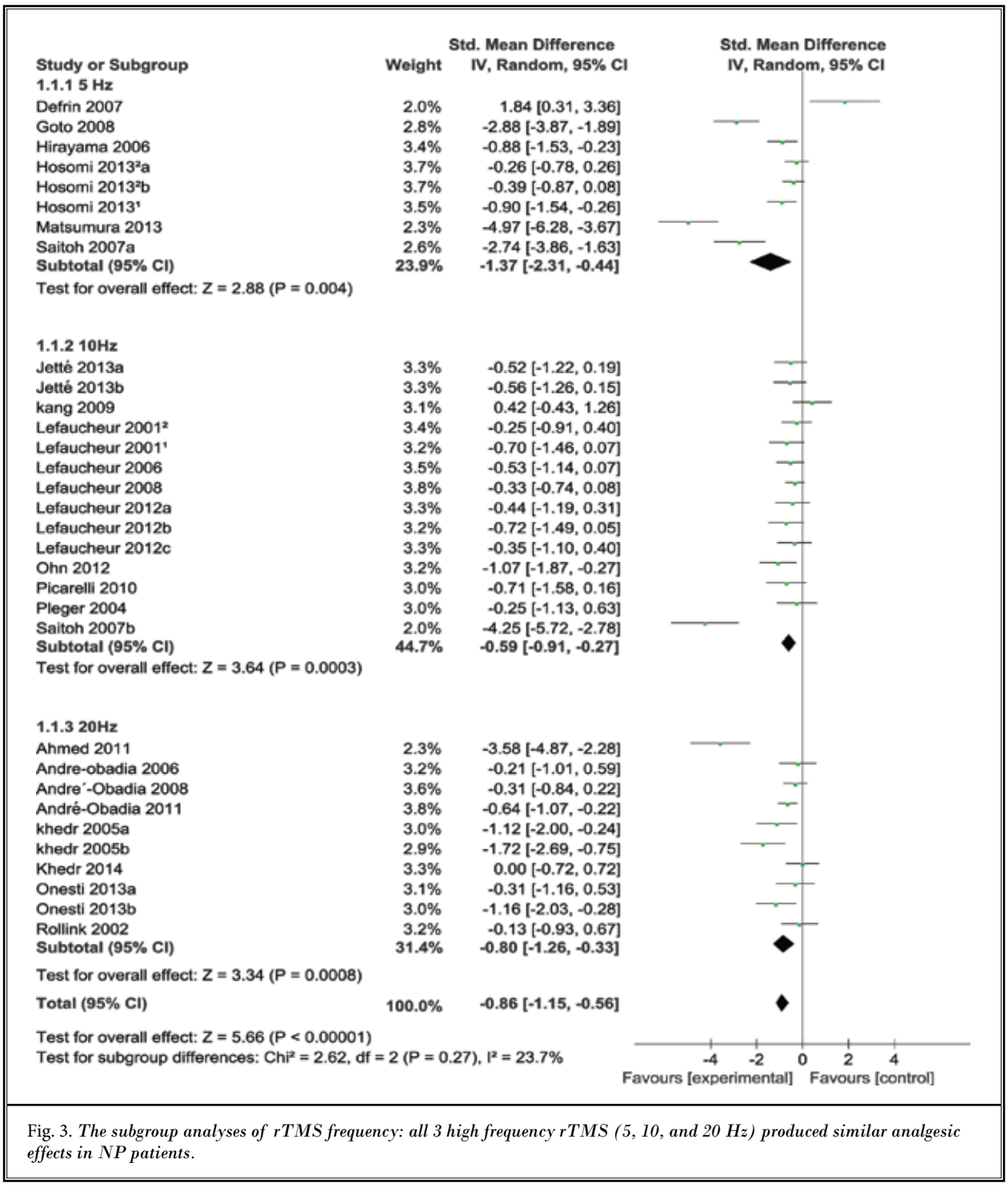

Fig. 3. *The subgroup analyses of rTMS frequency: all 3 high frequency rTMS (5, 10, and 20 Hz) produced similar analgesic effects in NP patients.*

