



## High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: A systematic review and meta-analysis



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### ABSTRACT

**Background:** High-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) has demonstrated mixed effects on chronic and provoked pain.

**Objectives/Methods:** In this study, a meta-analysis was conducted to characterise the potential analgesic effects of high-frequency rTMS over the DLPFC on both chronic and provoked pain.

**Results:** A total of 626 studies were identified in a systematic search. Twenty-six eligible studies were included for the quantitative review, among which 17 modulated chronic pain and the remaining investigated the influence on provoked pain. The left side DLPFC was uniformly targeted in the chronic pain studies. While our data identified no overall effect of TMS across chronic pain conditions, there was a significant short-term analgesia in neuropathic pain conditions only (SMD =  $-0.87$ ). In terms of long-lasting analgesia, there was an overall pain reduction in the midterm (SMD =  $-0.53$ , 24.6 days average) and long term (SMD =  $-0.63$ , 3 months average) post DLPFC stimulation, although these effects were not observed within specific chronic pain conditions. Surprisingly, the number of sessions was demonstrated to have no impact on rTMS analgesia. In the analysis of provoked pain, our data also indicated a significant analgesic effect following HF-rTMS over the DLPFC (SMD =  $-0.73$ ). Importantly, we identified a publication bias in the studies of provoked pain but not for chronic pain conditions.

**Conclusions:** Overall, our findings support that HF-DLPFC stimulation is able to induce an analgesic effect in chronic pain and in response to provoked pain. These results highlight the potential of DLPFC-rTMS in the management of certain chronic pain conditions and future directions are discussed to enhance the potential long-term analgesic effects.

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## Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) represents a safe and non-invasive treatment option for chronic pain that may benefit patients who do not respond to conventional pharmacological therapies [36,37,62]. Research into rTMS analgesia has focussed on two main targets: the primary motor cortex (M1) demonstrating a modest but transient analgesic effect [44], and the

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dorsolateral prefrontal cortex (DLPFC) as an alternative site being increasingly targeted [1,29,60]. The DLPFC, a brain region activated in response to acute pain and found to be reorganised in chronic pain [67], is believed to be associated with pain analgesia through its connectivity with the descending pain circuits [49,72]. Using functional imaging, studies have demonstrated that DLPFC-rTMS is able to modulate the activity of these descending pain circuits [51,70]. Thus, DLPFC-rTMS may be able to reduce pain in chronic pain conditions, as is currently supported by several studies including spinal cord injury [60], fibromyalgia [1], and migraine [65].

Nonetheless, the evidence surrounding the potential benefits of DLPFC-rTMS for chronic pain is mixed [22,31]. While some studies reported active DLPFC stimulation as superior to sham [9,12,68], other studies did not demonstrate this effect [2,21,27]. A recent systematic review of chronic pain conditions indicated a probable analgesic efficacy of DLPFC-rTMS (at 5 Hz or above) in fibromyalgia, although clear benefit was not observed in other pain conditions [44]. However, a Cochrane review indicated no analgesic effect following rTMS stimulation of the DLPFC [63]. More importantly, a number of papers have recently emerged that may challenge the overall conclusions of rTMS analgesia in the DLPFC [1,19,33,65].

Provoked pain represents an experimental protocol to investigate rTMS analgesia, with a series of studies demonstrating an analgesic influence of DLPFC-rTMS in healthy controls [24,26,51,66,70]. However, no study has systematically quantified the analgesic efficacy of DLPFC-rTMS in provoked pain, results of which may have relevance to rTMS analgesia in chronic pain.

The primary focus of the current study was to conduct a systematic review and meta-analysis to investigate the analgesic efficacy of rTMS over the DLPFC in chronic pain. We further examined the modulating impact of session number as it is suggested to be critical in rTMS analgesia [46]. We also evaluated rTMS analgesia over the DLPFC in provoked pain using meta-analysis, with the purpose to provide insights on the translation of rTMS analgesia to chronic pain. We focussed on sham-controlled high-frequency ( $\geq 5$  Hz) rTMS protocols as recent reviews consistently indicated no overall analgesic effect of low-frequency rTMS ( $\leq 1$  Hz) [44,63], although low-frequency rTMS is reported to have an effect in a few studies [32,41].

## Methods

### Protocol and registration

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [55]. The protocol was registered in the database of International Prospective Register of Systematic Reviews (CRD42020178742).

### Search strategy and selection criteria

A comprehensive electronic literature search was performed in PubMed, PsycINFO, The Cochrane Library and EMBASE to early December 2019 with no limit on starting date. The keywords used for the search were 'pain' AND ('TMS OR 'transcranial magnetic stimulation') AND 'prefrontal cortex'. The search results and process of article selection are described in the [Supplementary Material S1](#). It is noted that reference lists of full-text potentially eligible studies were also checked for missing studies. The same inclusion and exclusion criteria were used for the systematic review and meta-analysis in both chronic pain conditions and provoked pain, as outlined in [Table 1](#) and extensively described in the [Supplementary Material S2](#).

### Outcome measures

The outcome measures included pain intensity, headache frequency/days, and pain threshold based on the studies. Pain intensity was most often used across studies derived from validated measures such as visual analogue scales (VAS), verbal rating scales (VRS) or numerical rating scales (NRS). Headache frequency/days was often considered as the primary outcome in migraine studies [12,33,48,65]. In addition, pain threshold, a temperature or pressure that participants experienced as painful, was specified as the outcome measure in several provoked pain studies [10,18,24,26,58]. It is noted that outcome measures were extracted for consistency within respective areas. For instance, headache frequency in migraine conditions was extracted as the primary outcome.

### Data extraction

Mean, standard deviation (SD), and sample size were extracted for the outcome measures in each condition or group (i.e. active and sham). We first contacted the corresponding authors for additional data when they were not directly available from the article. In cases the standard deviation was not directly available in some studies [48,74], we estimated the standard deviation from the related figures or confidence of interval [35]. Details about data extraction are presented in the [Supplementary Material S3](#). It is noted that post-intervention measures of different time periods were extracted (i.e. short-term: 0 to  $\leq 1$  week post-intervention; mid-term: 1 to  $\leq 6$  weeks post-intervention; long-term:  $> 6$  weeks post-intervention) [63]. Moreover, data were averaged in cases where more than one data point was available for a certain time period (i.e. two data points were available in Refs. [2,27,60,68] in the short-term; two or three data points were available in Refs. [27,33,65,74] in the mid-term). As the DLPFC is believed to have extensive involvement in the emotional aspects of pain [72], we therefore extracted emotional pain responses where possible (e.g. pain unpleasantness, McGill Pain Questionnaire (MPQ) affective scale [53]).

### Assessment of risk of bias

Potential risk of bias was assessed using the Cochrane 'risk of bias' assessment tool [35]. The specific criteria (using low/high/unclear) are listed in the [Supplementary Material S4](#). Two reviewers (XC and XL) independently assessed the risk of bias and discrepancies between the reviewers were solved by consensus.

### Meta-analysis

#### Calculating effect sizes

Meta-analyses were performed using the MIX 2.0 computer program [4], which allows for the calculation of statistical significance of differences between means with 95% confidence intervals (CIs). The calculation of effect size was based on the standardised mean difference (SMD) using Hedge's adjusted  $g$ . Hedge's adjusted  $g$  is similar to Cohen's  $d$  but it adjusts for the small sample bias [34]. For SMDs, values of 0.2 were considered small, 0.5 as medium and 0.8 as large [20].

