Review

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Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC$_2$-NIN-CP)

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Abstract

Introduction: Chronic pain (CP) is highly prevalent and generally undertreated health condition. Noninvasive brain stimulation may contribute to decrease pain intensity and influence other aspects related to CP.

Objective: To provide consensus-based recommendations for the use of noninvasive brain stimulation in clinical practice.

Methods: Systematic review of the literature searching for randomized clinical trials followed by consensus panel. Recommendations also involved a cost-estimation study.

Results: The systematic review wielded 24 transcranial direct current stimulation (tDCS) and 22 repetitive transcranial magnetic stimulation (rTMS) studies. The following recommendations were provided: (1) Level A for anodal tDCS over the primary motor cortex (M1) in fibromyalgia, and level B for peripheral neuropathic pain, abdominal pain, and migraine; bifrontal (F3/F4) tDCS and M1 high-definition (HD)-tDCS for fibromyalgia; Oz/Cz tDCS for migraine and for secondary benefits such as improvement in quality of life, decrease in anxiety, and increase in pressure pain threshold; (2) level A recommendation for high-frequency (HF) rTMS over M1 for fibromyalgia and neuropathic pain, and level B for myofascial or musculoskeletal pain, complex regional pain syndrome, and migraine; (3) level A recommendation against the use of anodal M1 tDCS for low back pain; and (4) level B recommendation against the use of HF rTMS over the left dorsolateral prefrontal cortex in the control of pain.

Conclusion: Transcranial DCS and rTMS are recommended techniques to be used in the control of CP conditions, with low to moderate analgesic effects, and no severe adverse events. These recommendations are based on a systematic review of the literature and a consensus made by experts in the field. Readers should use it as part of the resources available to decision-making.

Keywords: tDCS, rTMS, Neuropathic pain, Nociceptive pain, Mixed pain

1. Introduction

Chronic pain (CP) is highly prevalent worldwide and has been acknowledged as a major public health problem in many countries.[40] Chronic pain has been recently suggested to be more prevalent in countries with low human development indices.[48,56] Indeed, pain affects 20% to 40% of the general population in Latin America (LA) and constitutes a major public health challenge.[39,88,92,93,112] The most frequent pain syndromes are osteoarthritis-related pain, low back pain (LBP), headaches, and neuropathic pain syndromes.[2,5,39,40,92,93,95] For instance, the lifetime prevalence of acute LBP is close to 70%, and it has been suggested that more than half will eventually experience chronification,[12,47] ranking chronic LBP as the first cause of years lived with disability[80,114] worldwide. Chronic pain has known associations with depressed mood, fatigue, and catastrophizing thoughts. It is also widely recognized that even for CP directly triggered by peripheral structures such as joint and muscle, there exist a wide range of central nervous system (CNS) modifications occurring in CP, leading to a series of central changes that will allow for the perpetuation and maintenance of the CP status.[9,71,72] Pain is linked to maladaptive plasticity in the CNS,[10,11,31,32,98–100] which is related to the severity of symptoms.[46,49,97]

Although the different pain syndromes have different treatments and response rates, CP is generally undertreated. For instance, LBP is the main reason why people seek medical attention, and still, up to 40% of patients persist with uncontrolled symptoms.[14] Neuropathic

Pain, which affects up to 7% of the general population, may be pharmacoresistant in up to 40% of cases.[25,111] This suggests that the current pharmacological agents available and the way they are used have provided relatively low efficacy as monotherapy strategies, with relatively high potential side effects, adding a supplementary layer of burden on patients, family members, and society already fighting against CP.[30] As an example, one can cite the relatively high number necessary to treat seen with first- and second-line treatments for neuropathic pain,[30] as well as the continuously alarming issue related to opioid misuse and abuse in the setting of noncancer CP treatment.[61]

The above limitations have stimulated the blossoming of several lines of research focused at innovative treatments for CP. These nonpharmacological approaches include a broad range of interventions, which are either potentially less expensive than conventional drug treatments (eg, mindfulness-based approaches) or supposed to act directly on CNS structures implicated in the occurrence of pain and positively affect a broader range of pain-associated symptoms such as fatigue, catastrophizing, and mood. Definitely, it has been reported that in some CP conditions such as fibromyalgia, nonpharmacological approaches can decrease not only pain intensity but may also have more efficacious effects in other domains such as sleep, cognitive complaints, and fatigue than pharmacological treatment.[86]

Among the currently available neuromodulation techniques, non-invasive brain stimulation (NIBS) has been extensively studied over the past 30 years to control CP. These techniques are known to influence neuronal cell membrane potential[23] or to induce its depolarization/hyperpolarization with different degrees of focality, cost, and complexity,[55,106] and can influence pain-processing regions in the CNS.[89,109,117,118] As a consequence, they are believed to drive plastic changes[120] that lead to better pain control and gain in function.

Several neuromodulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are cleared by numerous national and regional control agencies worldwide. However, there is a paucity of local or regional guidelines to guide clinicians on the best way to use these techniques. The analgesic effects of the most frequently used noninvasive neuromodulation techniques have been comprehensively scrutinized in recent reviews and meta-analyses, and most of these publications provided a broad view of the available evidence supporting the use of these techniques in some CP settings.[37,57,60,82] Although meta-analyses are the backbone of some policy and guideline recommendations,[21] they may be of limited use to guide the clinical recommendations of therapeutic interventions having numerous parametric variables or when the object of study has several subcategories. This is the case of neuromodulation approaches, with its different techniques and parametric variables (ie, frequency of stimulation, CNS target, and number of sessions) and CP, with its different pain syndromes, different etiologies, prevalence, and prognosis. More important, the different CP syndromes have very heterogeneous degree of evidence-based treatments available for their control. In such instances, a more individualized approach is preferred. As an illustration, one recent publication considered the adequate sample size of a NIBS trial to be of at least 400 patients,[81] and trials with lower numbers of patients were penalized (downgraded) and considered as inconsistent and imprecise, unless more participants were randomized. However, for some pain syndromes, these relatively high sample size values are unrealistic and virtually no treatment to date included this number of patients in any trial. For instance, a medium-sized double-blinded controlled trial to treat complex regional pain syndrome (CRPS) may add more to the already existing (scarce) literature on CRPS evidence-based treatment compared with a study of same sample size on the use of the same technique to treat neuropathic pain due to diabetes, a situation where several other therapeutic interventions have already shown to have significant analgesic effects.[28,115] Frequently, these clinically relevant nuances are missed out or diluted in recommendations based exclusively on meta-analyses.

