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Non-invasive motor cortex stimulation effects on quantitative sensory testing (QST) in healthy and chronic pain subjects: a systematic review and meta-analysis

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Abstract

One of the potential mechanisms of motor cortex stimulation by non-invasive brain stimulation (NIBS) effects on pain is through the restoration of the defective endogenous inhibitory pain pathways. However, there is still limited data on quantitative sensory testing (QST), including conditioned pain modulation (CPM), supporting this mechanism. This systematic review and meta-analysis aimed to evaluate the effects of non-invasive motor cortex stimulation on pain perception as indexed by changes in QST outcomes. Database searches were conducted until July 2019 to included randomized controlled trials that performed sham-controlled NIBS on the motor cortex in either healthy and/or pain population and assessed the QST and CPM. Quality of studies was assessed through the Cochrane tool. We calculated the Hedge's effect sizes of QST and CPM outcomes, their 95% confidence intervals (95% CI) and performed random-effects meta-analyses. Thirty-eight studies were included (1178 participants). We found significant increases of pain

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threshold in healthy subjects (ES=0.16, 95% CI=0.02 to 0.31, $I^2=22.2\%$) and pain population (ES=0.48, 95% CI=0.15 to 0.80, $I^2=68.8\%$); and homogeneous higher CPM effect (pain ratings reduction) in healthy subjects (ES=-0.39, 95% CI=-0.64 to -0.14, $I^2=17\%$) and pain population (ES=-0.35, 95% CI=-0.60 to -0.11, $I^2=0\%$) in active NIBs group compared with sham. These results support the idea of top-down modulation of endogenous pain pathways by motor cortex stimulation as one of the main mechanisms of pain reduction assessed by QST, which could be a useful predictive and prognostic biomarker for chronic pain personalized treatment with NIBS.

Introduction

Pain perception is a complex process influenced by sensory, cognitive, and emotional dimensions [72]; the multidimensional nature of pain requires different measurement approaches to understand the pathophysiology underlying pain syndromes [44]. Quantitative sensory testing (QST) assessments have been used to objectively measure pain in both healthy and pain populations [44]. Static QST – measured by pain threshold (PT) – assess the basal state of the nociceptive system, while dynamic QST evaluates the pain processing system: i) pain facilitation – measured by temporal summation (TS) – and pain inhibitory systems (the endogenous pain inhibitory system) – assessed by conditioned pain modulation (CPM) protocols [5; 51]. This latest evaluates the phenomena known as “pain inhibits pain” by testing the functioning and integrity of the endogenous descending inhibitory pathways [7]. The changes on QST measurements are useful to understand pain processes in healthy subjects, and they could be applied in pain populations as diagnostic biomarkers, and as a predictor of responsiveness to analgesic treatments [68].

Non-invasive motor cortex stimulation has shown an effect on pain facilitatory and inhibitory systems due to the activation of subcortical structures related to the endogenous pain modulation system as thalamus, cingulate gyrus, periaqueductal gray, subnucleus reticularis dorsalis (SRD), among others [30; 31]. Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) might restore the balance in the endogenous pain pathways as a top-down regulation, through subcortical nuclei such as thalamic nuclei and SRD) while preventing or reversing maladaptive plasticity leading to a decrease of pain perception [16]. tDCS delivers a subthreshold current from anode to cathode by two electrodes over the scalp, whereas rTMS uses magnetic fields in order to induce electrical changes in the brain activity [16]. Both of them are non-invasive brain stimulation (NIBS) techniques that have shown some efficacy in healthy subjects and pain-related syndromes [45; 46; 61]. Hence, these tools are appropriate options to modulate the pain perception processes reflected on QST changes. The NIBS effects on CPM can be related to endogenous pain pathways modulation [24], which can be used to understand this system disruption on different chronic pain conditions better and clarify the NIBS mechanism of action. Moreover, their effects on PT and TS can give us a better understanding of its impact on peripheral and central sensitization [70].

Even though the utility that would have to understand the NIBS effects on pain processes indexed by QST and that non-invasive motor cortex stimulation has been extensively studied in chronic pain [2; 27; 61], the knowledge on their effects on QST is still limited; especially

the pooled effect of two commonly used techniques for motor cortex stimulation (TDCS and rTMS) and in healthy and in subjects with pain. Thus, with this systematic review and meta-analysis, we aim to evaluate the effects that previous studies have shown of motor cortex stimulation on pain perception processes indexed by changes in static and dynamic QST outcomes, including PT, TS, and CPM.

Methods

A systematic review of the literature and meta-analysis was conducted following the recommendation of the Cochrane handbook [33], including the PRISMA guidelines (online supplementary material 1)[54].

Literature search and study selection

We searched in MEDLINE, EMBASE, Web of Science, Lilacs and Cochrane Central until July 31st, 2019 using a search strategy with the following search terms: “noninvasive brain stimulation” OR “transcranial magnetic stimulation” OR “transcranial direct current stimulation” AND “Diffuse Noxious Inhibitory Control” OR “Pain Threshold”. The full research strategy is shown in online supplementary Material 2. Duplicates were eliminated before selection. Previous to the title and abstract selection, two experienced reviewers (KPB and AC-R) agreed on a standard approach. Two random samples of fifty search results were pre-selected for the training and standardization process. After pre-selecting the articles based on the title and abstract, four reviewers (LC, ML, PM, and SG-L) selected the same articles for calibration purposes. Subsequently, we calculated the inter-rater agreement and kappa estimator, aiming for an inter-rater agreement of at least 90% (online supplementary material 3). Afterward, the citations were independently screened by the four reviewers (LC, ML, PM, and SG-L) in terms of titles and abstracts. Discrepancies between reviewers were resolved by a fifth reviewer (AC-R). Then, the four main reviewers independently assessed the full text of selected studies, and again the fifth reviewer resolved discrepancies.

Eligibility criteria

We searched for full-text articles restricted to English. Included articles had to have: a) enrolled either healthy subject and/or with a pain condition; b) performed NIBS such as tDCS or rTMS on the motor cortex compared to their respective sham; c) assessed the quantitative sensory testing including pressure (PPT), heat (HPT), cold (CPT) or electrical (EPT) pain thresholds; CPM; and TS; and d) designed as randomized controlled trials (RCTs), included parallel-group, crossover designs, and pilot studies.

Data extraction

In total, eight reviewers participated in the extraction process. Two of them (AC-R and SG-L) developed the extraction matrix. The extraction was performed in pairs (PM and ML; JB and SG-L; MG and LC) that extracted the same articles independently. All discrepancies between reviewers were solved by a seventh reviewer (KP-B). For each study, we extracted in a standardized spreadsheet the following: i) participant characteristics (sample size, condition, age, gender, drop-outs), ii) NIBS intervention protocol characteristics (stimulated area, electrode size, current intensity, pulse frequency, number of sessions, and session

duration), and iii) outcomes of interest (pain threshold, CPM, or/and Temporal summation). In case of missing or unclear information, we requested by email the values from the authors. We used WebPlotDigitizer v.3.11[66] to extract data from relevant graphs, and if a study only reported postintervention data, we determined whether to include the data in the analysis by studying baseline comparability on the graphs. If we were unable to contact the authors or extract the data graphically, we excluded the study from the quantitative analysis. Some of the included studies measured multiple variables to assess the QST outcome within-subjects (more than one body location for PT assessments – left arm, right arm, left leg, etc.). We were aware that computing different effect sizes for the same sample or overlapping sets of participants and treating them as completely unrelated effect sizes violate the basic assumptions of the traditional meta-analytic method. In those cases, we calculated a weight mean of the multiple variables to compute a unique measurement of the outcome of interest, in order not to lose relevant information.

Static QST outcomes

- a. PT: Corresponded to the smallest stimulus that was reported by subjects as painful. This could be measured by the different stimuli such as pressure with an algometer, heat, cold, or electrical stimulus. It was reported a lower pain threshold in different chronic pain conditions [44; 68]. We extracted and analyzed changes in stimulus units (kPA, centigrade degrees, etc.) and Standard deviation (SD) as a measurement of PT changes [59; 60].