The SMD method does not account for the differences in the scale directions. In this case, pain threshold has opposite directions compared to other pain measures. We therefore multiplied the mean values of pain threshold by  $-1$  to correct for the difference in scale direction [35].

#### Subgroup analyses

In the subgroup analyses, we examined the main effect and the interaction effect between rTMS intervention and chronic pain

**Table 1**  
Inclusion and exclusion criteria.

Inclusion	Exclusion
<b>Interventions</b>	High-frequency rTMS ( $\geq 5$ Hz) over the DLPFC to reduce pain
<b>Participants</b>	Pain as a primary symptom/outcome
<b>Comparisons</b>	Before and after intervention
<b>Control conditions</b>	Sham condition
<b>Study design</b>	Pre-post studies
<b>Outcomes</b>	Crossover or parallel group
<b>Data reported</b>	Pain intensity/unpleasantness/threshold/tolerance Or the reported primary pain outcome, e.g. headache frequency Data that enables analysis and estimation of effect size, including data from published figures or authors
<b>Publication type</b>	Peer-reviewed journal Written in English
	Other targets Not high-frequency rTMS No clear painful sensation No baseline measurement Not sham-controlled – No pain measure Unpublished data Data without Mean Data without SD/SEM Data without N Review article Case report Grey literature Non-English article

SD—standard deviation; SEM—standard error of mean; N—sample size; rTMS—repetitive transcranial magnetic stimulation; DLPFC—dorsolateral prefrontal cortex.

conditions (e.g. neuropathic pain, migraine, widespread pain and so on). The classification of chronic pain conditions was based on the International Classification of Diseases (ICD-11) [73]. Moreover, meta-analyses were performed on outcome measures of different time periods post-intervention. This was done in accordance with a recent Cochrane review [63] (short-term: 0 to  $\leq 1$  week post-intervention; mid-term: 1 to  $\leq 6$  weeks post-intervention; long-term:  $> 6$  weeks post-intervention). As provoked pain studies stimulated either left or right DLPFC, subgroup analyses were further performed based on the side of stimulation. In order to explore the association between potential short- and mid-term (or long-term) effects, hedge's  $g$  was extracted from each study and fitted into a regression model.

#### Meta-regression

As the number of sessions may modulate the efficacy of rTMS analgesia [46], a series of meta-regressions were performed to examine the influence of session number on the analgesic influence of high-frequency rTMS.

#### Test of heterogeneity and publication bias

In systematic reviews and meta-analyses, conclusions tend to be unclear when the results vary across studies. In this study, heterogeneity between studies was evaluated using the  $I^2$  statistics and the Galbraith plots were used to illustrate the extent of heterogeneity between studies. Details with regard to these two methods are described in the [Supplementary Material S5](#). We also used a number of methods to examine publication bias [16], including the selectivity funnel plot, Egger's regression test and the Begg-Mazumdar Kendall  $\tau$ , as well as the Bayesian approach. Details about these methods are provided in the [Supplementary Material S5](#).

#### Baseline differences

Post-intervention data were used in the meta-analysis as suggested by the Cochrane Handbook [35]. This method is also appropriate here as nearly all of the included studies reported baseline and post-intervention data instead of delta score. Baseline differences between active and sham stimulation were therefore examined on the baseline outcome measures. Specifically, meta-analytic estimates were evaluated between active and sham stimulation on the baseline data. We also explored covarying effects of baseline data. It is noted that meta-analysis programs do not allow to directly run covarying analyses. We therefore generated a mean

value by multiplying baseline data to post data [11]. This was done for the chronic and provoked pain separately.

## Results

### Selection of studies and characteristics

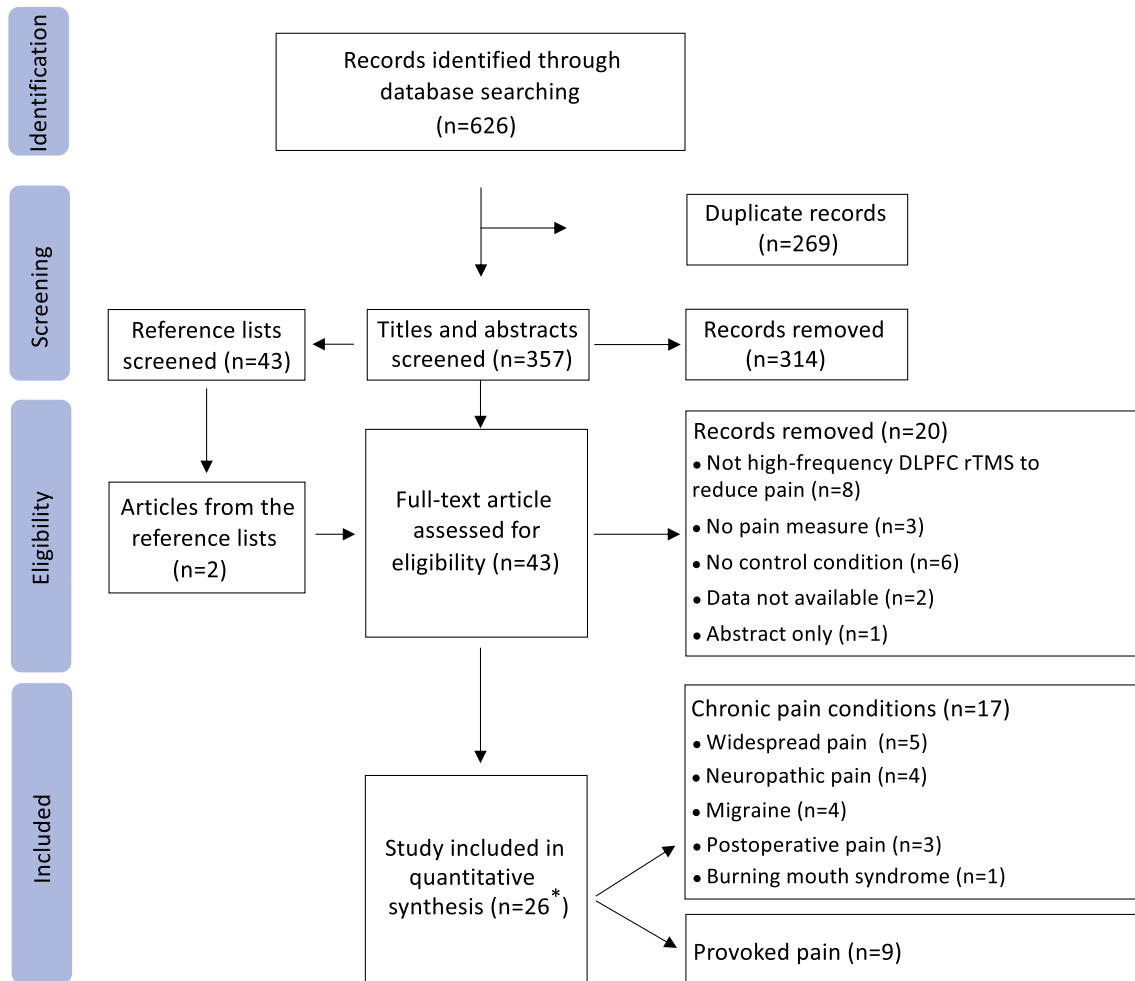
Online database searches identified a total of 626 records ([Fig. 1](#)). After duplicates were removed, 357 studies remained. Initial screening of the title and abstract was performed against the inclusion and exclusion criteria. After excluding 314 records from the initial screening, full-text versions of 43 studies were screened for eligibility. A total of 26 studies were included in the systematic review and meta-analysis, of which 17 studies were conducted among chronic pain conditions and 9 were provoked pain.