Another approach to synthesize clinical evidence and translate it into clinical practice is the guideline approach based on systematic reviews and standardized classification of trials and

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recommendations, which have been used in the NIBS context,[57,58,60] and provided similar findings in their literature review compared with previous meta-analyses, but lead to higher-level recommendations of some of the NIBS techniques by their respective consensus panel. Evidence-based consensus aims to guide professionals on the best way to treat certain clinical conditions, representing a community-based expression to guide decision-making, contextualized to current available resources already available for the medical condition under scrutiny.

Based on the paucity of regional clinically oriented recommendations for the potential use of NIBS in the treatment of patients with CP, the aim of this study was to perform a comprehensive and updated systematic review of all the NIBS used to relieve CP, classify studies according to the class of evidence they provide according to established categorizations,[16] and provide a consensus recommendations for the use of NIBS in clinical practice in LA and Caribbean region, with emphasis on the clinical significance of the interventions in context of the currently available treatments for each pain syndrome[26,27] regionally.

Recommendations were based on a modified Delphi design that included a systematic review of the literature, and formulation of recommendations by a consensus panel composed of pain and/or neuromodulation specialists, and a patient's representative, followed by a cost-estimation study based on the regional costs and treatment availability.

2. Methods

This study was based on a Delphi design that included the following rounds: (1) systematic review of the literature; (2) formulation of recommendations by a panel of specialists formed by pain and/or neuromodulation professionals assigned by local and regional pain and neuromodulation societies (ie, Latin-American Pain Societies and Pain Societies from many LA countries), as well as researchers having published substantial research on NIBS in CP based in LA; (3) anonymous voting of the recommendations used as the basis for a consensus panel; (4) formulation of the final recommendation document; and (5) external review made by 3 specialists on pain and neuromodulation, located outside LA and Caribbean region. A patient having experienced NIBS treatment for CP was also invited to participate. The final report was based on the AGREE statement.

The reviewed interventions were: (1) repetitive TMS (rTMS); (2) tDCS; (3) transcranial alternating current stimulation (tACS); (4) transcranial random noise stimulation; (5) cerebellar tDCS; (6) transcutaneous vagus nerve stimulation; and (7) external trigeminal nerve stimulation.

For the purpose of this consensus paper, randomized double-blinded clinical trials were reviewed if they used a comparison group (treated by a sham or a second active NIBS procedure) and included as main outcome measures any of the following: (1) pain intensity; (2) pain-related quality of life; (3) pain impact on daily life; (4) use of pain medication; (5) number of days or hours without pain; and (6) frequency of migraine attacks.

For methods concerning group membership, and target population preferences and views according to the AGREE recommendations, please refer to supplementary file 1 (S1), available at http://links.lww.com/PR9/A35.

2.1. Search methods

A systematic review of clinical trials was performed on Medline (via PubMed) independently by 2 authors (A.F.B. and A.M.B.L.F.). Inconsistencies were resolved by a third author (D.C.A.).

Descriptors and search strategy can be found at supplementary file 1 (S1), available at http://links.lww.com/PR9/A35.

2.2. Evidence selection criteria

The search was not delimited by sex, age, type of facility where the study was held, time, or language of publication. Double-blinded, sham-controlled studies with at least 10 CP patients per arm, treated by repeated sessions, were included. Exclusion criteria were: single case or case series reporting exclusively safety and tolerability data; single-session studies; literature reviews; and studies where pain was not the primary outcome, or where comorbidities included main psychiatric disorders (ie, major depression, schizophrenia, bipolar disorders, and drug addiction).

2.3. Strengths and limitations of the evidence

Strengths and limitations of the evidence were considered initially according to: (1) Study design—the study should have been designed to answer the clinical question regarding the effectiveness of neuromodulation in the control of pain. (2) Study methodology—the presence of randomization, blinding, allocation concealment, and appropriate data analysis was considered. (3) Appropriateness/relevance of primary and secondary outcomes were considered taking into account the items suggested by the IMMPACT recommendations for clinical trials involving interventions for patients with CP.[26] To score the studies according to IMMPACT, the following items were evaluated in each selected study: pain intensity, pain quality and temporal characteristics, physical functioning, emotional functioning, self-perception of improvement and patient satisfaction, and occurrence of adverse events. Then, for the presence of outcome data for each of the 6 subitems above, a point scoring system was used by the writing committee and approved by all the authors: if one of the abovementioned items was contemplated in the study, the study received "one point," and the sum of all points was calculated to assist consensus panel members in the task of providing recommendations.

2.4. Internal and external validity

The studies were also evaluated according to PEDro scale to assess external (item 1) and internal (items 2–11, score 0–10) validity.[68] The scoring considered the following items: (1) Eligibility criteria were specified; (2) Subjects were randomly allocated to groups; (3) Allocation was concealed; (4) The groups were similar at baseline regarding the most important prognostic indicators; (5) There was blinding of all subjects; (6) There was blinding of all therapists who administered the therapy; (7) There was blinding of all assessors who measured at least one key outcome; (8) Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; (9) All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by intention to treat; (10) The results of between-group statistical comparisons are reported for at least one key outcome; (11) The study provided both point measures and measures of variability for at least one key outcome. As eligibility criteria (external validity) were established initially as inclusion/exclusion criteria, the final score was presented only for internal validity (maximum score of 10).

2.5. Classification of studies

Based on the data collected by the steering committee, and in accordance with the IMMPACT recommendations and the PEDro assessment, studies were then classified according to classes of evidence[16] as:

Class I study was considered an adequately data-supported, prospective, randomized, sham-controlled clinical trial with masked outcome assessment in a representative population (n ≥ 25 patients receiving active treatment).[57]

It should include all 5 items below:

(1) Randomization concealment;
(2) Clearly defined primary outcomes;
(3) Clearly defined exclusion/inclusion criteria;
(4) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias;
(5) Relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences.