Dynamic QST outcomes

- a. TS: This protocol measured pain facilitation and was calculated as the difference between the pain rating after series of stimuli and the rating after a single stimulus after the series, expecting more pain after the application of stimuli in series [44; 68]. We extracted and analyzed changes in pain ratings and SD as a measurement of TS effect [59; 60]
- b. CPM: This protocol involved two conditions, the test stimulus (painful sensation) and the conditioned stimulus (cold water sensation). This protocol could be measured by the difference between pain threshold or pain rating after the test stimulus and after the conditioned stimulus. In healthy patients, we expected a decrease in pain score after the conditioned stimulus; however, in pain conditions, as the endogenous pain modulation system was impaired, higher pain scores would be perceived after the conditioned stimulus [58]. We extracted and analyzed changes in pain ratings and SD as a measurement of CPM effect [59; 60]

Risk of bias assessment

The risk of bias of the selected studies was evaluated by two reviewers (AC-R and SG-L) using Cochrane Risk of Bias Scale for RCTs [33]. In order to classify in the low, high, and unclear risk of bias, we followed the instructions stated in the Cochrane handbook for systematic reviews of interventions for RCTs [33]. In the event of any discrepancies between the two reviewers, a consensus was attempted to be reached by discussion. If a full

consensus could not be reached between the two reviewers after an exhaustive discussion, the opinion of a third reviewer was obtained (KP-B), and the proceeding majority consensus was taken.

Data Synthesis

The RCTs were presented separately according to the condition (healthy versus pain population), given the differences in the pain perception processes between these two groups. The QST outcomes were categorized according to the type of stimulation (tDCS or rTMS). Then, the effect sizes of QST outcomes and their 95% confidence intervals (95% CI) were calculated, and an exploratory meta-analysis was performed. Although with-in the treatment categories were interventions with different parameters, we decided to do an exploratory synthesis to compare across the spectrum of the available non-invasive motor cortex stimulation techniques. We adjusted Cohen's *d* to Hedge's *g* by applying a correction factor as Cohen's *d* has a slight bias to overestimate in small sample sizes. We assessed heterogeneity using an I^2 statistical, and we considered low heterogeneity when $I^2 < 40\%$ [33]. We considered it appropriate to use random-effects models due to the overall heterogeneity evaluation (in population and intervention) [23]. Moreover, we performed subgroup analysis, sensitivity analysis, and meta-regression as further evaluations of sources of heterogeneity. The publication bias was evaluated visual assessment (funnel plot) and by the Egger test. The data were analyzed using Stata v15.1 software (StataCorp LLC).

RESULTS

Overview

The search retrieved 5656 results; after removing duplicates, 4032 titles and abstracts were screened, and of these, 3877 were excluded. One hundred fifty-five studies were evaluated in full-text, 117 studies were excluded (online supplementary material 4). And finally, 38 studies were included [1; 6; 8-12; 14; 15; 18; 20-22; 25; 26; 32; 34; 36-38; 40; 41; 43; 49; 52; 53; 55-57; 62; 64; 65; 69; 73; 74; 76; 78], reporting 71 comparisons (1178 participants). A flow diagram of the search process is presented in Figure 1.

Regarding NIBS, 28 studies evaluated the effects of tDCS and 10 of rTMS. From them, nine studies (23.7%) assessed other interventions together with NIBS. Three evaluated the effects of exercise (7.6%), while the other six evaluated melatonin, intramuscular electrical stimulation, naloxone, ketamine, and remifentanyl (2.6% each). In terms of QST outcomes data, 33 studies reported PT: 20 in the healthy population (35 comparisons, 629 subjects) and 13 in pain conditions (17 comparisons, 462 patients); two reported TS (three comparisons, 38 patients); and 13 reported CPM outcomes: seven in the healthy population (ten comparisons, 169 subjects) and six in pain conditions (eight comparisons, 239 patients); and 11 reported more than one outcome. Besides, 23 (60.5%) performed the QST protocols in upper limbs, seven (18.4%) in lower limbs, two (5.3%) in both upper and lower, and six (15.8%) in other body areas. The included pain populations [1; 6; 12; 15; 20; 22; 37; 40; 41; 49; 52; 53; 62; 65; 69; 76] were heterogeneous including fibromyalgia four (25%), knee osteoarthritis three (18.8%), peripheral neuropathy two (12.5%), temporomandibular disorder one (6.3%), post-stroke pain one (6.3%), myofascial pain one (6.3%), postoperative

pain one (6.3%), and others three (18.8%) studies. Only seven (43.8%) reported pain duration and two (12.5%) sensory profile. A qualitative summary of included articles is provided in Tables 1 and 2.

Effect on outcomes

Pain threshold—We analyzed 20 RCTs [8-11; 14; 17; 18; 21; 22; 25; 26; 32; 34; 36; 38; 43; 55-57; 64; 73; 74; 78] (35 comparisons) with healthy population (n=629) (Figure 2a) to evaluate the NIBs effects on PT. We found a significant and homogenous PT increase (ES: 0.16, 95% CI:0.02 to 0.31; I²=22.2%) in favor to NIBs intervention compared to sham. When analyzing techniques separately, results were not significant, the 12 tDCS studies results in an effect size of 0.14 (95% CI:−0.03 to 0.31), while for the eight rTMS studies, the pooled effect size was 0.24 (95% CI:−0.03 to 0.50), and the combination of both (tDCS + rTMS) effect was −0.09 (95% CI:−0.55 to 0.38). No significant difference was found in the heterogeneity test between sub-groups (p=0.426).

Besides, we evaluated the PT changes due to NIBs interventions in pain population (n=492), from 14 RCTs [1; 6; 12; 15; 20; 37; 40; 41; 49; 52; 53; 62; 69; 76] (18 comparisons) (Figure 2b). We found a significant PT increase in favor to NIBs (ES: 0.48, 95% CI:0.15 to 0.89; I²=68.8%). However, we did not find differences (p=0.790) among tDCS (ES: 0.47, 95% CI:0.13 to 0.82) and rTMS effects (ES: 0.57, 95% CI:−0.12 to 1.25).

Conditioned pain modulation—We analyzed seven RCTs [11; 14; 21; 25; 26; 55; 64] (10 comparisons) with healthy population (n=303) (Figure 3a) that evaluate the NIBs effects on CPM effect (pain ratings reduction). We found a significant and homogenous higher CPM effect (ES: −0.39, 95% CI:−0.64 to −0.14; I²=17%) in favor to NIBs intervention compared to sham. The tDCS effect size was significant (ES: −0.50, 95% CI:−0.85 to −0.15); while the rTMS was not (ES: −0.20, 95% CI:−0.57 to 0.17). No significant difference was found in the heterogeneity test between sub-groups (p=0.195). Besides, we evaluated the CPM effects due to NIBs interventions in pain population (n=184), from six RCTs [1; 15; 20; 22; 65; 76] (eight comparisons) (Figure 3b) compared with healthy subjects, we found a significant and homogeneous CPM effect in favor to NIBs (ES: −0.35, 95% CI:−0.60 to −0.11; I²=0%). We did not find differences (p=0.266) among tDCS (ES: −0.33, 95% CI:−0.58 to −0.07) and rTMS effects (ES: −0.35, 95% CI:−0.60 to −0.11).

Temporal summation—We could not perform a meta-analysis due to lack of combinable data, from the 2 included studies [34; 49], one included a healthy population [34] and the other chronic pain patients [49].

Risk of bias assessment

Most of the selected articles (44.74%) had low risks of bias in several categories. However, most of them (60.53%) had problems when reporting randomization sequence generation and allocation concealment, even though they specified the allocation of the subjects was done by a random method, they did not specify how the randomization sequence was generated. Besides, most of them (73.68%) did not specify how they achieved the allocation concealment; therefore, they were classified as unclear regarding this item. Furthermore,

more than half of the selected articles (55.26%) presented a high risk of bias in the blinding component, as most of them did not blind the researcher performing the intervention. See Figure 4.

Subgroup, sensitivity, and meta-regression analysis

The sensitivity analysis showed that results did not change even if the study with the largest effect was removed from the analysis and also when we excluded one study at a time. Moreover, after subgroup analysis and meta-regression, the risk of bias level, the combination with other interventions, the number of sessions (less or more than one session), stimulation polarity (excitatory versus inhibitory) and type of stimulus (pressure, heat, cold or electrical stimulus) were not important sources of heterogeneity in the CPM analysis (online supplementary material 5). However, we identified substantial sources of heterogeneity ($I^2 > 60\%$) in the PT analysis (the use of NIBS combined with other interventions, the stimulation polarity [excitatory vs. inhibitory stimulation], and type of stimulus [pressure, cold, heat stimulus]). We evaluated the PT location (upper- and lower-limb) as a source of heterogeneity, we found, in the healthy population, a higher pooled effect size from studies with a lower limb as a location for the PT assessment compared with upper-limb location; however, we did not find this difference among the studies with pain population (online supplementary 5).