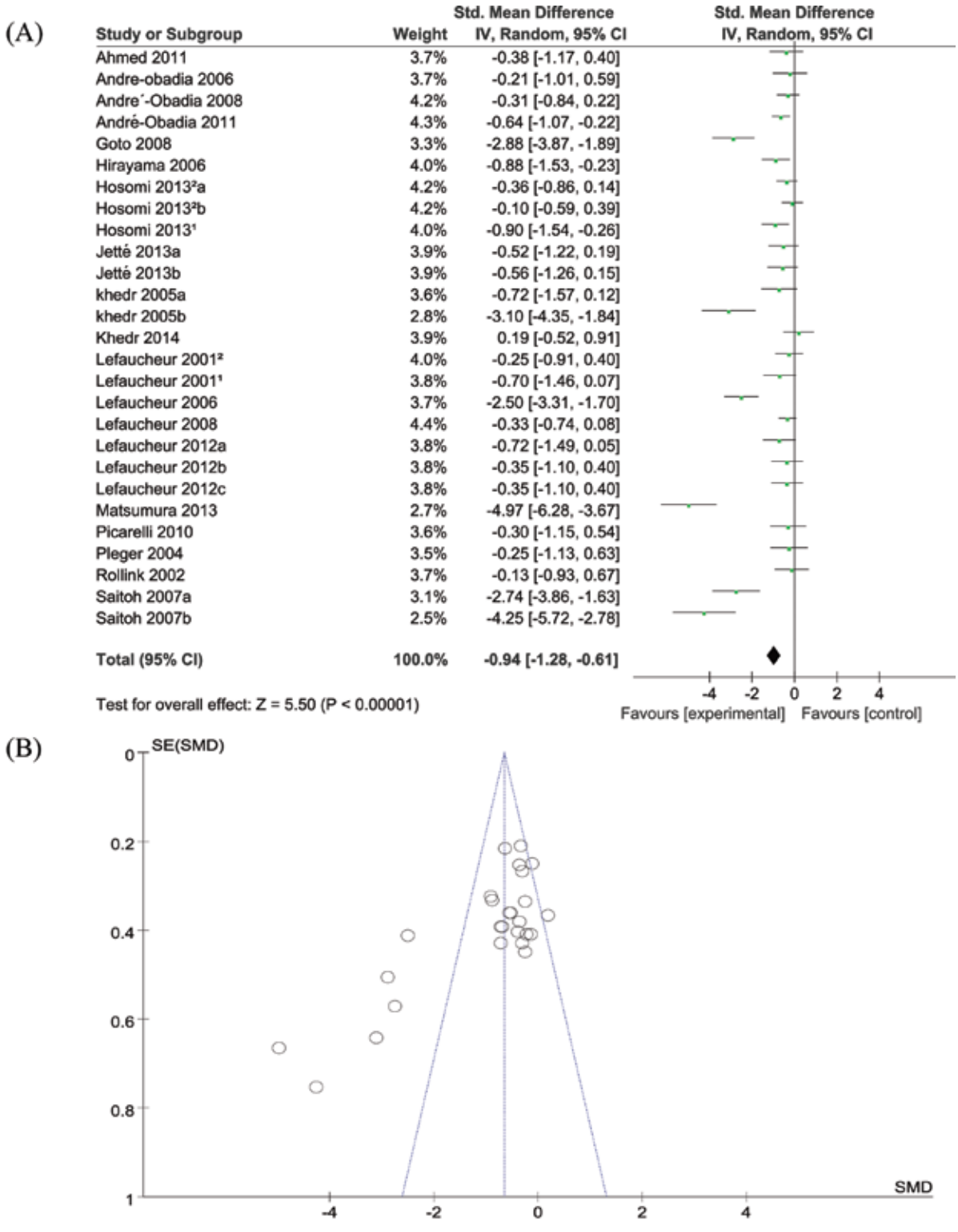

Fig. 4. *Forest plot and funnel plot following one session of HF-rTMS treatment.*

produced significant pain reduction (Figs. 5A-C, 6A-B, 7A-D), with the average maximal pain reduction found after 5 sessions of rTMS treatment (SMD = -1.22, 95%CI, -1.87 to -0.57; $P < 0.001$) (Fig. 6A).