Class II: Prospective matched-group cohort study in a representative population (n ≤ 25 patients receiving active treatment) with masked outcome assessment that meets (1)–(5) mentioned above or a randomized, controlled trial in a representative population that lacks one criteria (1)–(5).

Class III studies included all other controlled trials.

Class IV studies are uncontrolled studies, case series, and case reports (which were not included in this study).

For methodological information on the formulation of the recommendation based on the systematic review and consideration of benefits, harms, infrastructure, and cost estimation of the recommended techniques, please refer to supplementary file 1 (S1), available at http://links.lww.com/PR9/A35. Recommendations were based on standardized criteria as follows[16]:

(1) Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least 2 consistent, convincing class II studies;
(2) Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence;
(3) Level C rating (possibly effective, ineffective, or harmful) requires at least 2 convincing class III studies.

3. Results

Search was developed from June 2016 to June 2017, yielding 2048 studies, from which 1999 studies were excluded (**Fig. 1**). The final analysis was made with 49 studies, 24 of tDCS[3,4,7,8,17,24,29,33,36,41,42,54,65,66,75,78,83,90,94,105,108,110,113,116] and 22 of rTMS.[1,6,15,22,23,35,44,51–53,63,64,67,69,73,76,77,84,85,87,101,103] Countries involved in these studies are shown in supplementary file 2 (S2), available at http://links.lww.com/PR9/A35.

3.1. Transcranial electrical stimulation (transcranial direct current stimulation)

We searched for 6 types of transcranial electrical stimulation: (1) tDCS; (2) tACS; (3) transcranial random noise stimulation; (4) cerebellar tDCS; (5) transcutaneous vagus nerve stimulation; and (6) external trigeminal nerve stimulation. Among the above-mentioned types, only tDCS and tACS studies reached the standards to be included in the review. We included 24 parallel or crossover randomized controlled trial (RCT). Transcranial DCS was generally administered through a pair of 25- to 35-cm^2 sponge electrodes, 1-2 mA of amplitude, current density 0.04 to 0.06 mA/cm^2, for 20 minutes, during 5 sessions (range 3–18 sessions). High-density tDCS with 4 electrodes was investigated in only one study, as well as tACS. Those studies included 927 (38.62 ± 32.03/study) participants, with the maximum sample size of 135 participants.

Anodal tDCS stimulation of the primary motor cortex (M1—C3, C4, or Cz positions of the 10/20 international EEG system) with the cathode over the contralateral supraorbital area (Fp1 or Fp2) was used in 19 of the 24 studies treating participants with fibromyalgia, neuropathic pain (spinal cord injury [SCI], trigeminal neuralgia, lumbar radiculopathy, and diabetic polyneuropathy), myofascial pain associated with or not with temporomandibular joint disorder, HTLV-1 infection–related pain, chronic hepatitis C, abdominal pain, vestibulodynia, and episodic migraine (**Table 1**). Some studies positioned the anode over the left prefrontal dorsolateral cortex (F3 of the 10/20 international EEG system) and the cathode over Fp2 (**Table 2**), but they were less frequently used. In some occasions, the montages of the primary motor cortex and dorsolateral prefrontal cortex (DLPFC) were assessed in the same study. From the 4 studies that used this F3/Fp2 montage, 2 included fibromyalgia and 2 neuropathic pain participants (multiple sclerosis and trigeminal neuralgia). Other montages were also found and are described in **Table 3**.

The studies were generally well designed and did not approach pain intensity only, but also affective dimensions of pain, and physical and emotional functions. Sixty-two percent of studies contemplated ≥5/6 IMMPACT items (**Tables 1–3**, supplementary file 3 [S3], available at http://links.lww.com/PR9/A35). The most frequently neglected item was "self-perception of improvement." Stimulation was generally well tolerated, and none of the studies reported serious adverse events. PEDro classification of internal validity ranged from 6 to 9/10 (**Tables 1–3**; supplementary file 4 [S4], available at http://links.lww.com/PR9/A35), representing studies with adequate quality of evidence. Allocation concealment and blinding of the researchers who administered the techniques were the most common methodological limitation of the studies. This limitation could be mitigated in future studies by simply asking participants at the end of the study which group they participated using simple blinding assessment questionnaires.[23] Some technological improvements may also improve this issue, by the use of devices with built-in solutions to perform active or sham stimulation according to predetermined blinded and coded protocols, so that the therapist will not know the type of stimulation delivered once the stimulator setup is performed.

In general, benefit of the montages addressing the primary motor cortex (M1) was low to moderate (>20 or >30% decrease in pain intensity) at the end of sessions and follow-up. These results were of moderate benefit when tDCS was applied to patients with fibromyalgia and of no benefit when other musculoskeletal or neurological problems were studied. Results for tDCS in neuropathic pain were not so as consistent as those for fibromyalgia, suggesting a lesser analgesic effect in patients with neuropathic pain. Several studies were classified as class II (supplementary file [S3], available at http://links.lww.com/PR9/A35). Two studies were classified as class I,[42,66] both involving LBP participants. In one study,[42] anodal tDCS to M1 was shown to have significant analgesic effects when associated with peripheral electric stimulation. However, both studies reported negative effects of stand-alone tDCS. This information was incorporated in the recommendations as class A for ineffectiveness of M1 anodal tDCS for this painful syndrome.