Also, we performed a subgroup analysis by disease with 2 or more included studies (Knee OA and Fibromyalgia), we did not find any significant difference between conditions (online supplementary 5). Finally, we performed a subgroup analysis by conditions categorized by the underlying mechanisms: neuropathic pain states (peripheral neuropathy and poststroke pain), nociceptive states (osteoarthritis and low back pain), and nociplastic states (fibromyalgia); we found no difference in the CPM response between nociceptive and nociplastic states, but the PT increase was stronger in the nociplastic states (ES: 0.81, 95% CI: -0.01 to 1.63) compared with neuropathic and nociceptive (ES: 0.15, 95% CI: -0.24 to 0.54; ES: 0.38, 95% CI: -0.01 to 0.78; respectively)(online supplementary 5).

Publication bias

We did not find publication bias in the PT and CPM meta-analysis as indexed by symmetrical funnel plots and non-significant egger test analysis (online supplementary material 6)

DISCUSSION

Summary of results

We included 38 RCTs that have evaluated the effects of Non-invasive motor cortex stimulation on QST outcomes in healthy and pain subjects. The included studies were heterogeneous, had small sample sizes, and presented a low to moderate risk of bias with no publication bias. We found a significant increase in pain threshold and homogenous higher CPM effect (small to moderate effect size) in healthy subjects and pain disorders, in favor of NIBs group compared with sham. These effects seem robust and consistent since all

sensitivity analyses, subgroup analyses, and meta-regression could not identify any critical between-studies source of heterogeneity.

Motor cortex stimulation effects on pain threshold

Our meta-analysis found a small to moderate pooled effect of motor cortex stimulation by tDCS and rTMS on pain thresholds, these results are consistent with one of the postulated mechanisms of action of NIBs: modulation of pain by activation of subcortical structures related to the endogenous pain modulation system as the thalamus, cingulate gyrus, periaqueductal gray, subnucleus reticularis dorsalis, among others [30; 31]. This endogenous pain modulation system also could affect the pain threshold perception.

Regarding the type of stimuli to evaluate the PT changes, we included all the reported categories such as heat, cold, electrical, and mechanical pain stimulus. We did not find significant differences among the type of stimuli, which are consistent with previous literature [48]; this would be useful for future design experiments and to increase the comparability of different PT protocols.

Previous systematic reviews and meta-analysis [75] evaluated the effect of anodal tDCS on PT in healthy subjects compared to sham intervention. Similar to our results, they found a significant increase of PT (MD 12.57, 95% CI: 6.29 to 18.85), however, they did not report the results using a standardized effect size, which hinders the comparison with our findings.

Our findings by population show that both healthy and pain populations increased their PT values; however, we found higher increases in the pain population, these results could be explained due to a ceiling effect. In other words, pain neurocircuitry dysfunction provides a more extensive range of modulation of this system as there is a limit for the enhancement of the endogenous inhibitory pain system. This supports that non-invasive motor cortex stimulation is a brain-state dependent technique [35] with a high potential to modulate pain, especially in dysfunctional and maladaptive pain networks in chronic pain patients. However, due to the heterogeneous included pain populations, further studies are needed to elucidate the effects in specific pain conditions.

Motor cortex stimulation effects on conditioned pain modulation

In this metanalysis, both techniques (tDCS and rTMS) showed a similar direction effect in CPM effects both in health and in pain populations, although they have different mechanisms of action. In contrast to the PT results by population, the CPM effect was similar in both suggesting a higher neuroplasticity potential of the descending inhibitory pathways related to CPM effects and potentially less ceiling effect. It may also indicate that CPM is a better marker to address, understand and measure the mechanistic effects of motor cortex stimulation.

We hypothesize that non-invasive motor cortex stimulation could have modulated motor cortex excitability restoring the inhibitory effects on pain circuits, as seen in neuropathic pain and other types of pain [3; 47]. In fact, lack of inhibition by the motor cortex leads to decreased endogenous pain inhibitory pathways [13; 60]. This fact is supported by some studies that showed CPM as a possible predictor of chronic pain development [39; 60]. Also,

studies advocate that CPM could be used as a possible prognosis factor for pain sensitized patients and, therefore, could be used as a predictor of higher pain levels experience. One idea is also to explore CPM as a possible prognostic variable for tDCS and rTMS, as recently proposed in another trial [71]. Also, one possibility is also to use motor cortex stimulation to enhance the endogenous pain inhibitory system as to “prevent” pain in a healthy population exposed to a nociceptive stimulus [4; 28].

More well-powered studies are needed to validate the CPM biomarker as a predictor of motor cortex stimulation effects in pain populations and to elucidate the relationship of CPM effect and pain levels in specific chronic pain populations.

Heterogeneity of methods of QST and NIBS protocols

The behavioral protocols change across the studies, measuring different variables of pain processing with different QST protocols; almost half of the studies used pressure pain threshold, while others used heat, cold, or electric stimuli. On the other hand, cold water stimuli were the most frequently used as the conditioning stimulus in CPM. We found that the type stimulus in the PT protocols is an important source of heterogeneity in the meta-analysis of pain populations, however, the pooled effect sizes are similar among those subgroups (online supplementary 5). In this context, the different QST protocols should not be a source of heterogeneity. Additionally, different anatomical parts as the forearm, hand, feet, knee, among others, were used for the QST assessment. Although the healthy population should not be affected, in different pain conditions, these different locations would be related to peripheral and central sensitization. Therefore, the information of these results might contribute to the heterogeneity and accuracy of our findings.

Another factor of heterogeneity of significant value is the difference in the stimulation parameters. Even though we selected studies that had investigated the effects of the stimulation on the same cortical area, there are known differences between the underlying mechanisms of tDCS and rTMS and the number of sessions. However, we decided to do an exploratory pooled analysis [42; 50][43; 51][43; 51][43; 51][44; 52][44; 52][43; 50][43; 50][43; 50][42; 49][42; 49] because most of the included studies used an excitatory protocol over the motor cortex.

Additionally, the statistical approach to analyze the QST outcomes (e.g. proportion vs absolute numbers changes), the presence or not of follow-up, and quantity and duration variation of QST assessments across all the included studies (see table 1) highlight the need of acquiring more standardized data for a more precise QST outcomes changes evaluation.

tDCS and rTMS mechanisms to modulate QST

The quantitative sensory testing is a more objective measurement of pain perception processes [67]. It includes different tasks as sensory pain testing, pain threshold, conditioned pain modulation and temporal summation. These different measurements assess peripheral and central sensitization. The pain signal arrives in the dorsal horn and then crosses the midline just in front of the anterior commissure and sent the signal up by the spinothalamic tract to the thalamus and then to the sensory cortex [77]. Once pain signals arrive in the sensory area, it is processed and interpreted as a pain threshold [77]. Then, the signal sends

feedback via supraspinal structures as the primary motor cortex, sensory cortex, thalamus, and other structures as the cingulate gyrus, periaqueductal gyrus, rostral ventromedial medulla, subnucleus reticularis dorsalis and spinal cord, in order to enhance the endogenous pain modulation system decreasing the pain perception. In a healthy population, this mechanism is believed to contrast the pain stimulus [77]. However, in chronic pain, there is a disruption in this communication, decreasing the pain threshold and increasing pain perception [63]. This effect disrupts the endogenous pain pathway that thus can be measured with the CPM [58].

It is still unclear whether the differential mechanism of rTMS compared to tDCS on the motor cortex would represent a different mechanism of endogenous pain inhibitory system modulation though the final effect is similar. tDCS delivers a continuous transcranial subthreshold current inducing long-lasting modulation of the neuronal activity by mechanisms of long-term potentiation (LTP) and long-term depression (LTD) and therefore changing synaptic plasticity mechanisms [19; 29]. On the other hand, rTMS induces an action potential, and thus a response of the neuronal membrane and thereby, different frequencies of pulses can enhance or inhibit excitability in the targeted region [29] although some differences in the mechanisms, both of them have shown capability of inducing long term effects related to neuroplastic mechanisms of pain [29]. The rationale behind using motor cortex stimulation relies on the ability to potentiate the endogenous pain modulation system. Motor cortex stimulation ultimately modulates other circuits such as the thalamus and other structures as the sensory cortex, cingulate gyrus, periaqueductal gyrus, and subnuclear reticularis dorsalis. These structures control the inhibition/facilitation of pain perception and, ultimately, the PT and CPM effects. Hence, these techniques have the capacity to modulate these structures by a top-down modulation in healthy and pain conditions indexed by QST outcomes changes.