A range of chronic pain conditions were investigated which included widespread pain ( $n = 5$ ), neuropathic pain ( $n = 4$ ), migraine ( $n = 4$ ), postoperative pain ( $n = 3$ ), and burning mouth syndrome ( $n = 1$ ). [Table 2](#) summarises the characteristics of the included studies. Almost all of the chronic pain studies employed repeated-session protocols. All the chronic pain studies used left DLPFC as the stimulation target although with different location methods (e.g. 5 cm method, Beam F3 method [5]). Nearly all of the chronic pain studies employed 10 Hz rTMS (with intensity varying from 100 to 120% of resting motor threshold) with two studies using 20 Hz protocols [12,33], and one study delivering intermittent Theta Burst Stimulation [65]. In total ten chronic pain studies assessed potential follow-up effects of two weeks or longer post stimulation. Pain intensity and headache frequency/days were the primary outcome measures, and the pooled dataset was very consistent in using a certain outcome measure within specific chronic pain conditions (e.g. headache frequency in migraine).

Provoked pain studies stimulated both the left ( $n = 6$ ) and right ( $n = 3$ ) DLPFC, but the stimulation frequency remained the same across studies (10 Hz with intensity varying from 80 to 110% of resting motor threshold). Single-session protocols were widely used except that two studies induced sustained muscle pain and delivered five sessions of rTMS [26,66]. Pain intensity and threshold were the primary outcome measures.

### Risk of bias

Risk of bias varied across studies ([Supplementary Material S6](#)). Chronic pain studies tended to report adequate sequence



**Fig. 1.** Flow diagram of selected studies ( $n$  = number of articles). A total of 26 studies were included in the quantitative synthesis. \* Borckardt et al., 2014 was entered as two studies as it included active rTMS conditions of single and double sessions.

generation, adequate double blinding as well as more complete outcome data. While provoked pain studies had adequate blinding of participants and complete outcome data, these studies also had unclear to high risk in sequence generation and the blinding of assessors. In addition, crossover studies, although the number was limited, tended to be free from carry-over effects.

#### Chronic pain conditions

Chronic pain studies were separated into short-term, mid-term, and long-term datasets based on the follow-up assessments (see *Methods*).

#### Short-term effects

Overall, high-frequency rTMS over the DLPFC did not reduce chronic pain in short term ( $SMD = -0.43$ ,  $p = 0.10$ ) (Fig. 2). Further analyses within each chronic pain condition indicated a significant rTMS analgesia in neuropathic pain conditions ( $SMD = -0.87$ , 95% CI:  $[-1.56, -0.18]$ ,  $p = 0.01$ ). Meanwhile, high-frequency rTMS over the DLPFC showed no effect among other chronic pain conditions (widespread pain:  $p = 0.30$ ; migraine:  $p = 0.94$ ; burning mouth syndrome had no synthesis  $p$  value).

#### Mid-term effects

Pooled analysis indicated that high-frequency rTMS over the DLPFC had an analgesic effect in medium term (2–6 weeks follow-up) ( $SMD = -0.53$ , 95% CI:  $[-0.92, -0.13]$ ,  $p = 0.01$ ). However, this effect was not strong enough to be observed in any specific pain conditions (neuropathic pain:  $p = 0.09$ ; widespread pain:  $p = 0.16$ ; migraine:  $p = 0.28$ ; burning mouth syndrome had no synthesis  $p$  value) (Fig. 3A). A regression analysis on eight eligible studies revealed a trend positive association between short- and mid-term analgesia ( $F_{1,7} = 5.73$ ,  $p = 0.05$ ,  $R^2 = 0.49$ , Beta = 0.70).

#### Long-term effects

Only three studies evaluated follow-up effects longer than six weeks, and the results revealed a significant pain reduction post high-frequency rTMS over the DLPFC ( $SMD = -0.63$ , 95% CI:  $[-1.11, -0.15]$ ,  $p = 0.01$ ) (Fig. 3B). No subgroup analyses were undertaken for these data given the limited number of studies.

#### Meta-regression

Meta-regression analyses indicated that the number of sessions has no effect on rTMS analgesia in either short-term ( $p = 0.45$ ) or mid-term ( $p = 0.93$ ) pain outcome (Fig. 3C).

**Table 2**  
Characteristics of included studies.

Author, year	Pain condition	Gender (size = m:f)	Age (Mean ± SD/ range)	Hemisphere of TMS stimulation	Stimulation frequency and intensity (RMT%)	Number of sessions	Pain measure	Mid-term assessment	Long-term assessment
Atlas et al., 2019	Fibromyalgia	30 = 0:30	47.47 ± 8.76	Left	10 Hz, 90%	15	Pain intensity		
Avery et al., 2015	Chronic widespread pain	18 = 0:18	53.17 ± 9.09	Left	10 Hz, 120%	15	Pain intensity	1 month	3 months
Borckardt et al., 2008	Postoperative pain	20 = mostly women	42.3	Left	10 Hz, 100%	1	Pain intensity		
Borckardt et al., 2009	Neuropathic pain	4 = 1:3	46 ± 11.17	Left	10 Hz, 100%	3	Pain intensity		
Borckardt et al., 2014a <sup>a</sup>	Postoperative pain	56 = 17:39	49.05 ± 12.13	Left	10 Hz, 110%	2	Pain intensity		
Borckardt et al., 2014b <sup>b</sup>	Postoperative pain	54 = 16:38	47.46 ± 10.87	Left	10 Hz, 110%	1	Pain intensity		
Brighina et al., 2004	Migraine	11 = 4:7	47 ± 7	Left	20 Hz, 90%	12	Headache frequency	1 month	
Cheng et al., 2019	Fibromyalgia with MDD	14 = 7:7	50 ± 11	Left	10 Hz, 100%	10	Pain intensity		
Conforto et al., 2014	Migraine	14 = n/a	38.8 ± 11.9	Left	10 Hz, 110%	23	Headache days		
de Oliveira et al., 2014	Central poststroke pain	21 = 10:11	56.33 ± 10.71	Left	10 Hz, 120%	10	Pain intensity	4 weeks	
Fitzgibbon et al., 2018	Fibromyalgia	26 = 2:24	45.61 ± 12.88	Left	10 Hz, 120%	20	Pain intensity	1 month	
Granato et al., 2019	Migraine with medication overuse headache	14 = n/a	18–65	Left	20 Hz, 100%	10	Headache frequency	2 weeks	10 weeks
Leung et al., 2018	mTBI related headache	29 = 23:6	34.03 ± 8	Left	10 Hz, 80%	4	Pain intensity	4 weeks	
Nardone et al., 2017	SCI with neuropathic pain	12 = 9:3	43.08 ± 13.19	Left	10 Hz, 120%	10	Pain intensity	1 month	
Sahu et al., 2019	Migraine	41 = 10:31	30.78 ± 8.28	Left	80%, iTBS	10	Headache frequency	4 weeks	12 weeks
Short et al., 2011	Fibromyalgia	20 = mostly women	53 ± 13.53	Left	10 Hz, 120%	10	Pain intensity	2 weeks	
Umezaki et al., 2016	Burning mouth syndrome	20 = 18:2	63.85 ± 9.56	Left	10 Hz, 110%	10	Pain intensity	2 weeks	
Borckardt et al., 2007	Thermal pain	20 = 11:9	31.65	Left	10 Hz, 100%	1	Pain threshold		
de Andrade et al., 2011 <sup>c</sup>	Cold pain	24 = 16:8	28.6 ± 5.4	Right	10 Hz, 80%	1	Pain intensity		
de Andrade et al., 2014 <sup>d</sup>	Cold pain	24 = 15:9	29.1 ± 5.5	Right	10 Hz, 80%	1	Pain threshold		
De Martino et al., 2019b <sup>e</sup>	NGF injection	30 = 12:18	26.45 ± 1.2	Left	10 Hz, 110%	5	Pressure pain threshold		
Martin et al., 2013	Thermal pain	23 = 9:14	26.17 ± 6.5	Left	10 Hz, 110%	1	Pain intensity		
Nahmias et al., 2009 <sup>f</sup>	Cold pain	26 = 13:13	27 ± 6.9	Right	10 Hz, 80%	1	Pain threshold		
Seminowicz et al., 2018 <sup>g</sup>	NGF injection	30 = 12:18	26.45 ± 1.2	Left	10 Hz, 110%	5	Pain intensity		
Taylor et al., 2012 <sup>d</sup>	Thermal pain	24 = 12:12	24.82 ± 2.79	Left	10 Hz, 110%	1	Pain intensity		
Taylor et al., 2013 <sup>d</sup>	Thermal pain	14 = n/a	18–45	Left	10 Hz, 110%	1	Pain intensity		