In general, montages stimulating the left prefrontal dorsolateral cortex were less commonly used and generally resulted in less
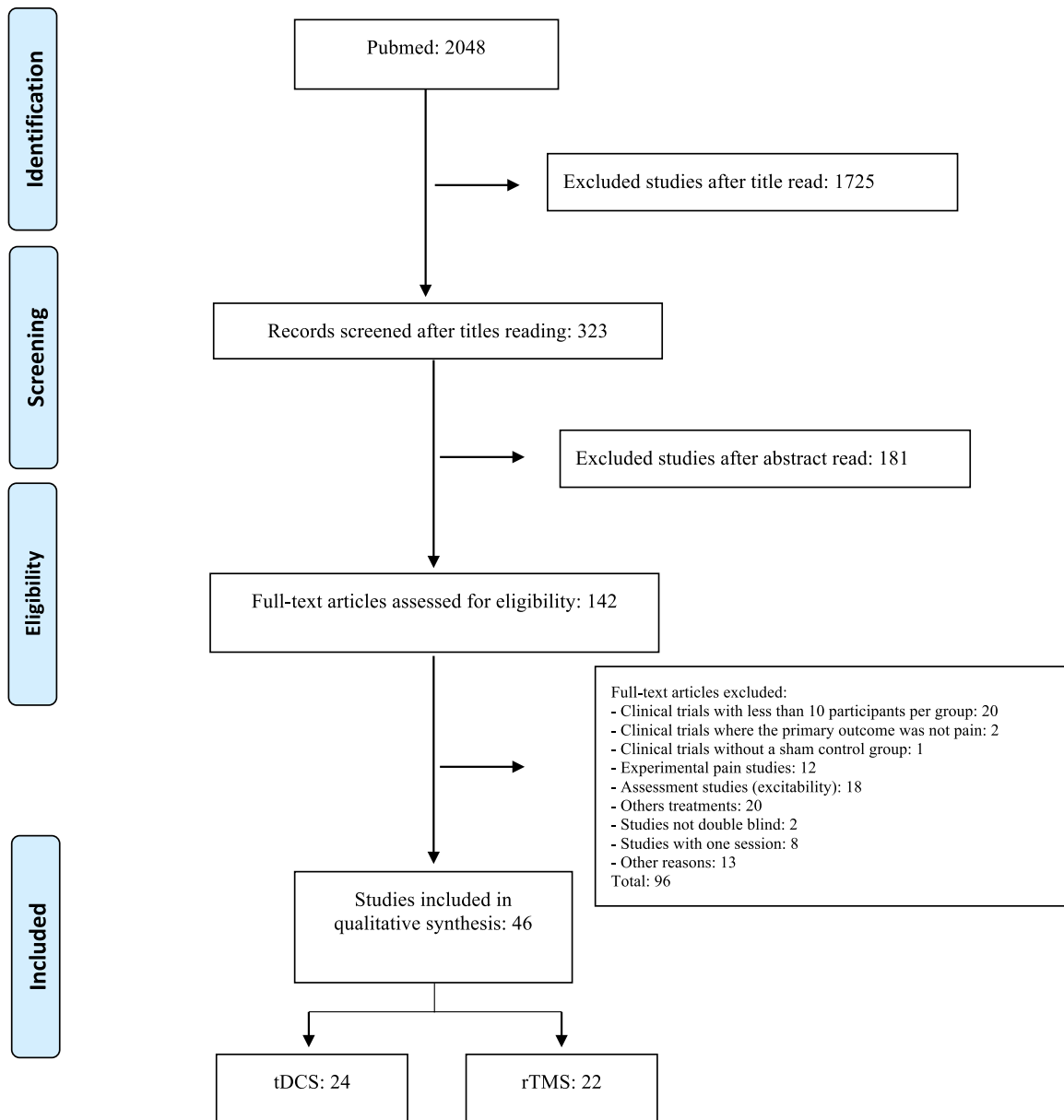
Figure 1. Study flowchart. rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

benefit. Other tDCS montages and one tACS intervention showed to be beneficial, but the number of studies was small. Gabis et al.[36] showed that a 77-Hz tACS for 8 days was moderately effective in reducing spinal pain and headache. Antal et al.[3] showed that a tDCS montage with the cathode over Cz and the anode over Oz was also moderately effective in reducing migraine-related pain, but at the end of 18 sessions, and not at the end of 5 sessions of tDCS. Donnell et al.[24] showed that a 2 × 2 multipolar tDCS montage targeting the motor cortex was not effective to control pain just after the end of 5 sessions, but was highly effective in the 6-week follow-up. Finally, To et al.[108] showed that a bifrontal montage (anode over F3 and cathode over F4) and a montage targeting the C2 dermatome were moderately effective in reducing pain in fibromyalgia, whereas the first montage was also effective to reduce fatigue.

In the vast majority of studies, transcranial electrical stimulation was administered along with pharmacological treatment, frequently including CNS-acting medications such as tricyclic antidepressants and anticonvulsants. In 6 studies, tDCS was administered together with other interventions such as visual illusion,[104] aerobic exercises,[75] manual therapy,[83] soft tissues stretching, hot packs, and low-level ultrasound,[94] general rehabilitation procedures,[90] and peripheral electrical stimulation (PES).[43] In 3 of those studies,[43,75,104] an additive effect of tDCS was shown, enhancing the overall effects on pain and other outcome measures.

3.2. Repetitive transcranial magnetic stimulation

Our review distinguished between 2 types of TMS: (1) classic "superficial" rTMS; and (2) deep rTMS. Studies were also divided according to cortical target location: (1) primary motor cortex (M1); and (2) non-M1 (eg, DLPFC and primary sensory cortex). Twenty-two parallel or crossover RCTs were included, using multiple sessions of stimulation (**Tables 4–6**). Repetitive

Table 1

tDCS efficacy with anode over M1 (C3/4) and cathode over supraorbital area (Fp1/2).