The potential therapeutic implications of NIBS are plausible, specially using motor cortex stimulation, however these results seem brain-state dependent [35] and possible disease-related, even though we reported here a possible larger modulation of PT in nociplastic pain syndromes, such as fibromyalgia, the small sample size and higher heterogeneity among the current evidence difficult to draw a definitive conclusion.

Limitations

Some factors may limit these results and thus should be interpreted with caution. One crucial factor, as mentioned, is the heterogeneity of the QST measurement and the NIBS protocols. Chronic pain patients presented different syndromes across the studies that result in different mechanisms of pain and differential responsiveness to the stimulation. To address this problem, we decided to divide the results in healthy, and pain conditions as combining the pain population with healthy subjects could bias the results. Another limitation is the inclusion of pilot studies and not adequately justified sample size calculation by a statistical power analysis. Finally, as shown by Cochrane risk bias indexes, some of the studies included did not describe the randomization accurately and/or blinding procedures, thus leading to potentially lower quality of the data included in the analysis. However, the comprehensive and systematic methodology used in this study assures the high-quality

summary of all the studies to date in the field and motivates the conduct of future research with improved design.

Conclusion

This meta-analysis suggests a significant small to moderate effect of non-invasive motor cortex stimulation on PT and CPM in healthy and pain populations. This supports the idea of top-down modulation of endogenous pain pathways by motor cortex stimulation as one of their primary mechanism of action on pain. These biomarkers could be useful in the treatment follow-up of chronic pain patients. However, validation requires further investigation under strict methodological settings, and with an evaluation of specific chronic pain populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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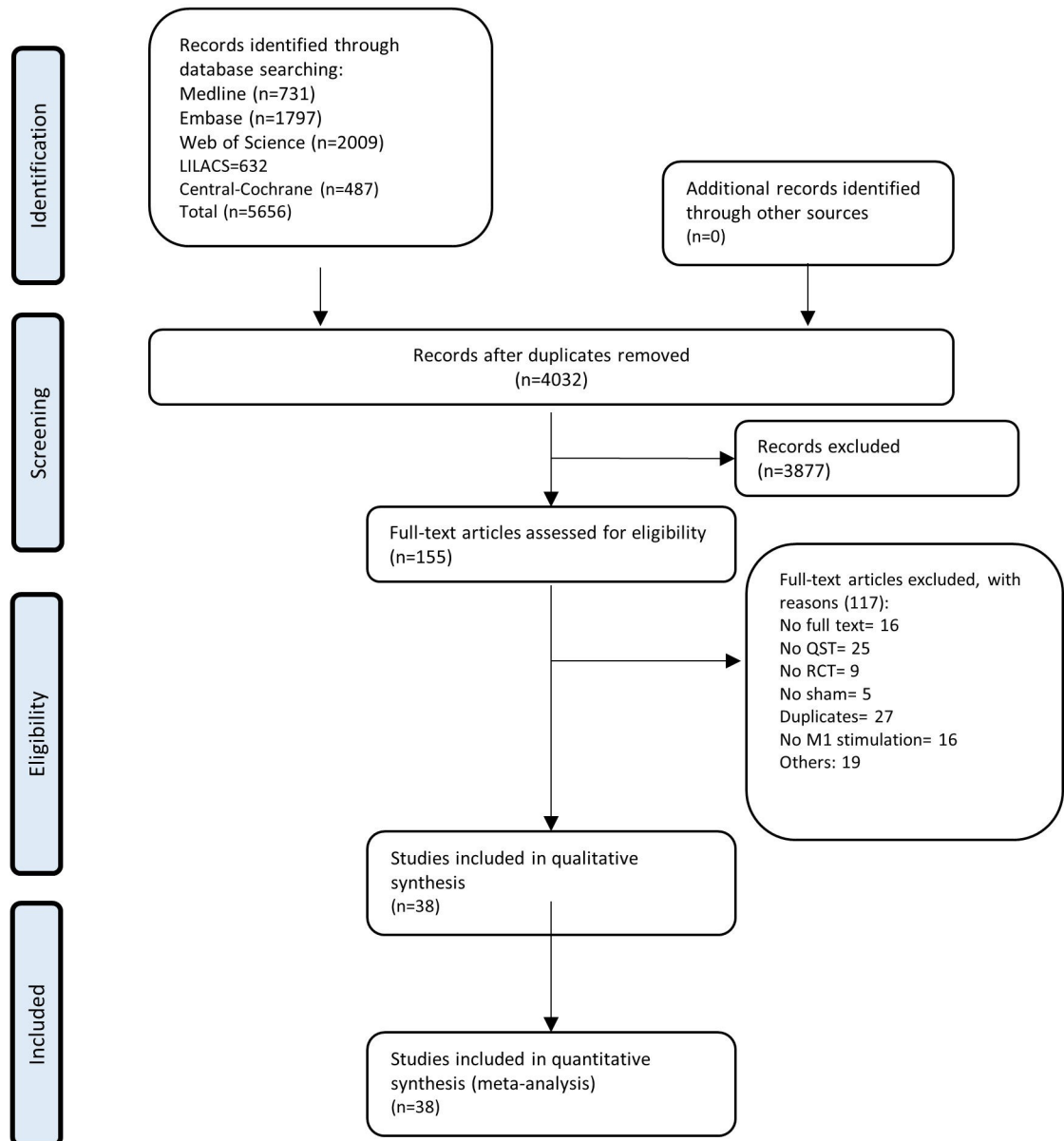


Figure 1.
Flow diagram of the search and selection process.

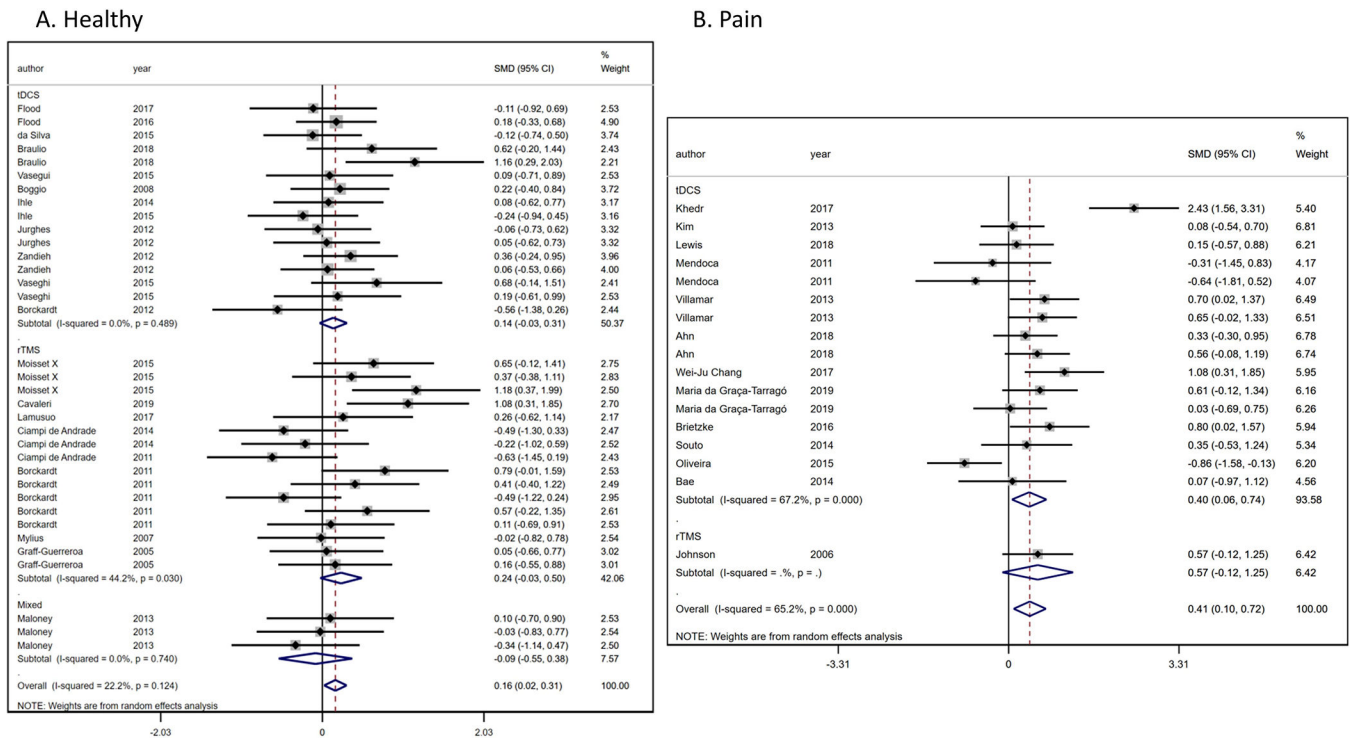


Figure 2. Forest-plot of Pain threshold in A) healthy population and B) pain conditions.