MDD-major depressive disorder; mTBI- mild traumatic brain injury; SCI- spinal cord injury; NGF- nerve growth factor; m-males; f-females; RMT-resting motor threshold.

<sup>a</sup> Data were taken from real-real session.

<sup>b</sup> Data were averaged from two real TMS sessions.

<sup>c</sup> Data were taken from 5-degree, saline injection condition.

<sup>d</sup> Data were taken from saline injection condition.

<sup>e</sup> Data were taken from right ECRB (left DLPFC).

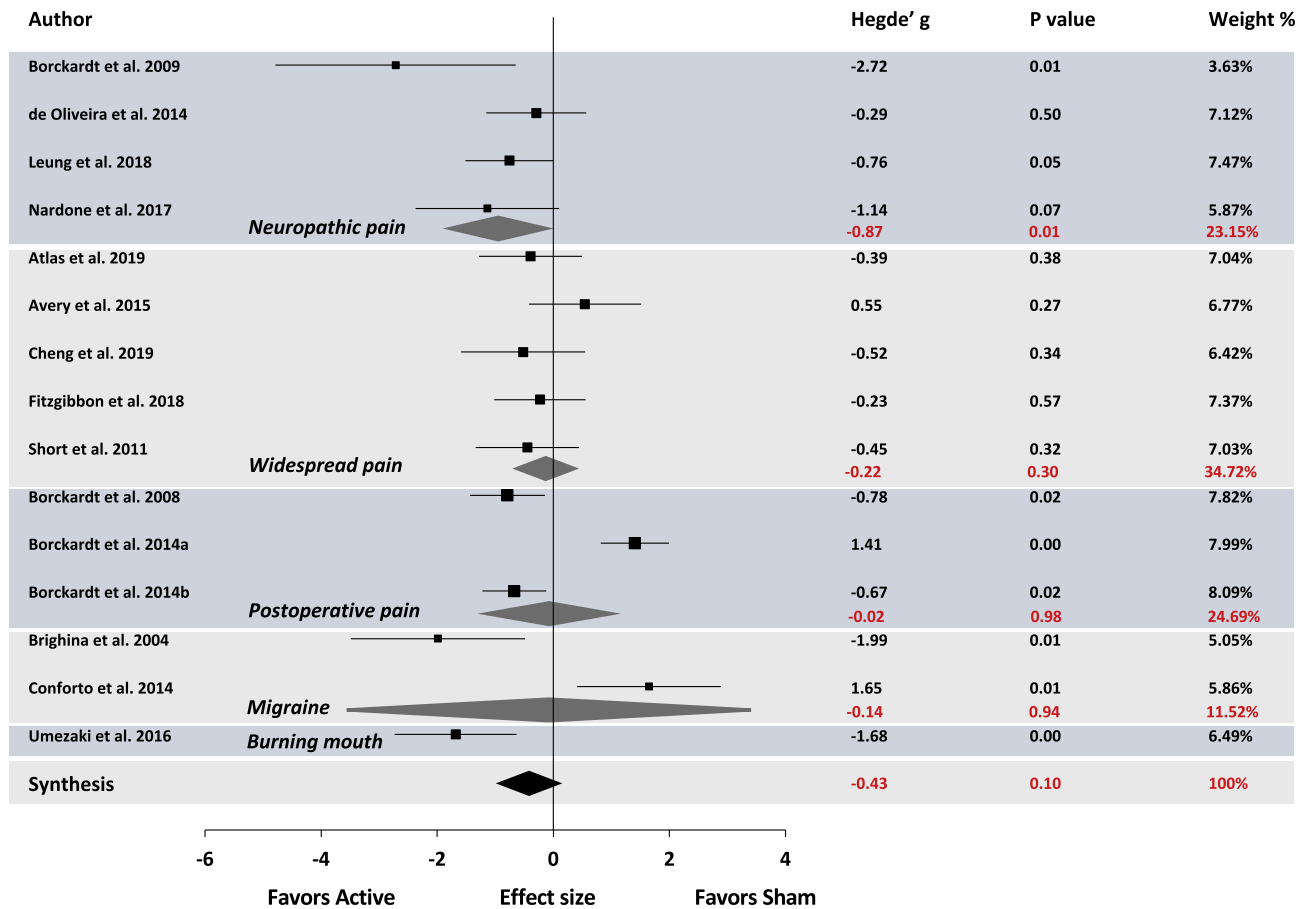
<sup>f</sup> Data were taken from left hand (right DLPFC), 5 min and cold pain condition.

<sup>g</sup> Data were taken from the end of the fifth session.