Secondary Outcome

To better evaluate the long-term analgesic effect of rTMS, the data were extracted from studies containing 5 sessions of treatment. Five studies (25,34,35,43,44) with follow-up data at one month after rTMS, 2 studies with 2 months data (25, 34), and one study with 3 months data (44) were included for analysis. The pooled analgesic effect was significant at one month after rTMS (SMD = -0.96, 95%CI, -1.55 to -0.37, $P < 0.05$),

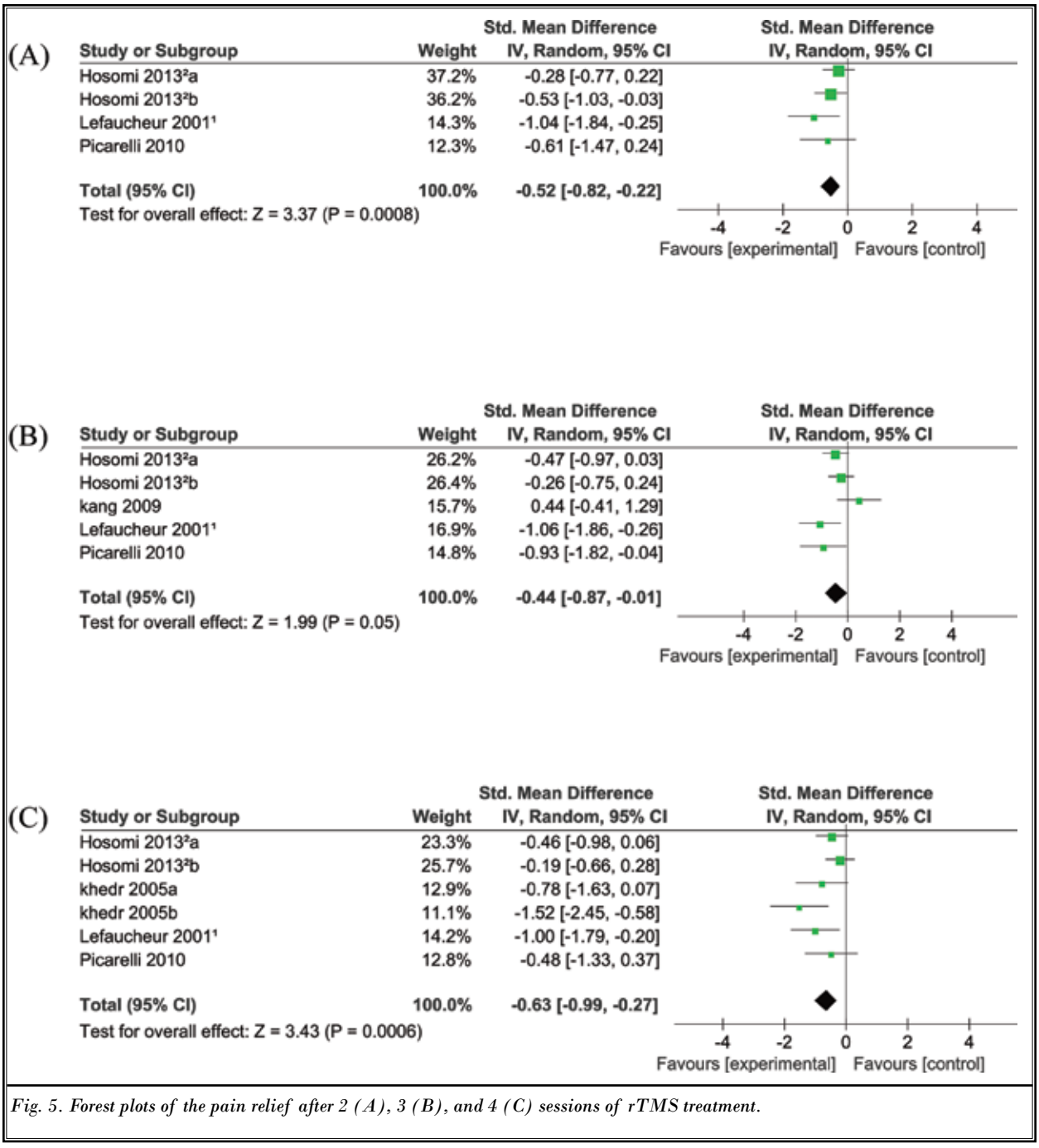

Fig. 5. Forest plots of the pain relief after 2 (A), 3 (B), and 4 (C) sessions of rTMS treatment.