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, duration, electrode sizes, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/last follow-up)	Main clinical findings	Recommendation of benefit/harm
Fibromyalgia						
Fregni et al., 2006[33]; data also in F3-Fp2	II	RCT parallel (n = 11 active and n = 11 sham), IMMPACT 6/6, and PEDro 8/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: >50% active vs <30% sham* 3 months of follow-up: >30% active vs <30% sham*	Decrease in pain intensity at the end of the protocol. The effects on pain intensity were sustained at 3 months of follow-up	High benefit at the end of sessions and moderate benefit in the follow-up
Valle et al., 2009[110]; data also in F3-Fp2	II	RCT parallel (n = 14 active and n = 14 sham), IMMPACT 5/6, and PEDro 7/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 10 consecutive sessions	End of 10 sessions: >30% active vs <30% sham* 60 days of follow-up: >30% active vs <30% sham*	Decrease in pain intensity and increase in quality of life (FIQ) at the end, 30 and 60 days after the end of the protocol.	Moderate benefit at the end of sessions and follow-up
Riberto et al., 2011[90]	II	RCT parallel (n = 11 active and n = 11 sham), IMMPACT 5/6, and PEDro 7/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 10 consecutive sessions + multidisciplinary pharmacological and nonpharmacological intervention	End of 10 sessions: no differences between groups NS 4 months of follow-up: no differences between groups, NS	No effects on pain intensity and PPT, increase in SF-36 pain domain scores in active tDCS as compared to sham tDCS and standard treatment	Without benefit
Fagerlund et al., 2015[29]	II	RCT parallel (n = 25 active and n = 25 sham), IMMPACT 4/6, and PEDro 6/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: <30% in both groups, NS No follow-up	Decrease in pain intensity after the 4th day of intervention, but small clinical significance. Small increase in FIQ and SCL-90 in the active group	Low benefit at the end of sessions
Mendonça et al., 2016[75]	II	RCT parallel (n = 16 active and n = 16 sham), IMMPACT 5/6, and PEDro 8/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions tDCS + 12 of aerobic exercises (3× week) + pharmacological	End of 5 sessions: >30% tDCS + AE vs <30% tDCS alone* and vs <30% AE alone* 2 months of follow-up: >30% tDCS + AE vs <30% tDCS alone, <30% AE alone, NS	Decrease in pain intensity and anxiety more prominent in tDCS + aerobic exercises. Aerobic exercises alone were better than tDCS alone.	Moderate benefit for the association tDCS + AE at the end of sessions and follow-up. Low benefit for tDCS alone at the end of sessions and follow-up
Neuropathic pain						
Spinal cord injury, Soler et al., 2010[104]	II	RCT parallel (n = 40), IMMPACT 6/6, and PEDro 8/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 10 consecutive sessions tDCS + visual illusion + pharmacological	End of 10 sessions: <30% tDCS + VI vs <30% other groups* 12 weeks of follow-up: <30% tDCS + VI vs <30% other groups*	Decrease in pain intensity tDCS + VI. The benefits of this combined intervention were better and longer lasting than either intervention alone (tDCS or visual illusion alone)	Low benefit at the end of sessions and follow-up
Spinal cord injury, Wrigley et al., 2013[116]	II	RCT crossover (n = 10), IMMPACT 4/6, and PEDro 9/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: no differences between groups, NS 6 months of follow-up: no differences between groups, NS	Individuals with longstanding neuropathic SCI pain, tDCS focused over M1 does not provide pain relief.	Without benefit
Trigeminal neuralgia, Hagenacker et al., 2014[41]	III	RCT crossover (n = 10), IMMPACT 3/6, and PEDro 8/10	1 mA, 20′, 4 × 4 anode (0.08 mA/cm^2) and 5 × 10 cathode (0.02 mA/cm^2), and 14 consecutive sessions	End of 14 sessions: <30% active × <30% increase sham, NS No follow-up	No effects in the whole group with pain. Decrease in pain intensity (>30%) in participants with purely paroxysmal pain. Those with permanent pain did not benefit at all. No effects on electrophysiological outcomes.	Without benefit
Painful diabetic polyneuropathy, Kim et al., 2013[54]; data also in F3-Fp2	II	RCT parallel (n = 20 active and n = 20 sham), IMMPACT 6/6, and PEDro 7/10	2 mA, 20′, 5 × 5 Electd (0.08 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: >30% active vs <30% sham* 1 month of follow-up: <30% active vs <30% sham*	Decrease in pain intensity, CGI, anxiety, and increase PPT during and intervention and at follow-up. No effects of tDCS on sleep and BDI.	Moderate benefit at the end of sessions and low benefit at follow-up.

Table 1 (*continued*)

tDCS efficacy with anode over M1 (C3/4) and cathode over supraorbital area (Fp1/2).