**Heterogeneity and publication bias**

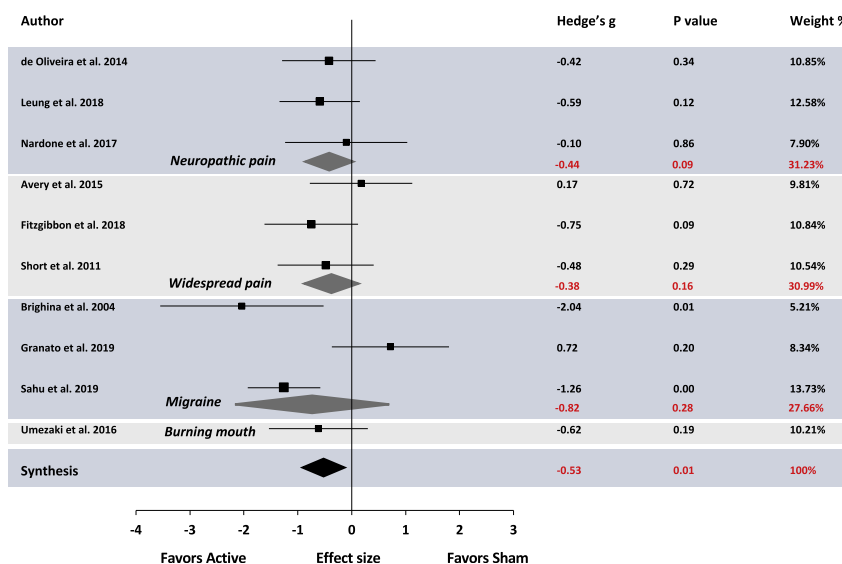
Galbraith plot indicated heterogeneity in the dataset, with more than 5% of the dots beyond two standard errors of the population effect (Fig. 4A). The test of heterogeneity was significant ( $Q = 80.14$ ,

$p = 0.001$ ,  $I^2 = 80.04\%$ ). Visual inspection of the selectivity funnel plot indicated an asymmetry in the shape (Fig. 4B), with each line in the funnel representing different levels of significance (0.01, 0.05, and 0.1). However, more objective statistics of Begg's test

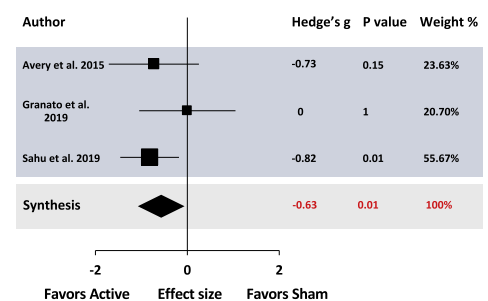


**Fig. 2.** Forest plot of the Hedge's adjusted g analysis for pooled effects of DLPFC-rTMS on short-term pain outcome. Overall, high-frequency rTMS over the DLPFC reduced chronic pain (SMD = -0.56,  $p = 0.03$ ), with the effect being most notably in neuropathic pain conditions (SMD = -1.20,  $p = 0.03$ ). DLPFC and rTMS denotes the dorsolateral prefrontal cortex and repetitive transcranial magnetic stimulation, respectively. SMD denotes standardised mean difference.

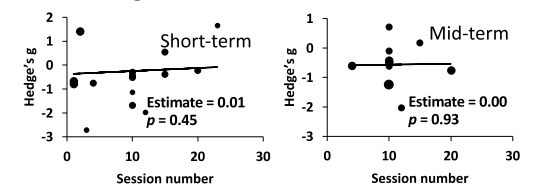
**A. Mid-term synthesis**



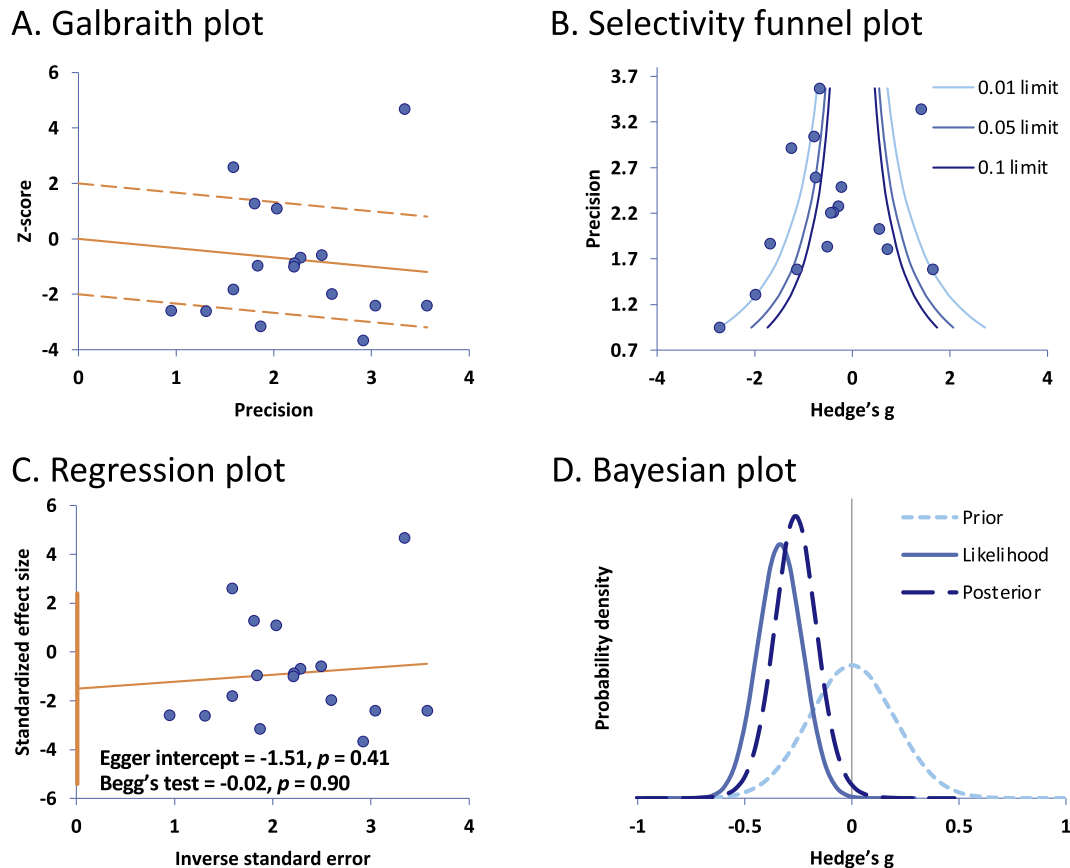
**B. Long-term synthesis**



**C. Meta-regression**



**Fig. 3.** Mid- and long-term syntheses as well as meta-regression results. (A) High-frequency rTMS over the DLPFC had an analgesic effect on mid-term pain outcome (SMD = -0.40,  $p = 0.04$ ). But this effect was not significant in any specific pain conditions ( $p_s > 0.05$ ). (B) High-frequency rTMS over the DLPFC showed no effect on long-term pain outcome ( $p > 0.05$ ). (C) Meta-regression analyses revealed no effect of session number on rTMS analgesia in either short-term or mid-term pain outcome.



**Fig. 4.** Series of tests for heterogeneity and publication bias for the effects of DLPFC-rTMS on pain outcome (all 17 studies). (A) Galbraith plot suggested heterogeneity with more than 5% of the data beyond two standard errors of the population effect. (B) Selectivity funnel plot indicated slight publication bias with a few studies showing asymmetry towards decreased pain. (C) Regression plot suggested no publication bias with Egger's and Begg's test ( $p_s > 0.05$ ). (D) Bayesian triplot indicated slight publication bias with the likelihood effect size ( $-0.32$ ) comparable as the estimated effect size ( $-0.50$ , all 17 studies).

( $\tau = -0.02$ ,  $p = 0.90$ ) and Egger's regression test ( $t = -1.51$ ,  $p = 0.41$ ) indicated no evidence of publication bias (Fig. 4C). In addition, the Bayesian analysis yielded smaller effect size ( $-0.26$ ) compared to the estimated effect size ( $-0.42$ , results of all 17 studies) (Fig. 4D). These combined analyses suggested a minimal possibility of publication bias in the chronic pain dataset.