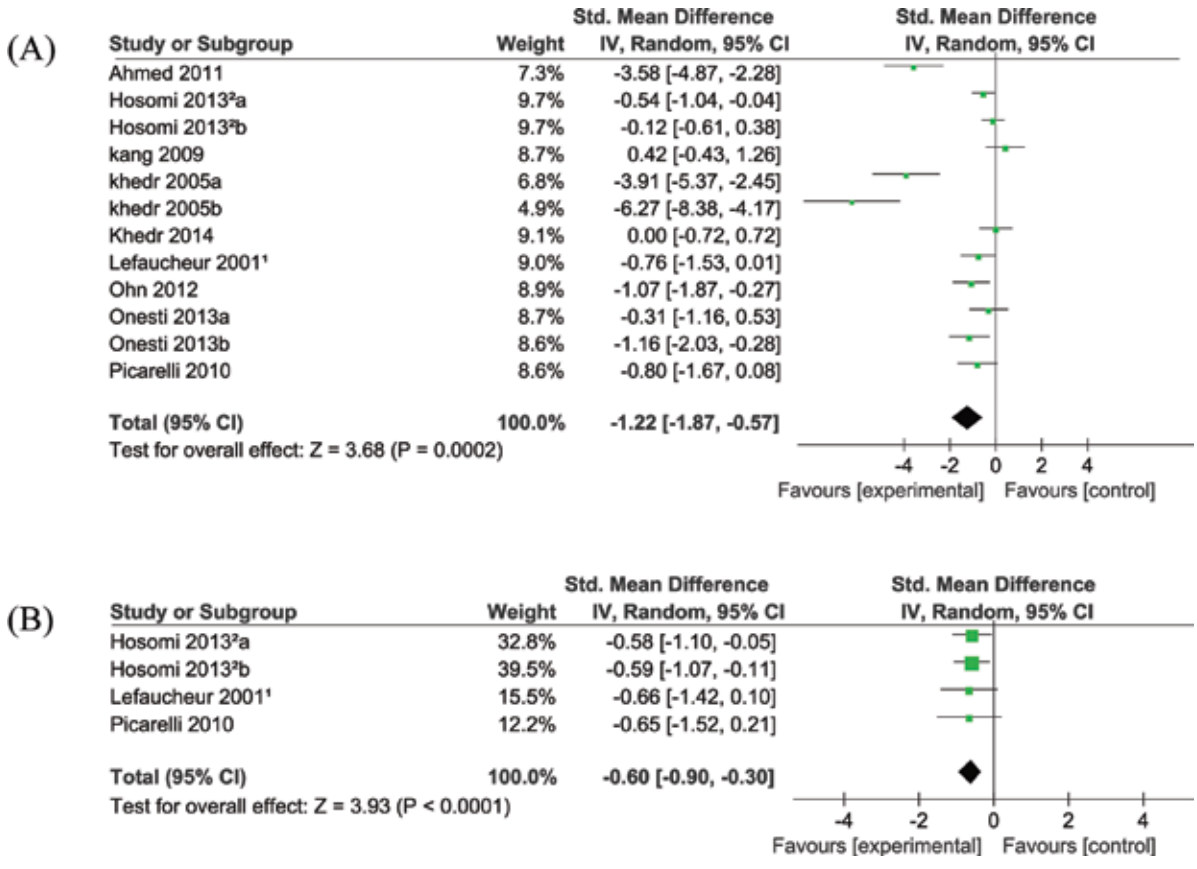

Fig. 6. *Forests plot of pain relief after 5 (A) and 6 (B) sessions of rTMS treatment.*

but not so at 2 months after rTMS (SMD = -1.05 (95%CI, -2.15 to 0.05, $P > 0.05$) (Fig. 8). It should be noted that the data of 2 and 3 months follow-up was too limited to be computed for a valid conclusion.

Discussion

To the best of the current knowledge, this is the first meta-analysis to assess the optimal parameters of rTMS therapy for NP. Our analyses show that although one session of rTMS treatment is effective in pain reduction, greater pain relief occurred after 5 sessions of rTMS treatment. Furthermore, the pain relieving effect of multiple rTMS (5 sessions) treatment can be maintained for at least one month.