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, duration, electrode sizes, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Other pain syndromes						
Myofascial pain syndrome, Sakrajai et al., 2014[94]	II	RCT parallel (n = 16 active and n = 15 sham), IMMPACT 4/6, and PEDro 8/10	1 mA, 20′, 5 × 7 Electd (0.028 mA/cm^2), and 5 consecutive sessions + pharmacological + stretching, ultrasound, and hot packs	End of 5 session: <30% active vs <30% sham* 1 month of follow-up >50% active, >50% sham, NS	tDCS combined with standard treatment appears to decrease pain intensity and may improve PROM, faster than standard treatment alone	Low benefit at the end of sessions and no benefit at follow-up
HTLV-1, Souto et al., 2014[105]	II	RCT parallel (n = 10 active and n = 10 sham), IMMPACT 5/6, and PEDro 9/10	2 mA, 20′, 5 × 5 Electd (0.08 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: >50% active vs >30% sham, NS No follow-up	No effects of active stimulation over sham for reducing pain intensity in HTLV-1–infected patients with chronic low back and/ or lower limbs pain	Without benefit
Chronic myofascial TMD, Oliveira et al., 2015[83]	II	RCT parallel (n = 16 active and n = 16 sham), IMMPACT 5/6, and PEDro 9/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions + 10 sessions of manual therapy and exercises	End of 5 session: >30% active vs >30% sham, NS 5 months of follow-up >50% active vs >50% sham, NS	No additional benefit in adding tDCS to exercises for the treatment of chronic TMD in young adults	Without benefit at the end of sessions or follow-up
Chronic hepatitis C, Brietzke et al., 2015[17]	II	RCT parallel (n = 14 active and n = 14 sham), IMMPACT 4/6, and PEDro 9/10	2 mA, 20′, 5 × 5 or 5 × 7 Electd (0.057–0.08 mA/ cm^2), and 5 consecutive sessions + pharmacological	End of 5 session: >50% active vs >30% sham, NS No follow-up	Decrease in pain intensity in both groups (no interaction time × group); tDCS increase in BDNF serum levels and improved PPT.	Without benefit
Chronic abdominal pain, Volz et al., 2016[113]	II	RCT parallel (n = 10 active and n = 10 sham), IMMPACT 5/6, and PEDro 8/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: >30% active vs <30% sham* 1 week of follow-up: >30% active vs <30% sham, NS	Decrease in pain intensity after sessions, but not at follow-up. The analgesic effects observed were unrelated to inflammation and disease activity.	Moderate benefit at the end of sessions and no benefit at follow-up
Provoked vestibulodynia, Morin et al., 2017[78]	II	RCT parallel (n = 19 active and n = 20 sham), IMMPACT 6/6, and PEDro 9/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 10 consecutive sessions	End of 10 sessions: <30% active vs <30% sham, NS 3 months of follow-up: <30% active vs <30% sham, NS	No effects of tDCS in reducing pain during intercourse, vestibular sensitivity, or psychological distress, and to improve sexual function	Without benefit
Low back pain, Hazime et al., 2017[43]	I	RCT factorial (n = 23 tDCS + PES, n = 23 PES, n = 23 tDCS, and n = 23 sham), IMMPACT 5/6, and PEDro 9/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 12 sessions (3×/week) + pharmacological	End of 12 sessions: <30% active vs <30% sham* 6 months of follow-up: <30% active vs <30% sham, NS	No effects of tDCS alone in reducing pain with minimum clinical significance value established as 2 points in 0–10 NRS. Clinically significant pain reduction (>50%) when tDCS was combined with PES.	Low benefit at the end of sessions and follow-up
Low back pain, Luedtke et al., 2015[66]	I	RCT (n = 135: n = 67 active and n = 68 sham), IMMPACT 6/6, and PEDro 9/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm^2), and 5 consecutive sessions + pharmacological	End of 5 sessions: no differences between groups, NS 24 weeks of follow-up: no differences between groups, NS	Transcranial direct current stimulation alone or in combination with cognitive behavioural management is inefficient for the reduction of pain and disability in patients with nonspecific chronic low back pain	Without benefit
Chronic pain syndromes (trigeminal neuralgia, poststroke pain syndrome, back pain, and fibromyalgia), Antal et al., 2010[4]	II	RCT crossover (n = 12), IMMPACT 3/6, and PEDro 9/10	1 mA, 20′, (4 × 4 cm over the M1 and 5 × 10 cm over the contralateral orbit, 62.5 mA/cm^2 over the M1 and 12 mA/cm^2 at the reference electrode), and 5 consecutive sessions + pharmacological	End of 5 sessions: >30% active vs <30% sham* 28 days of follow-up: <30% active vs increase <30% sham*	Decrease in pain intensity at days 3, 4, 5, and 7, 14, 28 days of follow-up. Only data from 12 patients were retained for analysis, according to inclusion criteria.	Moderate benefit at the end of sessions and low benefit follow-up

Table 1 (continued)

tDCS efficacy with anode over M1 (C3/4) and cathode over supraorbital area (Fp1/2).

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, duration, electrode sizes, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Episodic migraine, Auvichayapat et al., 2012[7]	II	RCT parallel (n = 37: n = 20 active and n = 17 sham), IMMPACT 3/6, and PEDro 9/10	1 mA, 20′, and 20 consecutive sessions + pharmacological	End of 4 weeks: >30% active vs <30% control* 12 weeks of follow-up: no differences between groups, NS	Decrease pain intensity in the active relative to sham group at the 4 and 8 weeks follow-up points, while there was no statistically significant reduction at 12 weeks.	Moderate benefit at the end of sessions, low benefit at 8 weeks of follow-up, and no benefit at 12 weeks of follow-up

* Statistically different at $P < 0.05$.

AE, aerobic exercise; BDI, Beck Depression Inventory; BDNF, brain-derived neurotropic factor; CGI, Clinical Global Impression Questionnaire; Electd, electrode; FIQ, Fibromyalgia Impact Questionnaire; NRS, Numeric Rating Scale; NS, nonsignificant statistical difference; PES, peripheral electrical stimulation; PPT, pressure pain threshold; PROM, pain range of motion; RCT, randomized controlled trial; SF-36, Short-form 36 Questionnaire; SCL-90, Symptoms Checklist 90; SCI, spinal cord injury; tDCS, transcranial direct current stimulation; TMD, temporomandibular joint disorder; VI, visual illusion.

TMS was more frequently administered using superficial coils targeting M1, at high frequency (10–20 Hz) in sessions comprising 1500 to 3000 pulses. Repetitive TMS was also applied to DLPFC (**Table 5**) and with a deep rTMS technique (**Table 6**). Studies included 798 (36.27 ± 19.73/study) participants, with a maximal sample size of 100.[67]

High-frequency rTMS over M1 was the most common approach, and it was more frequently compared with sham stimulation in parallel-design studies. Deep rTMS and superficial TMS to target outside M1 were rarely performed. In the vast majority of studies, rTMS was administered along with pharmacological treatment, frequently including CNS-acting medications such as tricyclic antidepressants and anticonvulsants. In some studies, physiotherapy was also performed during sessions, and in one study physiotherapy was performed as part of the protocol and was standardized in all patients.[87] Head-to-head studies in NIBS were rare and only one has so far compared 10-Hz rTMS over M1 against anodal tDCS to the same target.[6] In this study, which included 3 consecutive daily sessions of stimulation in patients with peripheral neuropathic pain due to radiculopathy, rTMS was superior to tDCS and sham, and its effects outlasted the stimulation session for a few days.

Table 2

tDCS efficacy with anode over left DLPFC (F3) and cathode over supraorbital area (Fp2).