#### Baseline differences

Meta-analysis revealed no baseline difference in pain experience between active and sham stimulation in the pooled dataset, which ruled out the possibility of baseline differences impacting on meta-analytic estimates (SMD = 0.001, 95% CI:  $[-0.22, 0.22]$ ,  $p = 0.99$ ) (see Supplementary Material S7). When multiplying baseline data to post data, meta-analysis revealed decreased pain in the active compared to the sham stimulation (SMD =  $-2.81$ , 95% CI:  $[-4.69, -0.92]$ ,  $p = 0.003$ ).

#### Emotional aspects of pain

Pain unpleasantness and MPQ affective scale [53] were used as emotional pain outcomes in a few studies [2,8,27,29,60,74]. Secondary analysis revealed a short-term trend decrease ( $p = 0.052$ ) in emotional pain in the active compared to the sham DLPFC (see Supplementary Material S8).

#### Provoked pain

#### Synthesis

Pooled analysis indicated that high-frequency rTMS over the DLPFC significantly reduced provoked pain (SMD =  $-0.73$ , 95% CI:

$[-1.36, -0.11]$ ,  $p = 0.02$ ) (Fig. 5). Further analyses found that this analgesic effect was dominated by left DLPFC-rTMS (SMD =  $-1.10$ , 95% CI:  $[-1.97, -0.22]$ ,  $p = 0.01$ ), while no significant effect was observed on the right-side stimulation ( $p > 0.05$ ) (see Supplementary Material S9).

#### Heterogeneity and publication bias

Galbraith plot indicated heterogeneity in the dataset, with more than 5% of the dots beyond two standard errors of the population effect (Fig. 6A). The test of heterogeneity was also significant ( $Q = 39.15$ ,  $p = 0.001$ ,  $I^2 = 79.57\%$ ). There was an asymmetry in the shape of the selectivity funnel plot (Fig. 6B). Begg's test ( $\tau = -0.11$ ,  $p = 0.68$ ) indicated no evidence of publication bias (Fig. 6C), but Egger's regression test ( $t = -10.15$ ,  $p = 0.01$ ) indicated the possibility of publication bias (Fig. 6C). In addition, the Bayesian analysis yielded smaller effect size ( $-0.40$ ) compared to the estimated effect size ( $-0.73$ ) (Fig. 6D). These combined analyses suggested the possibility of publication bias in the dataset.

#### Baseline differences

Meta-analysis based on the baseline data indicated the absence of baseline difference in pain between the active and sham group (SMD = 0.15, 95% CI:  $[-0.27, 0.58]$ ,  $p = 0.48$ ) (see Supplementary Material S10). When multiplying baseline data to post data, meta-analysis revealed decreased provoked pain in the active compared to the sham stimulation (SMD =  $-3.98$ , 95% CI:  $[-7.79, -0.17]$ ,  $p = 0.04$ ).

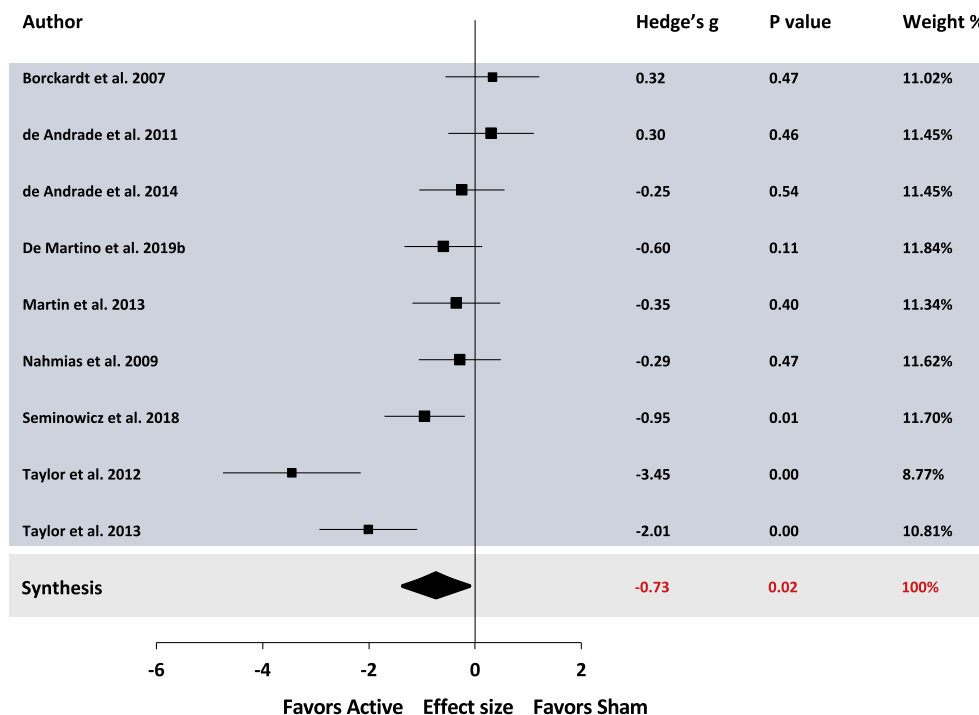


Fig. 5. Forest plot of the Hedge's adjusted g analysis indicated decreased provoked pain post DLPFC-rTMS (SMD = -0.73, p = 0.02).

**Discussion**

The present study was designed to quantify the potential analgesic effects of high-frequency rTMS over the DLPFC in both chronic and provoked pain. Our analysis of chronic pain indicated a significant pain reduction in neuropathic pain conditions in the short term. Chronic pain studies tended to deliver repeated sessions and there was an overall analgesia in both the midterm and long term. In addition, our data demonstrated a significant reduction in provoked pain post DLPFC-rTMS. Finally, we found evidence of publication bias for provoked pain but not for chronic pain conditions.

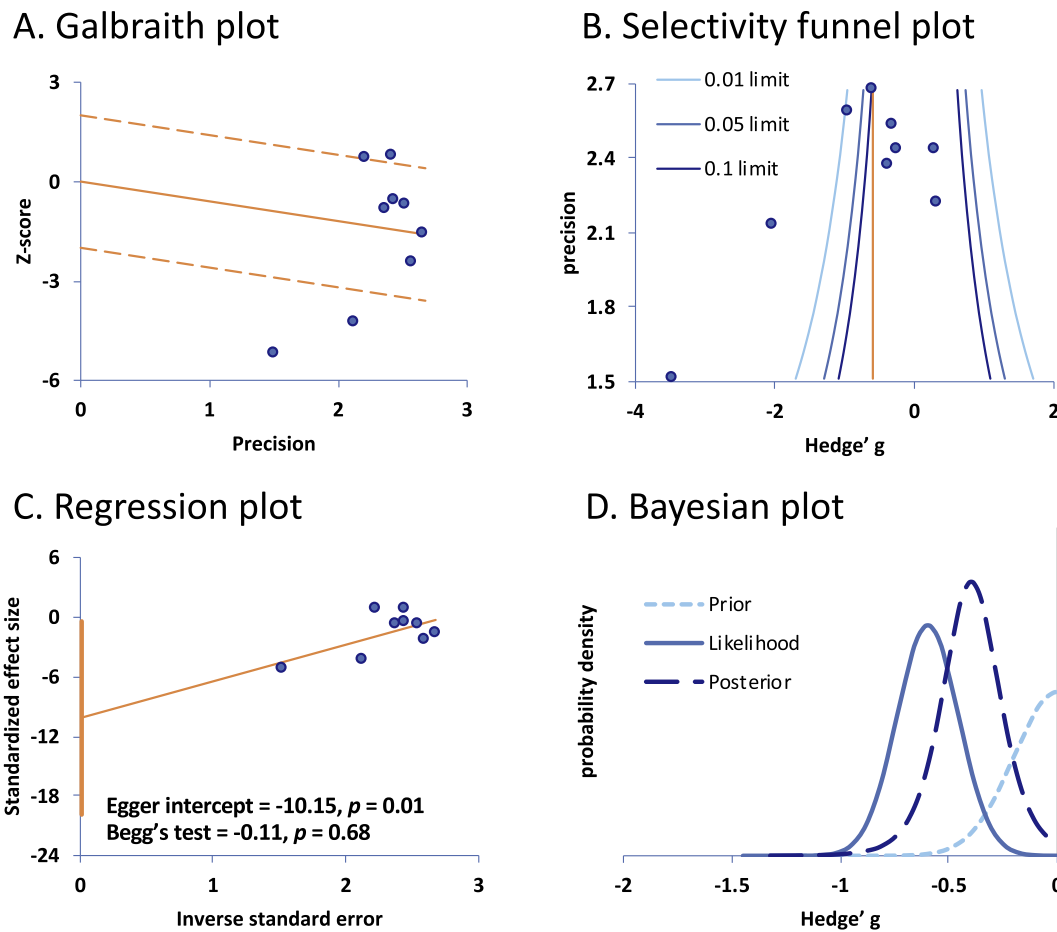
*rTMS over the DLPFC in the management of chronic pain*