So far there is not enough clinical evidence to determine the long-term effect of rTMS therapy (longer than 2 months post-treatment). In Picarelli et al's trial (44), no persistent difference in pain reduction was found after 3 months follow-up between rTMS therapy and sham controls. It is conceivable that if the acute effects of rTMS parameters can be established for NP, it will pave the way for more labor intensive and more costly long observation studies of rTMS therapy trials in future

This results are consistent with the views recently expressed by Lefaucheur et al (49) and Ohn et al (42), who proposed that rTMS could be a useful therapeutic method for NP when multiple sessions of rTMS intervention were given. A recent NP study has shown that 5 daily sessions of 20Hz rTMS over the motor cortex produced long-lasting pain relief in patients with phantom pain (25). In a comprehensive review, Leo et al also suggested that multiple sessions of high frequency rTMS on motor cortex could relieve pain (50). Thus, current findings suggest that multiple sessions of rTMS are effective for relieving chronic pain of NP.

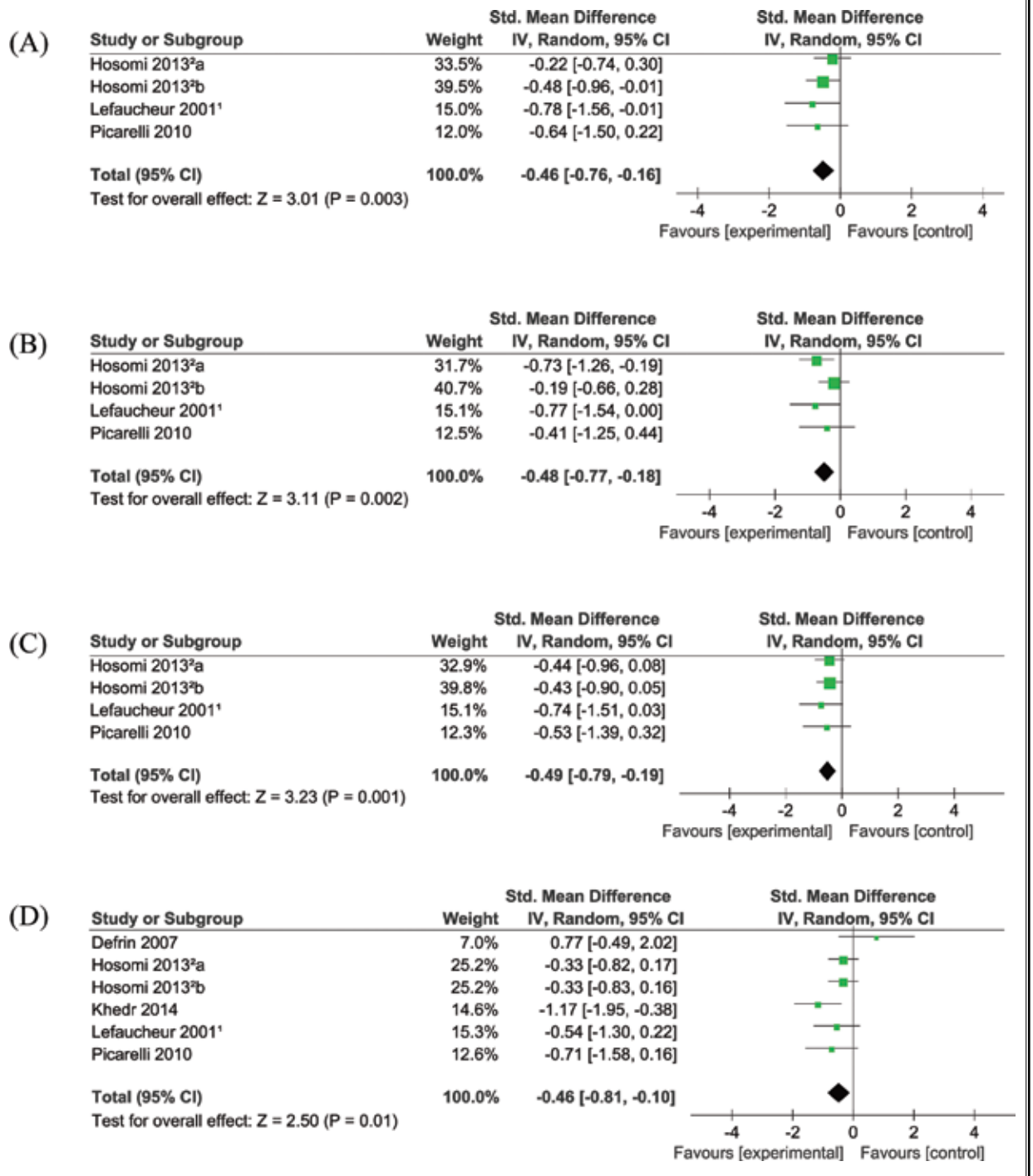

Fig. 7. *Forest plot after 7 (A), 8 (B), 9 (C), and 10 (D) sessions of rTMS treatment.*