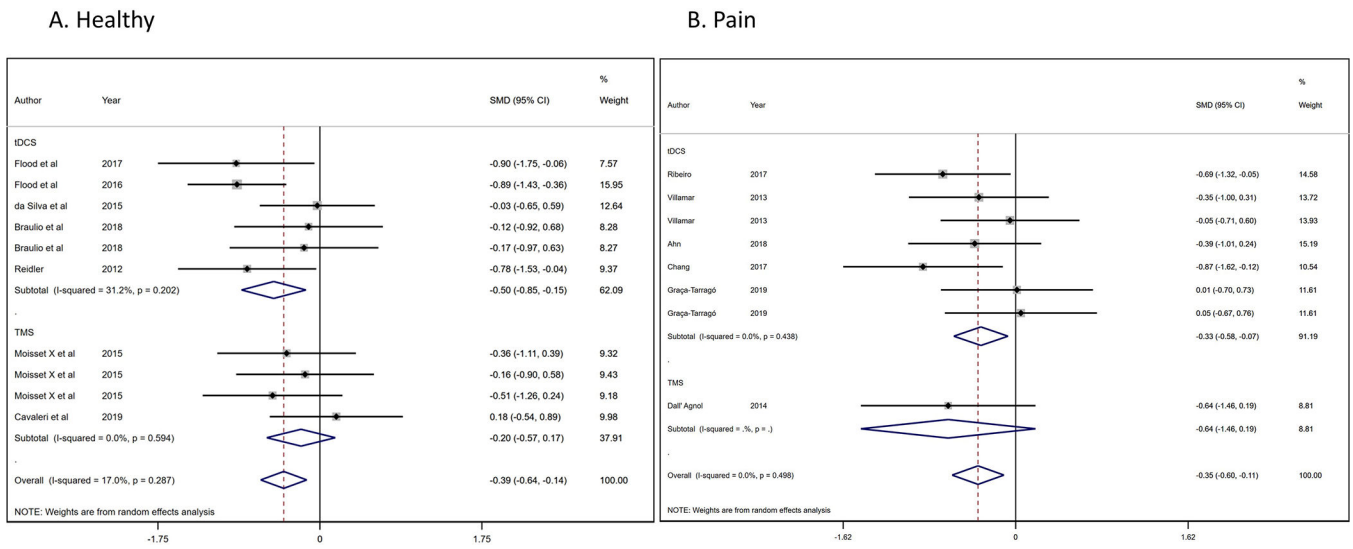


Figure 3. Forest-plot of conditioned pain modulation in A) pain conditions and B) healthy population.

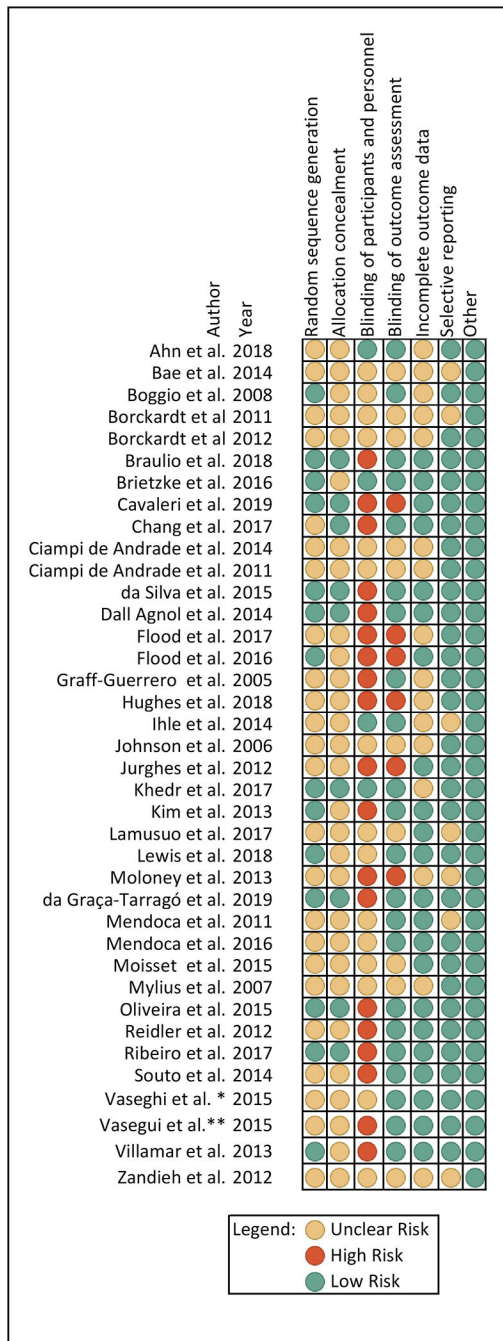


Figure 4.
Risk of bias

General information from the tDCS studies included in the meta-analysis

Author	Country	Design	Condition	Pain duration	Sensory Profile For Patient N (%)	Participants	Anode	Cathode	Motor cortex stimulation parameters				QST protocol			
									Intensity (mA), Stim duration (cm2), duration (min)	Number of sessions	Device	Concomitant therapy	Pain threshold	TS	CPM	Device
Mendoza et al. (2011)	Brazil	Parallel	Fibromyalgia	Not reported	Not reported	30 participants: A. 6 (83.4% females) Mean age: 41.8 yrs. B. 6 participants in c-tDCS SO (100% females) Mean age: 43.5 yrs. C. 6 participants in a-tDCS MI (83.4% females) Mean age: 44.5 yrs. D. 6 participants in a-tDCS SO (100% female) Mean age: 42.6 yrs. E. 6 participants in s-tDCS (100% female) Mean age: 43.5 yrs	Cervical and thoracic spine (between the scapulas)	C3	2 mA, 16 cm2 on cranially sponges; 80 cm2 on extracranial sponges., 20 min	1	Universal Pulse generator (941 NEMESYS, Quark Medical Products, Brazil)	No	PPT was assessed by a pressure algometer in the 18 pre-established points for the diagnosis of fibromyalgia			Pressure algometer (Pain Diagnostics & Thermographics Corporation, Great Neck, NY)
Kim et al. (2013)	Korea	Parallel	Painful diabetic polyneuropathy	2-5 years; 29 (48.3%) patients >5 years 31 (61.7%)	Not reported	60 participants: A. 20 participants in a-tDCS MI (55% females) Mean age: 59.6 yrs. B. 20 participants in s-tDCS (60% females). Mean age: 61.6 yrs. C. 20 participants in a-tDCS DLPTC (60% females). Mean age: 63.5	C3	SO	2 mA, 25 cm2, 20 min	5	Phosor II PM850 anodal tDCS was used (IOMED, Salt Lake City, UT, USA)	No	PPT was measured by an algometer over the more painful sole region			Commander algometer (TECH Medical Industries, Salt Lake City, UT, USA)
Villamar et al. (2013)	US	Crossover	Fibromyalgia	10.7 years (with Fibromyalgia)	Not reported	18 participants (83% females) Mean age: 50.3 yrs. A. a-HD-tDCS: B. c-HD-tDCS: C. s-HD-tDCS	C3	(Cz, F3, T7, P3)	2 mA, 20 min	1	Model 1224-B; Soterix Medical Inc	No	PPT was measured by a pressure algometer over 1) the area of the forearm 2 cm distal to the lateral epicondyle; 2) the suprapatellar muscle; 3) the occiput	Difference of PPT before and after the immersion of the left hand in cold water (10-12 C)		Commander Algometer (TECH Medical, Salt Lake City, UT)
Bae et al. (2014)	Korea	Parallel	Central post stroke pain	Not reported	Tingling 7 (50) Burning 4 (28.6) Numbness 1 (7.1)	14 participants: A. 7 participants in a-tDCS (43 % females). Mean age: 51.1. B. 7 participants in s-tDCS (57 % females). Mean age: 52.3.	C3/C4 contralateral to paralyzed side	SO	2 mA, 35 cm2, 20 min	9	Phosor II AutoModel PM850; USA	No	Cold and heat pain over the thenar area of hand			Thermal sensory analyzer (TSA-II, MEDOC Co. Ltd., Israel)
Souto et al. (2014)	Brazil	Parallel	Pain in HTLV-1	Not reported	Neuropathic pain 13 (65) Noceptive 7 (35)	20 participants: A. 10 participants in a-tDCS (80% females) Mean age: 47.8 yrs. B. 10 participants in s-tDCS (70% female). Mean age: 36.1	C3	SO	2 mA, 25 cm2, 20 min	5	Electro-stimulator (Striat, Ibmamed, Brazil)	No	PPT was assessed by a pressure algometer over the tibial tuberosity			Pressure algometer (Pain Diagnostic & Thermographics Great Neck, New York)
Oliveira et al. (2015)	Brazil	Parallel	Temporomandibular disorder	31.75 (SD 20.15) months	Not reported	32 participants: A. 16 participants in a-tDCS and exercises (94% females) Mean age: 23.8 yrs. B. 16 participants in s-tDCS and exercise (88 % females). Mean age: 25.5 yrs.	C3/C4 contralateral to pain	SO	2 mA, 20 min	5	Striat, Ibmamed, Sao Paulo Brazil.	Exercise	PPT was assessed by a pressure algometer over the anterior and posterior regions of the TMJ condyle, suboccipital muscles, upper portion of the trapezius and levator scapulae			Mechanical pressure algometer (Face Dial, Wagner Instruments, Greenwich, CT, USA)
Brietzke et al. (2016)	Brazil	Parallel	Chronic Hepatitis C	Not reported	Not reported	28 participants: A. 14 participants in a-tDCS (35% female) Mean age: 53.86 yrs. B. 14 participants in s-tDCS (14% female) Mean age: 36.57 yrs.	C3	SO	2 mA, 25-35 cm2, 20 min	5	Not specified	No	PPT was measure with an algometer over the right antecubital fossa			Algometer device (TECH Medical Industries, Salt Lake City, UT).