Our synthesis demonstrated a short-term analgesic effect of rTMS over the DLPFC in neuropathic pain. This is different from previous reviews which indicated no clear evidence on the analgesic efficacy of DLPFC-rTMS [44,63]. In contrast to the recent systematic review by Lefaucheur et al. [44], our meta-analysis included an additional five clinical trials [1,2,19,33,65]. These studies are valuable additions to this field and they increased the overall sample sizes significantly (at least 6% increase each in the weight percentage, see Figs. 2 and 3). In contrast to the meta-analysis by O'Connell et al. [63], rTMS analgesia over the DLPFC was further classified into specific chronic pain conditions in this synthesis. While the M1 has been frequently used in the management of neuropathic pain [36,38,43,47], we provide the first quantitative synthesis of high-frequency rTMS over the DLPFC as an alternative target in the management of neuropathic pain.

In contrast to neuropathic pain, our data demonstrated no significant effect of DLPFC-rTMS in widespread pain. The classification of widespread pain here included mainly fibromyalgia (4 studies) as well as one study conducted in chronic widespread pain. All these studies uniformly delivered 10 Hz rTMS to the left DLPFC. Lefaucheur et al. [44] reviewed a probable effect of high-frequency DLPFC-rTMS in fibromyalgia. Our synthesis did not demonstrate a

significant reduction in pain intensity in the fibromyalgia conditions. It is interesting that two trials found significant improvement in physical functioning (i.e. physical role, fatigue) post DLPFC stimulation [1,29]. Altas et al. [1] further compared the efficacy of M1 with DLPFC in which M1 had better outcome in pain intensity while DLPFC group reported greater improvement in physical role functioning. These findings highlight the potential benefits of DLPFC-rTMS in improving physical functioning in fibromyalgia, and therefore the possibility that DLPFC stimulation may improve aspects of pain experience beyond pain intensity. Following completion of the current meta-analysis, two additional trials using DLPFC stimulation were published. In one study, DLPFC-rTMS was able to reduce fibromyalgia stiffness but not pain intensity [6]. A recent study has also explored the efficacy of low-frequency rTMS in the management of fibromyalgia, demonstrating a significant pain reduction in the active group [69].

In terms of migraine, the synthesis revealed no significant analgesic effect by high-frequency rTMS over the DLPFC. It is noted that rTMS protocols varied across the migraine studies dramatically (i.e. 10 Hz, 20 Hz, and iTBS). Variances in rTMS protocols are possibly associated with different even opposite rTMS effects in migraine. Moreover, a few migraine trials tended to report follow-up effects without providing short-term assessments [33,65], which in a way limits the synthesis across studies although follow-up effects have more clinical relevance. Similarly, the pooled dataset indicated no significant pain reduction in postoperative pain post high-frequency rTMS stimulation of the DLPFC. Moreover, these studies were performed by the same group [7,8], although a large RCT was reported. Overall, the evidence is limited surrounding the beneficial effects of DLPFC-rTMS in postoperative pain. In addition, only one study investigated rTMS analgesia over the DLPFC in people suffering from burning mouth syndrome [74], along with a case study in medication-resistant burning mouth syndrome [75]. Although the former reported dramatic pain reduction in the rTMS group, it is still too early to determine rTMS analgesia in this pain condition based on limited evidence.



**Fig. 6.** Series of tests for heterogeneity and publication bias for the effects of DLPFC-rTMS on provoked pain. (A) Galbraith plot suggested heterogeneity with more than 5% of the data beyond two standard errors of the population effect. (B) Selectivity funnel plot indicated slight publication bias. (C) Egger's test but not Begg's test suggested publication bias. (D) Bayesian triplot indicated publication bias with the likelihood effect size (-0.60) comparable as the estimated effect size (-0.73).

The clinical application of rTMS in pain management relies on its capacity to generate long-lasting analgesia [45]. We evaluated the follow-up effects of DLPFC-rTMS and found significant pain reduction at both mid- and long-term follow-up. Moreover, the average follow-up effect was 24.6 days (midterm) and 3 months (long term) post stimulation, respectively. These findings highlight the potential of DLPFC-rTMS in maintaining analgesia and thus the clinical application in pain management. However, the mid- or long-term follow-up effect was not strong enough to be observed in specific pain conditions. These null results may be associated with overall short treatment durations (average 11.1 treatment sessions in mid-term follow-up studies and 11.7 sessions in long-term follow-up studies). Although these treatment durations are comparable to psychological or behavioural therapies for chronic pain [56], they would be considered short relative to rTMS for depression, which typically comprises 20–30 treatment sessions delivered over 4–6 weeks [52,64]. It is possible that the short treatment length may be limiting the degree of response [30]. Moreover, a 'maintenance' phase of rTMS protocols may help to create long-lasting analgesia [46]. In rTMS protocols for pain management, an 'induction' phase of daily (or similar) sessions has been recommended, followed by a 'maintenance' phase of less frequent sessions [46]. Indeed, a recent multicentre trial revealed that four weekly rTMS sessions over the M1 generated significant follow-up effect at four weeks whereby induction sessions (five daily sessions) did not [36]. These studies highlight the significance of

maintaining rTMS analgesia and it is important for future studies to investigate the long-lasting analgesia of DLPFC-rTMS by introducing maintaining sessions.

We also evaluated the modulating influence of session number and results indicated that session number had no impact on either short-term or mid-term rTMS analgesia. It is widely accepted that repeated sessions are necessary for rTMS to generate accumulated influence in clinical settings [46]. It is believed that in the motor cortex pain reduction is maximal beyond the time of stimulation and could last for days following a single rTMS session compared to sham stimulation [42]. It is worth noting that nearly all of the included studies delivered multiple sessions. Moreover, ten sessions delivered within a two-week period have been used most often [19,27,33,60], which only accounts for the 'induction' phase of rTMS protocols in pain management (see discussions above). Our null findings on total session number may indicate that this factor is less critical in the induction phase relative to delivery of continuously spaced sessions for rTMS to generate long-lasting analgesia. However, further investigations are needed to validate this argument. In prior work, three to five daily sessions per week for two weeks were recommended in the induction stage, whereas it appears important to deliver continuous intermittent sessions to 'responders' for long-term analgesia [46].