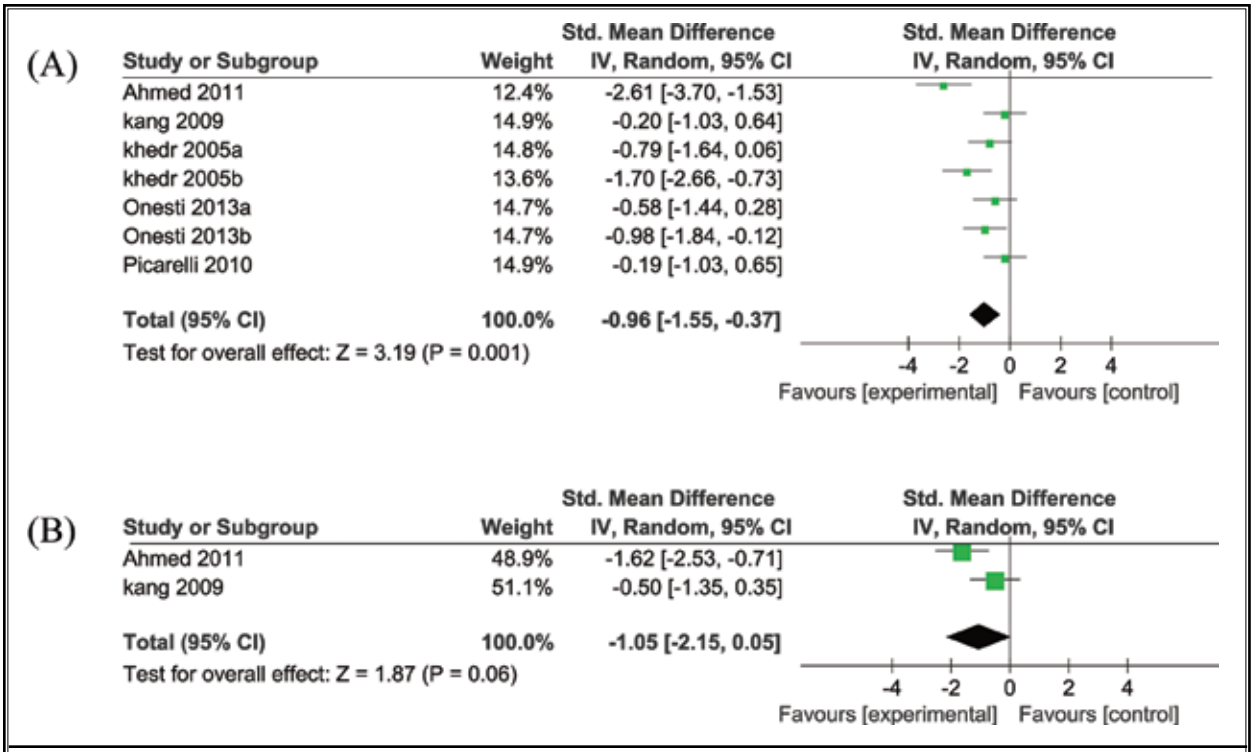

Fig. 8. *Forest plots at one month follow-up (A) and 2 months follow-up (B) after the end of rTMS treatment*