Author	Country	Design	Condition	Pain duration	Sensory Profile Per Patient N (%)	Motor cortex stimulation parameters					QST protocol				
						Anode	Cathode	Intensity (mA), Spange area (cm ²), duration (min)	Number of sessions	Device	Concomitant therapy	Pain threshold	TS	CPM	Device
Mendonça et al. (2016)	Brazil	Parallel	Fibromyalgia	138.5 (SD 95.91)	Not reported	C3	SO right	2mA, 35cm ² , 20min	5	Monophasic current device (DC stimulator, NeuroCom, Germany)	Aerobic exercise	PPT was measured with a pressure algometer over the lateral region of the uppermost portion of the anterior tibialis.			Pressure algometer (Wagner Instruments, USA)
Chang et al. (2017)	Australia	Parallel	Knee Osteoarthritis	8.10 (SD 6.38) years	Not reported	C3/C4 contralateral	SO	1 mA, 35 cm ² , 20 min	16	STIMULATOR, neuroConn, Jümenau, Germany	Exercise	PPT was measured with an algometer the ipsilateral tibialis anterior and ipsilateral extensor carpi radialis longus and eight sites at the worst knee (inferomedial, inferolateral, lateral, superolateral, superior, superomedial, medial, centre of the patella). HPT was measured at the worst knee (medial knee joint line, patella and lateral knee joint line) and both forearm line)	Difference of PPT over the worst knee and the contralateral forearm, before and after heat conditioned stimulation		Hand-held pressure algometer (FORCE-TEN FDx compact digital force gauge, Wagner Instruments, USA). Conditioned pain modulation system (Thermal Sensory Analyser, TSA-2001, Q-Sense-CPM Medoc Ltd, Ramat Yishai, Israel).
Kheidr et al. (2017)	Egypt	Parallel	Fibromyalgia	6.08 (SD 2.59) years	Not reported	C3	Comalateral arm (extra-cephalic)	2 mA, 24 cm ² , 20 min	10	Not specified	No	MPT was measured by an electronic model of Von Frey unit.			Von Frey electronic device (BIO-CIS software)
Ribeiro et al. (2017)	Brazil	Parallel	Chronic foot pain going on hallux valgus surgery	Not reported	Not reported	C3	SO	2 mA, 35 cm ² , 20 min	2	Not specified	No	HPT measure over the ventral mid forearm with a temperature going from 32C to 52 C	Difference of HPT before and after the immersion of dominant hand in cold water (0-1 C)		Computer Pelier-based device thermode (30x30mm)
Ahn et al. (2018)	US	Parallel	Knee Osteoarthritis	Not reported	Not reported	C3/C4 contralateral	SO	2 mA, 35 cm ² , 20 min	5	Soterix Clinical Trial direct current stimulator (Soterix Medical Inc., New York, NY, USA)	No	HPT over the ipsilateral forearm and index knee and PPT over the index knee, quadriceps and trapezius	Determine the changes of the PPT on the trapezius and during the hand in the cold water immersion		Handheld digit pressure algometer (Wagner, Greenwich, CT, USA). Computer-controlled TSA-II Analyzer (Medoc Ltd., Ramat Yishai, Israel)
Lewis et al. (2018)	New Zealand	Parallel	Upper limb neuropathic pain	7.05 (SD 7.94) years	Not reported	C3/C4 contralateral to the affected upper limb	SO	1 mA, 35 cm ² , 20 min	5	HDCell (MagStim Co, UK)	No	PPT measured by a handheld transducer over the abductor pollicis longus and the contralateral tibialis anterior.	Ten standardized punctate pressure algometers applied using 225.1 g of Von Frey filament (1 Hz of frequency) to the abductor pollicis brevis muscle.		Handheld transduce (Somedic, Sweden)
da Graça-Tarragó et al. (2019)	Brazil	Parallel	Knee Osteoarthritis	Not reported	Not reported	C3/C4 contralateral	SO	2 mA, 35 cm ² , 30 min	5	Not specified	No	PPT was assessed by an electronic algometer in the patellar tendon of the leg with the sclerotomal hyperalgesia.	Difference of PPT in the patellar tendon before and after the immersion of the non-dominant hand in cold		Electronic algometer (J-Tech Medical/Industries, Midvale, UT, USA)

Author	Country	Design	Condition	Pain duration	Sensory Profile Per Patient N (%)	Participants	Motor cortex stimulation parameters					QST protocol					
							Anode	Cathode	Intensity (mA), Spange area (cm ²), duration (min)	Number of sessions	Device	Concomitant therapy	Pain threshold	TS	CPM	Device	
Boggio et al. (2008)	Brazil	Crossover	Healthy	-	-	20 participants (65% females). Mean age: 21 yrs.	C3/C4 contralateral	SO	2 mA, 35 cm ² , 30 min	5	Schneider Electronic, Gleichen, Germany	Intramuscular electrical stimulus	Electrical stimulus was applied to the right index finger			Digitimer DS-7A electrical stimulator (Herefordshire, England)	
Borckardt et al. (2012)	US	Parallel	Healthy	-	-	24 participants (75% female). Mean age: 26.58 A. 13 participants with active HDCS. B: 11 participants in the sham group	C4	4.7 cm radius from anode	2 mA, 20 min	1	Not specified	No	HPT and CPT where assessed over the left arm (5 cm from the wrist) and PPT was assessed over the median of the first anestheticrometer over the dorsal surface of the distal phalange of left digit minimi	20 brief suprathreshold thermal stimuli for the first 10 min of the first 30-second wind-up trial were assessed		HPT and CPT via ATS thermode from the Medoc Ad. Medical Systems Ltd, Durham, NC PPT: JTC Life Sciences (Woodland Hills, CA) Electric vonFrey Anesthesiometer with rigid tips. Thermal-wind up: CHEPS thermode from the Medoc Pathway System	
Jürgens et al. (2012)	Germany	Crossover	Healthy	-	-	17 participants (47% females) Mean age: 24.9 yrs. A: a-tDCS, B: c-tDCS, C: s-tDCS	C3	C4	2 mA, 35 cm ² , 15 min	1	Battery-powered constant current stimulator (DC-Stimulator; neuro-Conn, Ilmenau, Germany)	No	PPT was assessed by a pressure gauge device. MPT was assessed by a weighted pinprick stimuli over the libnar part of both hands	10 pinprick stimuli (256 mN, repeated at a 1/s rate within a small area of about 1 cm ²)		Pressure gauge device (FDN100, Wagner Instruments, Greenwich, CT, USA)	
Reidler et al. (2012)	US	Crossover	Healthy	-	-	15 participants (60% females) Mean age: 36.7, Groups: A: a-tDCS, B: s-tDCS	C3	SO	2 mA, 35 cm ² , 20 min	1	DC generator (Activa Dose, Salt LakeCity, UT)	No	PPT was applied over the right libnar region			Commander Algotometer, JTECH Medical, Salt Lake City, UT	
Zandieh et al. (2012)	Iran	Crossover	Healthy	-	-	22 participants (45% females) Mean age: 27.9 yrs. Groups: A: a-tDCS, B: c-tDCS, C: s-tDCS	C3	SO	2 mA, 35 cm ² , 15 min	1	Not specified	No	CPT was assessed on the right hand (up to elbow) with a tank with cold water 3(+0.5) C.			Not specified	
Mohney et al. (2015)	Ireland	Crossover	Healthy	-	-	20 male participants, Mean age: 21.5 yrs. Groups: A: a-tDCS and real rTMS, B: c-tDCS and real rTMS, C: s-tDCS and real rTMS, D: s-tDCS and sham rTMS.	SO	C3	2 mA, 35 cm ² , 15 min 1 mA, 25 cm ² , 10 min	1	tDCS (NewRonika, Italy)	stimulation of C3 with 1 Hz rTMS	CPT and HPT were assessed over the palmar libnar in both sides.			Difference of PPT measured before and after the immersion of the hand into cold water (10–12 C)	TSA-2001 NeuroSentry Analyzer apparatus (Medoc, Ramat Yishai, Israel)
Ihle et al. (2014)	Germany	Crossover	Healthy	-	-	16 participants (62% female) Mean age: 27 yrs. Groups: A: c-tDCS, B: a-tDCS, C: s-tDCS	C3	SO	2 mA, 16 cm ² , 15 min	1	DC-Stimulator (NeuroConn, Ilmenau, Germany)	No	HPT over the right volar forearm			Pellier device (TSAII, Medoc, Israel)	
daSilva et al. (2015)	Brazil	Crossover	Healthy	-	-	20 male participants divided in 3 random sequences of: A: a-tDCS + melatonin, B: s-tDCS + melatonin, C: s-tDCS + placebo. Mean age: 25.37 yrs. Second group: Mean age: 25.67 yrs. Third group: Mean age: 25.60 yrs.	C3	SO	2 mA, 35 cm ² , 20 min	1	Not specified	No	HPT over the mid-forearm (from 32 C to a maximum of 52 C).			Computer Pellier-based device/thermode (30x30 mm)	