It is important to recognise that most of the included studies had a high bias risk for sample size (i.e. mainly around 10 participants in the active arm). As an exception, Sahu and colleagues have

recruited more than forty migraineurs and demonstrated a significant pain relief following DLPFC-rTMS [65]. Overall, this aspect may bias upward the effect size that can be derived from prior research. As a result, we recommend future works considering utilising a more conservative estimate of effect size relative to that derived in this meta-analysis. Based on sample size calculation [28], for a two-group (real and sham) between-factors repetitive (pre to post) design, at least seventeen patients are needed in each arm to achieve a medium effect size (Cohen's  $d = 0.5$ ) with the alpha and Power set to 0.05 and 0.8 respectively.

Interestingly, our data demonstrated a short-term trend decrease ( $p = 0.052$ ) in emotional pain in the active compared to the sham DLPFC (see [Supplementary Material S8](#)). This finding is consistent with the role of the DLPFC in modulating brain regions involved in pain emotions such as the anterior cingulate cortex and insular cortex [17,72]. However, DLPFC-rTMS to reduce emotional dimensions of pain is still unclear in specific chronic pain conditions due to the small number of studies in which it was considered as one of the secondary outcome measures [2,27].

Our data provided latest and novel synthesis on the analgesic efficacy of DLPFC-rTMS compared to existing reviews. There are a number of reviews on TMS analgesia, including those that assess across chronic pain conditions [31,63] and those that assess specific conditions including fibromyalgia [50], spinal cord injury pain [3,61], migraine [40], neuropathic pain [47], and complex regional pain syndrome [59]. Two review articles have specifically examined the analgesic efficacy of DLPFC-rTMS in which unclear evidence was reported [45,63]. However, only a few studies ( $n = 5$ ) were included in the aforementioned studies [45,63]. Here we specifically focussed on the DLPFC target and systematically quantified many more recent studies (17 in total). Our data have further specified the potential analgesic effects by investigating the subgroup effects, potential long-lasting impact as well as covarying influence of session number.

#### *DLPFC-rTMS analgesia in provoked pain*

Provoked pain represents a valuable model to investigate rTMS analgesia in chronic pain as well as the mechanisms of action [23,24,70,71]. Our data indicated decreased provoked pain post high-frequency rTMS over the DLPFC. Moreover, there was no baseline differences in pain experience between the active and sham group in the pooled dataset. Mylius et al. [57] systematically reviewed prior studies of rTMS analgesia in provoked pain and the DLPFC emerged as a promising target for pain management. Our data further confirm this argument by providing direct quantitative synthesis with latest evidence [24,26,66,70]. Aside from acute pain, multiple sessions of DLPFC-rTMS were able to reduce provoked sustained muscle pain and soreness designed to model the development of long-term muscle pain [25,26,66]. Overall, this meta-analysis provides evidence that DLPFC is an effective target in pain management which may have direct relevance for the treatment of chronic pain.

Our provoked pain data also demonstrated a hemispheric difference in rTMS analgesia in which left DLPFC-rTMS produced analgesia whereas stimulation of the right hemisphere had no significant effect. Interestingly, in chronic pain studies, only the left DLPFC has been stimulated, leaving the efficacy of right DLPFC rTMS unknown. More broadly, no study has yet investigated whether the analgesic effect of rTMS in chronic pain is lateralised to left-DLPFC stimulation only. Beyond the prefrontal cortex, high-frequency rTMS to the primary motor cortex contralateral to the pain side is also suggested to have a protective effect on neuropathic pain, but in that context this is simply due to contralateral motor cortical representation of the body [45].

#### *Risk of bias and publication bias*

Risk of bias can affect the results of a meta-analysis. Our data indicated that chronic pain studies tended to be adequate in the generation of random sequence, double-blinding, as well as in the report of outcome data. However, the sample sizes were small, and the follow-up assessments tended to be not long enough. Nonetheless, future studies testing DLPFC-rTMS effects on chronic pain may wish to have larger sample sizes as well as long-term follow-ups. Provoked pain studies had the same potential risk of small samples, alongside inadequate performances in the selection and allocation of participants. Future studies can lower the risks by adopting RCT protocols. Recent TMS reviews have highlighted the need for assessing the consistency in outcome measures across trials [39,63]. Our data have shown a high level of consistency in outcome measures across studies on certain chronic pain conditions (neuropathic pain: pain intensity in all four studies; widespread pain: pain intensity in all five studies; migraine: headache frequency/days in all four studies; postoperative pain: pain intensity in all three studies).

The presence of publication bias may also have an impact on the results of a meta-analysis. Several methods were therefore used to test publication bias in this study. There was no clear evidence of publication bias in the chronic pain dataset. However, we did observe a possibility of publication bias in the provoked pain dataset. It is possible that potential variables were confounding the results, such as the total number of studies and the sample sizes in each study.

#### *Strengths and limitations*

There are some strengths in this study. We presented the latest evidence-based quantitative review of potential analgesic effects of DLPFC-rTMS. These effects were further specified in chronic pain conditions. We also evaluated the modulating impact of session number and timing of measurements. There are also some limitations in this study. Although our data demonstrated significant DLPFC-rTMS analgesia in the mid- and long-term synthesis, these findings were not strong enough to be observed within each chronic pain condition or disorder. The number of studies is small in each category and these findings need to be validated in future trials. There is no consensus in the definition of long-lasting rTMS analgesia. We were therefore consistent with the assessment of long-lasting analgesia in a recent Cochrane review [63] and averaged data points in a certain time period. We examined the modulating impact of session number, but other potential modulating factors (e.g. stimulation intensity) were not systematically assessed due to the small number of studies. Our data indicated a positive correlation between the short- and mid-term analgesia. However, this was based on the overall effect size across studies, rather than individual patient response from short- to mid-term evaluation. Findings at the individual level would provide stronger evidence on the continuation, or relationship, of analgesic effects from short- to long-term. In addition, navigation systems were barely used to locate the DLPFC in the included studies. Aside from offering increased targeting accuracy, another advantage of MRI-based neuronavigation, is that it can be used to retrospectively identify disease relevant brain connections and networks mediating positive treatment outcomes, such that these can be prospectively targeted in future work to improve treatment outcomes [13–15]. In the absence of neuronavigation, the Beam F3 method enables the DLPFC to be targeted with high accuracy [5,54]. Lastly, publications from languages other than English were excluded which might have an impact on publication bias.

## Conclusions

High-frequency rTMS over the DLPFC demonstrate a significant short-term analgesia in neuropathic pain conditions. More importantly, there is an overall continuous analgesia lasting up to three months although more studies are needed to validate this effect in each chronic pain conditions. Moreover, we synthesise latest evidence and provide the first quantitative synthesis in which high-frequency rTMS over the DLPFC is able to decrease provoked pain. Overall, our findings suggest that the DLPFC is a promising target in the management of certain chronic pain conditions by means of rTMS.

## Financial disclosures

None declared.

## Declaration of competing interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.07.004>.

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