In this meta-analysis, only the HF-rTMS trials were included, and no different pain-alleviating effects were presented among 5Hz, 10Hz, and 20Hz HF-rTMS. It is known that HF-rTMS enhances neuronal firing efficacy whereas low-frequency rTMS (LF-rTMS) has the opposite effect (51). Lefaucheur et al (48) studied the pain-relief effect of rTMS at 0.5 and 10Hz in 18 patients with intractable unilateral hand pain. They concluded that 10Hz rTMS, but not 0.5Hz rTMS was effective in pain reduction. In a separate study Lefaucheur et al (39) showed that HF-rTMS could improve thermal sensory perception in the painful region of NP and the improved warm sensation perception was correlated with pain relief only after HF-rTMS but not after low frequency. Saitoh et al (47) tested rTMS therapy at 1Hz, 5Hz, and 10Hz in 13 NP patients, and showed that 10Hz rTMS was more effective in pain relief than 5Hz rTMS, while 1Hz rTMS was ineffective. Similar findings of effective pain control by high frequency rTMS (5 – 20Hz) have also been reported by multiple labs (18,43,52). However, Sampson et al (53) reported that 4 of 9 patients had significant pain relief, and 3 of them were rapid onset of relief, after 1Hz low frequency rTMS for 5 days per week for 3 weeks. Thus prolonged repeated LF-rTMS could still be a potentially optional analgesic therapy for NP patients who are insensitive to HF-rTMS.

There are 2 main central ascending pain pathways: the laterospinothalamic tract and the medial lemniscal pathway (paleospinothalamic). The laterospinothalamic tract projects to the insular and to the somatosensory cortex; the other to the insular, anterior cingulated cortex, and prefrontal cortex. The ipsilateral and/or contralateral M1 of the pain site was selected in most rTMS studies. Hirayama et al (31) concluded that the M1 was the best target for rTMS treatment of intractable pain, in spite of the fact that M1, the postcentral gyrus (S1), premotor area (preM), and supplementary motor area (SMA) are located adjacently. Sampsonet al (53) and Borckardt et al (54) showed that stimulation of the prefrontal cortex also had an analgesic effect.

The mechanism underlying the analgesic effect of rTMS is still unknown. Studies of motor cortex stimulation (MCS) suggested that MCS may result in direct inhibition of brain regions involved in the emotional response to pain and/or induced indirect mechanisms that will trigger descending inhibitory pathway to act at the dorsal horn level. rTMS may have a similar