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, duration, electrode sizes, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Fibromyalgia						
Fregni et al., 2006[33]; data also in C3/4-Fp1/2	II	RCT parallel (n = 11 active and n = 11 sham), IMMPACT 6/6, and PEDro 8/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm²), and 5 consecutive sessions	End of 5 sessions: <30% active vs <30% control, NS 21 days of follow-up: <30% active vs <30% control, NS	Small impact of anodal tDCS over left DLPFC on pain intensity	Without benefit at the end of sessions or follow-up
Valle et al., 2009[110]; data also in C3/4-Fp1/2	II	RCT parallel (n = 13 active and n = 14 sham), IMMPACT 5/6, and PEDro 7/10	2 mA, 20′, 5 × 7 Electd (0.057 mA/cm²), and 10 consecutive sessions	End of 10 sessions: >30% active vs <30% sham, NS 60 days of follow-up: <30% active vs <30% sham, NS	Decrease in pain intensity and increase in quality of life (FIQ) at the end of the treatment protocol, but not sustained at 30 and 60 days of follow-up.	Moderate benefit at the end of sessions, but not at follow-up
Neuropathic pain						
Multiple sclerosis, Ayache et al., 2016[8]	II	RCT crossover (n = 16), IMMPACT 5/6, and PEDro 6/10	2 mA, 20, 5 × 5 Electd (0.08 mA/cm²), and 5 consecutive sessions	End of 3 sessions: <30% active vs <30% increase sham* 3 days of follow-up: <30% active vs <30% sham, NS	Decrease in pain intensity, but not clinical analgesic effect 3 and 7 days after tDCS, with decrease in VAS and BPI total score. No effects on neuro-psychological parameters.	Low benefit at the end of sessions, but not at follow-up
Painful diabetic polyneuropathy, Kim et al., 2013[54]; data also in C3/4-Fp1/2	II	RCT parallel (n = 20 active and n = 20 sham), IMMPACT 6/6, and PEDro 7/10	2 mA, 20′, 5 × 5 Electd (0.08 mA/cm²), and 5 consecutive sessions + pharmacological	End of 5 sessions: <30% active vs <30% sham, NS 1 month of follow-up: <30% active vs <30% sham, NS	No effects of active stimulation over sham in pain intensity, CGI, anxiety, PPT, sleep, and BDI	Without benefit

* Statistically different at $P < 0.05$.

BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; CGI, Clinical Global Impression Questionnaire; DLPFC, dorsolateral prefrontal cortex; Electd, electrode; FIQ, Fibromyalgia Impact Questionnaire; NS, not significant statistical difference; PPT, pressure pain threshold; RCT, randomized controlled trial; tDCS, transcranial direct current stimulation; VAS, Visual Analogue Scale.

Table 3

tDCS with other montages and tACS efficacy.

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, duration, electrode sizes, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Anode Cz, cathode Oz, for migraine/Antal et al., 2011[3]	III	RCT parallel (n = 13 active and n = 13 sham), IMMPACT 2/6, and PEDro 9/10	1 mA, 15′, 5 × 7 Electd (0.028 mA/cm^2), and 18 sessions 3 times/week + pharmacological	End of 18 sessions: with aura >30% active vs <30% sham* No follow-up	Decrease in migraine-related days, intensity of pain during the attacks, and duration of the attacks in the active group, but not between groups; decrease pain intensity in a 0–3 pain score. Participants with aura presented better outcomes.	Moderate benefit at the end of sessions
tACS, for low back pain, cervical pain, and headache/Gabis et al., 2009[36]	II	RCT parallel (n = 58 active and n = 61 sham), IMMPACT 4/6, and PEDro 9/10	Self-tolerated until 4 mA, 8–20′, 77 Hz, 8 consecutive sessions for active, and 0.75 mA, 50 Hz for sham + pharmacological	End of 8 sessions: >30% active vs <30% sham* 3 months of follow-up: >30% active vs <30% sham*	Decrease pain after 3 weeks and 3 months after the last session in the active group over sham. Treatment also impacted positively sleep, pain frequency, and pain medication usage.	Moderate benefit at the end of sessions and follow-up.
High-density tDCS, for chronic myofascial TMD/Donnell et al., 2015[24]	III	RCT parallel (n = 12 active and n = 12 sham), IMMPACT 5/6, and PEDro 5/10	2 mA, 20′, 4 Electd (high-density tDCS), and 5 consecutive sessions + pharmacological	End of 5 sessions: <30% active vs <30% sham, NS 6 weeks of follow-up: >50% active vs <50% sham*	More responders (>50% pain reduction) in the active group at 1-month follow-up, pain-free mouth opening at 1-week follow-up, and pain area and intensity reduction contralateral to the stimulated hemisphere.	Without benefit at the end of sessions and high benefit at follow-up
Bifrontal (anode F3 and cathode F4) and occipital (C2 dermatome, anode left, and cathode right) tDCS for fibromyalgia/ To et al., 2017[108]	II	RCT parallel (n = 11 DLPFC, n = 15 occipital, and n = 16 sham), IMMPACT 5/6, and PEDro 6/10	1.5 mA, 5 × 7 Electd, 20′, and 8 sessions 2 times/week + pharmacological	End of sessions: >30% bifrontal vs >30% occipital vs <30% sham* No follow-up	Repeated sessions of occipital tDCS decrease pain, but not fatigue. Repeated sessions of bifrontal tDCS decrease pain and fatigue.	Moderate benefit at the end of sessions

* Statistically different at $P < 0.05$.
DLPFC, dorsolateral prefrontal cortex; Electd, electrode; NS, not significant statistical difference; RCT, randomized controlled trial; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TMD, temporomandibular joint disorder.