Author	Country	Design	Condition	Pain duration	Sensory Profile Per Patient N (%)	Participants	Anode	Cathode	Motor cortex stimulation parameters				QST protocol				
									Intensity (mA), Sponge area (cm ²), duration (min)	Number of sessions	Device	Concomitant therapy	Pain threshold	TS	CPM	Device	
Vasighi et al. (2015)	Australia	Crossover	Healthy	-	-	12 participants (67% females). Mean age: 23.6 yrs. Groups: A, a-tDCS M1, B, c-tDCS S1, C, s-tDCS DLPFC, D, s-tDCS	C3	SO	2 mA, 35 cm ² , 20 min	1	Melatonin	No	PPT was measured by a pressure algometer over the first dorsal interosseous				Pressure algometer (model: FDX 50, Wagner, USA)
Vasighi et al. (2015)	Australia	Crossover	Healthy	-	-	12 participants (67% females). Mean age: 23.6 yrs. Groups: A, a-tDCS M1, B, a-tDCS S1, C, a-tDCS DLPFC, D, s-tDCS, E, no tDCS	C3	SO	0.3 mA, 3 cm ² over the target area and 12 cm ² over the reference, 20 min	1	tDCS stimulator (IntelecAdvancedTherapy System; Chattanooga, Vista, CA, USA)	No	PPT was measured by a pressure algometer over the first dorsal interosseous				Pressure algometer (model: FDX 50, Wagner, USA)
Flood et al. (2016)	Australia	Crossover	Healthy	-	-	30 males. Mean age: 23.9 yrs. A, a-tDCS; B, s-tDCS; HD-tDCS	C3	Cz, F3, T7, F3	2 mA, 20 min	1	A HD-tDCS multi-channel stimulation interface (Model 4X1-C2, Soterix Medical, New York, NY) attached to a 1x1 low-intensity direct current stimulator (Model 1300, Soterix Medical)	No	PPT with a handheld pressure algometer over the index finger.	Difference of PPT over the index finger, before and after the hand immersion in cold water for 4 minutes (2 -1°C)			Algometer (Wagner Force Dial FDK 20, Wagner Instruments, Greenwich, CT)
Flood et al. (2017)	Australia	Crossover	Healthy	-	-	12 males. Mean age: 24.42 yrs.	C3/C4	Cz, F3/F4, T7, P3/P4	2 mA, 20 min	1	A HD-tDCS multi-channel stimulation interface (Model 4X1-C2, Soterix Medical, New York, NY) attached to a 1x1 low-intensity direct current stimulator (Model 1300, Soterix Medical)	No	PPT was assessed by a pressure algometer over the dorsal surface of the index finger of the non-dominant hand	Difference of PPT over the index finger, before and after the cuff occlusion of the non-dominant arm (Conditioned stimulus)			Algometer (Wagner Force Dial FDK 20, Wagner Instruments, Greenwich, CT)
Brullis et al. (2018)	Brazil	Parallel	Healthy	-	-	48 participants: A, 12 male participants in a-tDCS + placebo. Mean age: 26.09 yrs. B, 12 male participants in a-tDCS + remifenamil. Mean age: 27.33 yrs. C, 12 male participants in s-tDCS + placebo. Mean age: 26.09 yrs. D, 12 participants in s-tDCS plus remifenamil. Mean age: 26.08 yrs.	C3	SO	2 mA, 35 cm ² , 20 min	1	Not Specified	No	HPT over the mid-forearm (from 3°C to a maximum of 53°C).	Three identical HPT stimuli of 6 in the NPS hand immerse in cold water for 60 s, after 30 s, the dominant hand in cold water was rated.			Not specified
Hughes et al. (2018)	UK	Crossover	Healthy	-	-	Eight participants (25% female). Mean age: 27.4 yrs.	C3/C4 contralateral to the pain testing	SO	2 mA, 16 cm ² , 20 min	1	Battery driven stimulator neuroConn GmbH, Ilmenau, Germany	No	Electrical stimulus (TS)	Trains of transcutaneous electrical stimulation consisted of five biphasic rectangular pulses at 200 Hz at the Retromalleolar pathways of sural nerve (TS).			Current stimulator (DST7A, Digitimer, UK)

a-tDCS: active-tDCS; AE: Aerobic Exercise; C3:left central lobe position based on 10–20 EEG system; C4:right central lobe position based on 10–20 EEG system; Cz: Vertex position based on 10–20 EEG system; CPT: Cold Pain Threshold; CPM: Conditioned Pain Modulation; c-tDCS: cathodal-tDCS; DC: Direct Current; DLPFC: Dorsolateral Prefrontal Cortex; EIMS: Electrical Intramuscular Stimulation; F3: left DLPFC location based on 10–20 EEG system; F4:right DLPFC location based on 10–20 EEG system; HPT: Heat Pain Threshold; HD-tDCS: High Definition-tDCS; M1: Primary Motor Cortex; mA: milliampere; mN: millineutron; MPT: Mechanical Pain Threshold; P3: left Parietal lobe location based on 10–20 EEG system; P4: Right Parietal lobe location based on 10–20 EEG system; PPT: Pressure Pain Threshold; QST: Quantitative Sensory Testing; rTMS: repetitive Transcranial Magnetic Stimulation; SD: Standard Deviation; s-tDCS: sham-tDCS; SO: Supraorbital; T7: Temporal lobe location based on 10–20 EEG system; TMJ: Temporal-Mandibula Junction; r TS: Temporal Summation; tDCS: Transcranial Direct Current Stimulation.