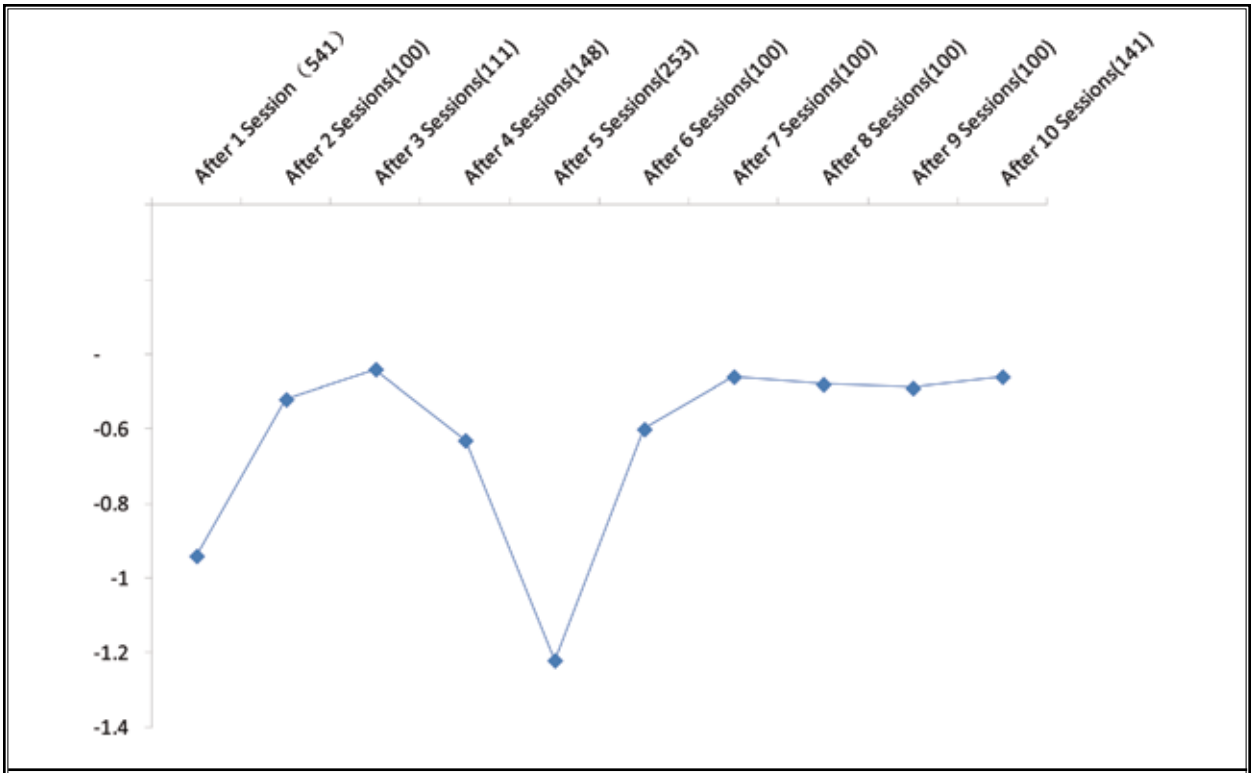

Fig. 9. *The effect sizes (Y-axis) over the course of the different points of treatment (X-axis). The digits in parentheses represent numbers of patients corresponding for each forest plot.*

mechanism to that of MCS (16). Another possibility was that rTMS relieved the pain through improving the blood flow of the affected area. It is known that there is a relative decrease in cerebral blood flow (rCBF) during chronic pain (55), and rTMS stimulation over the M1 significantly increased rCBF in NP patients in positron emission tomography. (PET) studies (55,56).

Several functional magnetic resonance imaging (fMRI) studies of post-stroke central pain showed significantly decreased activity in the secondary somatosensory cortex, including the insula, prefrontal cortex, and putamen in rTMS responders, whereas no change was noted in nonresponders (42). A functional imaging study by Goto et al (30), tracking the fibers of the corticospinal tract (CST) and thalamocortical tract (TCT) using diffusion tensor imaging (DTI), suggested the importance of the intactness of CST and TCT for rTMS-induced pain reduction as the rTMS-effective responders had higher delineation ratio of the CST and the TCT than the rTMS-ineffective responders. Likewise, the results of Leung et al's (16) meta-analysis also pointed to the importance of the overall intactness of the pain modulatory pathways in affecting the potential analgesic effect of rTMS. In Ohn et al's report (42), the integrity of the superior TCT in the ipsilesional hemisphere showed significant correlation with changes of VAS score after rTMS. In addition, Ahmed et al (25) inferred that VAS score reduction induced by rTMS of the M1 was correlated with an increase in cerebral beta-endorphin, which is known to be an analgesic factor in the nervous system. In short, the plastic changes from the structure and function of brain areas relative to emotion induced by rTMS may be connected to pain relief. In spite of these experimental data, the therapeutic mechanism of rTMS for NP remains speculative at this stage.

Although analysis of different rTMS sessions (Fig. 9) revealed greater analgesic effect of one and 5 sessions of rTMS treatment, respectively, it is noted that 6 out of 27 one-session trials showed exceptional analgesic response after rTMS. After excluding these 6 single session rTMS data, the effective size of one session rTMS treatment was reduced to 0.42, 95% CI -0.56 to -0.28, but still at a significant level ($P < 0.01$).

Similarly, although the 5-session rTMS treatment induced the maximal analgesic effect, 3 out of the 12 5-session trials showed exceptional analgesic response to rTMS treatment. And excluding these 3 trials has reduced the analgesic effect of 5-session rTMS to a level similar to that of other sessions of rTMS. Furthermore, we found that these trials with exceptional analgesic response to 5-session HF-rTMS were conducted in patients with central post-stroke pain (25,35,42). This suggests that the differential analgesic effect of rTMS may depend on the neuroanatomical origins of the NP pathophysiology, with more effective rTMS treatment response in NP originated from the "top" (supraspinal, cranial, or spinal) rather than the "bottom" (nerve root or peripheral nerve) (16). Overall, HF-rTMS appears to be a promising effective and alternative treatment for certain chronic NP, especially if its analgesic effects can be proven in NP patients who are resistant to drug treatment.

Conclusion

Although single session HF-rTMS is effective in acute pain relief of NP, multiple sessions of HF-rTMS (5 sessions) could be more effective for relieving the pain of NP, especially for post-stroke NP. Because only a limited number of trials evaluated the long-term effects of HF-rTMS at one and 2 months post rTMS treatment, further large-scale controlled trials including clearly defined pain subgroups with both acute and long-term observations (up to 3 months) are needed to validate and expand the current findings and to reveal the underlying mechanisms of rTMS.

Acknowledgments

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