General information from the rTMS studies included in the meta-analysis

Articles	Country	Design	Condition	Pain Duration	Sensory Profile	Participants	Motor Cortex Stimulation Parameters					QST Protocol			Device		
							Target coil type	frequency	Intensity % of motor threshold	Total number of pulses	Device	Number of sessions	Concomitant Therapies or motor tasks	Pain threshold		TS	CPM
Johnson et al. (2006)	Australia	Crossover	Chronic back pain	Not reported	Not reported	17 participants (50% females). Mean age: 43.5 yrs. A) a-rTMS. B) s-rTMS.	left M1/S1 figure 8 coil	20	95	500	MagStim Super Rapid stimulator	1	No	HPT and CPT were measured over the thenar eminence of the right hand	TS was assessed using a modified Alderson-Sedlitz test (Basile, Marzetti, & Meloni, Italy)	Difference of pain score of the heat stimuli over the forearm before and after the immersion of the opposite hand in cold water (0–1°C)	Thermal Sensory Analyzer (TSA-200) device (Medoc Ltd)
Dall Agnol et al. (2014)	Brazil	Parallel	Myofascial pain syndrome	Not reported	Not reported	24 female participants. A: 12 participants in a-rTMS. Mean age: 45.83 yrs. B: 12 participants in s-rTMS. Mean age: 44.83 yrs.	C3, figure 8 coil	10	80% RMT	1600	MagPro X100 (MagVenture Company, Lucernemarken, Denmark)	1	No	HPT was measured with a Pelitec-based thermode over the mid-forearm from 32°C up to a maximum 52°C		Computer Pelitec-based device thermode (30 × 30 mm) (Heat Pain Stimulator-1.1.10, Brazil)	
Giaffri-Guerrero et al. (2005)	Mexico	Parallel	Healthy	-	-	180 participants (45% female). Mean age: 19 yrs. Experiment 1: A) 15 participants in a-rTMS L-DLPFC. B) 15 participants in a-rTMS R-MC. C) 15 participants in s-rTMS L-MC. E) 15 participants in s-rTMS Experiment 2: A) 15 participants in a-rTMS L-DLPFC. B) 15 participants in a-rTMS R-DLPFC. C) 15 participants in a-rTMS L-MC. D) 15 participants in a-rTMS L-MC. E) 15 participants in s-rTMS	C3, figure 8 coil	1 Hz	100% MT	900	Mc-b70 transducer, Dantec MagPro, Medical A/S, Skovlunde, Denmark	1	No	PPT was measured by an electronic algometer over the distal phalanx of the fifth finger. CPT was measured with a computerized Pelitec-based thermode over the hand in cold water (8±1) and reporting the pain threshold. HPT was assessed with an infrared generator over the forearm.		Electronic pressure algometer with a modified Randall-Sedlitz test (Basile, Marzetti, & Meloni, Italy) Infrared generator (Basile Pannari, Test, Milan, Italy)	
Mylius et al. (2007)	Germany	Crossover	Healthy	-	-	12 participants (50% females) Mean age: 22.3 yrs. Group: A) a-rTMS. B) s-rTMS	C3/C4 contralateral to induced pain, figure 8 coil	10 Hz	80% RMT		Medtronic MagPro stimulator (Medtronic Functional Diagnostics, Skovlunde, Denmark)	1	No	Pain threshold by electrical stimulation on the left calf over the subcutaneous course of sural nerve.		Not specified	
Borckardt et al. (2011)	US	Crossover	Healthy	-	-	75 participants (60% female). Mean age: 29.95 Groups: A: 15 participants in rTMS at 1 Hz. B) 12 participants in rTMS at 10 Hz. C) 13 participants in 10 Hz 80% RMT. D: 13 participants in 10 Hz 100% RMT. E: 12 participants in 50 Hz triplets at 90% of active motor threshold (then burs)	C3, figure 8 coil	1 Hz	80%	1200	NeuroStim Model 2100, NeuroStim Inc., Malvern, PA	1	No	PPT was measured with a electrostimulation device over the digit III of the right hand	TS was assessed measuring a anesthesiometer over pulses (1 per 1.5 s) for 30 seconds over the left forearm	PPT: Digital Electrofrequency Anesthesiometer (DTF model Alderson-Sedlitz; Woodland Hills, CA, USA) TS: The Medoc PATHWAY Pain & Sensory Evaluation System (Medoc Ltd, Israel)	
Ciampi de Andrade et al. (2011)	France	Crossover	Healthy	-	-	36 participants: A: 12 participants in a-rTMS M1 (33% females). Mean age: 30.2 yrs. B: 12 participants in a-rTMS DLPFC/PMC (25% females). Mean age: 29.2 yrs. C: 12 participants in s-rTMS (42% females). Mean age: 29 yrs.	C4, figure 8 coil	10 Hz	80% RMT	1500	MagPROX 100 machine (MagVenture Tonika Elektronic, Farum, Denmark)	2	Naloxone or placebo	CPT was measured with a Somedic thermode over the left thenar eminence.		Somedic thermode (Somedic AB, Stockholm, Sweden)	
Ciampi de Andrade et al. (2014)	France	Crossover	Healthy	-	-	36 participants: A: 12 participants in a-rTMS M1 (25% females). Mean age: 30.6 yrs. B: 12 participants in a-rTMS DLPFC/PMC (33% females). Mean age: 29.2 yrs. C: 12 participants in s-rTMS (42% females). Mean age: 29 yrs.	C4, figure 8 coil	10 Hz	80% RMT	1500	MagPROX 100 machine (MagVenture Tonika Elektronic, Farum, Denmark)	2	Ketamine or placebo	CPT was measured with a Somedic thermode over the left thenar eminence.		Somedic Thermotest Somedic AB, Stockholm, Sweden)	
Moisset et al. (2015)	France	Crossover	Healthy	-	-	"14 participants (50% females). Mean age: 26.9 yrs. Groups: A) prolonged continuous TBS (pcTBS). B) intermittent TBS (iTBS). C) classical 10 Hz rTMS. D) sham stimulation"	C3, figure 8 coil	Prolonged pcTBS: Three pulses at 50 Hz (i.e. 60 ms) repeated 400	80% RMT	1200	MagPro 100 machine (MagVenture Tonika Elektronic, Denmark)	1	No	CPT was measured with a thermode over both the thenar eminences and over the left foot.		Somedic thermotest (Somedic AB, Stockholm, Sweden)	

Articles	Country	Design	Condition	Pain Duration	Sensory Profile	Participants	Target coil type	Motor Cortex Stimulation Parameters				QST Protocol			
								Frequency	Intensity % motor threshold	Total number of pulses	Device	Number of sessions	Concomitant Therapy or motor tasks	Pain threshold	TS
Lamasuo et al. (2017)	Finland	Crossover	Healthy	-	-	10 participants (70% females). Mean age:	C3, figure 8 coil	Intermittent TBS; 20 trains (3 pulses at 50 Hz repeated 10 times at 200 ms intervals) with an intertrain interval of 8 s (total of 600 pulses in 20 min and 20 s)	80% RMT	600	Nexstim Ltd., Helsinki, Finland) with a double eight-shaped coil giving biphasic pulses (Nexstim Ltd., Focal Bipulse 8-coil)	1	No	was measured before and after the immersion of the left foot in cold water (4–8°C)	TS device (Medoc Ltd., Rehovot, Israel)
Cavaleri et al. 2019	Australia	Parallel	Healthy	-	-	30 participants. Group: A. 15 participants in a-rTMS (47% of females). Mean age: 25.9 yrs. B. 15 participants in a-rTMS (47% of females). Mean age: 22.7 yrs.	C3, figure 8 coil	1 Hz	90% RMT	1200	Magsstim Super Rapid2 (Magstim Co Ltd, Dyfed, United Kingdom)	5	No	"PPT was measured with an algometer over the right (injected with nerve growth factor) ECRB muscle"	Algonometer (Somedic, 1 cm 2probe, Norra Mellby, Sweden)

a-tDCS: active-tDCS; a-rTMS: active repetitive Transcranial Magnetic Stimulation; C3:left central lobe position based on 10–20 EEG system; C4:right central lobe position based on 10–20 EEG system; CPM: Conditioned Pain Modulation; CPT: Cold Pain Threshold; c-tDCS: cathodal tDCS; DLPFC: Dorsolateral Prefrontal Cortex; ECRB: Extensor Carpi Radialis Brevis; EIMS: Electrical Intramuscular Stimulation; HPT: Heat Pain Threshold; iTBS: intermittent Theta Burst Stimulation; L-DLPFC: Left Dorsolateral Prefrontal Cortex; L-MC: Left-Motor Cortex; MI: Primary Motor Cortex; pcTBS: prolonged continuous Theta Burst Stimulation; PMC: Primary Motor Cortex; PPT: Pressure Pain Threshold; QST: Quantitative Sensory Testing; R-DLPFC: Right Dorsolateral Prefrontal Cortex; R-MC: Right Motor Cortex; RMT: Resting Motor Threshold; rTMS: repetitive Transcranial Magnetic Stimulation; S1: Primary Somatosensory Cortex; SO: Supraorbital; s-rTMS: sham-repetitive Transcranial Magnetic Stimulation; s-tDCS: sham-tDCS; TBS:Theta Burst Stimulation; tDCS: Transcranial Direct Current Stimulation; TS: Temporal Summation.