Interestingly, in this same study, the placebo effect of sham-tDCS and sham-rTMS was similar and not significantly different.[6] Few studies performed maintenance sessions of stimulation after an induction period (when sessions occur daily for 5–10 consecutive days). In these studies, it was shown that maintenance sessions performed weekly, fortnightly, and even monthly could maintain the effects triggered during the induction period.[76] The induction/maintenance strategy is currently used for the treatment of major depression, and is sound and safe on clinical and practical basis; however, it cannot be fully recommended in the treatment of CP due to the still limited amount of data available using this strategy. Deep rTMS was only performed in 2 studies (**Table 6**), both targeted the leg area representation of M1 in peripheral neuropathic pain patients with the H (Hesed)—coil.[84,101] In both, deep rTMS showed positive results, being short-lived (only present 1 hour after the stimulation) in one.[101]

The studies were generally well designed and did not approach pain intensity only but also how it influenced the affective dimension of pain, as well as physical and emotional function. Sixty-eight percent of studies contemplated ≥5/6 IMMPACT items (**Tables 4–6**; supplementary file 5 [S5], available at http://links.lww.com/PR9/A35). The item most frequently neglected was "self-perception of improvement." PEDro classification for rTMS studies ranged from 3 to 9/10 (supplementary file 6 [S6], available at http://links.lww.com/PR9/A35). The major problems concerned blinding, especially of the therapist, and allocation concealment. Blinding the therapist to rTMS is virtually impossible, except for certain devices (TMS coils delivering active or placebo stimuli without an operator's knowledge), developed with this aim. However, many alternatives to patients' blinding are available and should be incorporated in the studies, the same for allocation concealment. Also, the use of a formal blinding assessment questionnaire is highly recommended and could overcome these potential biases as mentioned above for tDCS.

Two studies were ranked as class I, both on neuropathic pain.[44,69] Virtually, all the superficial rTMS studies targeting M1 at high frequency (>5 Hz) were positive compared with placebo. All included studies targeting DLPFC were negative (**Table 5**). According to the systematic review at the end of stimulation, most studies found moderate/high effect for rTMS, whereas the effect was more frequently low/moderate after the maintenance sessions. After-effects assessed weeks to months after the end of treatment were variable and only performed in a few studies.

Table 4

High-frequency rTMS over M1 (C3/4) efficacy.

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, coil type and orientation, frequency, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Fibromyalgia						
Passard et al., 2007[85]	II	RCT parallel (n = 15 active and n = 15 sham), IMMPACT 5/6, and PEDro 7/10	80% RMT, F8, posterior–anterior, left M1, 10 Hz (2000 p), and 10 consecutive sessions + pharmacological	End of 10 sessions: >30% active vs <30% sham* 60 days of follow-up: no differences between groups, NS	Decrease in pain intensity and increase in quality of life for up to 2 weeks after treatment. The analgesic effects were observed from the fifth stimulation onwards and were not related to changes in mood or anxiety.	Moderate benefit at the end of sessions, but not at follow-up
Mhalla et al., 2011[76]	II	RCT parallel (n = 20 active and n = 20 sham), IMMPACT 5/6, and PEDro 9/10	80% RMT, F8, posterior–anterior, 10 Hz, 1500p, 5 consecutive sessions (induction phase), and 1 sessions at weeks 1, 2, 3, 5, 7, 9, 13, 17, and 21 (maintenance phase) + pharmacological	End of 5 sessions: <30% active vs <30% sham* Maintenance phase: (weekly, fortnightly, and monthly stimulations) <30% active vs <30% sham* 25 weeks of follow-up: <30% active vs <30% sham*	Decrease in pain intensity from day 5 to week 25. Increase in quality of life. Analgesic effects associated with quality of life and directly correlated with changes in intracortical inhibition	Low benefit at the end of sessions, maintenance phase, and follow-up
Boyer et al., 2014[15]	II	RCT parallel (n = 19 active and n = 19 sham), IMMPACT 5/6, and PEDro 9/10	90% RMT, F8, anterior–posterior, left M1, 10 Hz, 2000 p, 10 consecutive sessions over 2 weeks (induction phase), and 4 sessions: 1 session at weeks 4, 6, 8, and 10 (maintenance phase) + pharmacological	FIQ score: End of 10 sessions: no differences between groups, NS 11 weeks of follow-up: <30% active vs <30% sham*	Increase in quality of life (FIQ) at 11 weeks in mental component of SF-36 and increase in right medial temporal metabolism	No pain intensity reduction at 11 weeks, but QoL improved. Low benefit at follow-up
Neuropathic pain						
Khedr et al., 2015[53] (cancer-related NeP)	III	RCT parallel (n = 17 active and n = 17 sham), IMMPACT 4/6, and PEDro 7/10	80% RMT, F8, orientation NR, hand M1 contralateral to the painful side, 20 Hz, 2000 p, and 10 consecutive sessions + pharmacological NR	End of 10 sessions: >30% active vs <30% sham* 1 month of follow-up: no differences between groups, NS	Decrease in pain intensity after the end of 10 sessions. This effect was maintained for 2 weeks. Significant positive correlations between the percentage of pain reduction and HAM-D after the 10th session and 15 days later were recorded.	Moderate benefit at the end of sessions and follow-up (day 15 after stimulation). Without benefit at 1 month
Attal et al., 2016[6]	II	RCT crossover (head-to-head stimulation between both sham and active groups), parallel comparison between active (tDCS or rTMS) and sham (n = 23 active and n = 12 sham), IMMPACT 5/6, and PEDro 9/10	80% RMT, F8, anterior–posterior, hand M1, 10 Hz, 3000p, and 3 consecutive sessions + pharmacological	End of 3 sessions: >30% rTMS active vs <30% sham* tDCS active × sham: no differences between groups, NS No follow-up	Decrease in pain intensity (rTMS) and rTMS was more effective than tDCS and sham. Active rTMS decreased the total NPSI score with effects over PCS, BPI interference score, or mood. Active rTMS decreased cold pain thresholds	rTMS = moderate benefit at the end of sessions; tDCS = without benefit at the end of sessions
Hosomi et al., 2013[44]	I	RCT crossover (n = 34 active + sham and n = 36 sham + active), IMMPACT 6/6, and PEDro 9/10	90% RMT, F8, orientation NR, M1 (face, hand, or foot), 5 Hz, 500p, and 10 consecutive sessions + pharmacological	Right after and 60 minutes after stimulation <30% active vs <30% sham* 17 days of follow-up: no differences between groups, NS	Decrease in pain intensity and SF-MPQ in short term. PGIC were significantly better in real rTMS during the period with daily rTMS. No significant cumulative improvements in VAS, SF-MPQ, and BDI.	Low benefit right after stimulation and 60 minutes after stimulation. Without benefit at day 17
Postherpetic neuralgia/Khedr et al., 2005[52]	II	RCT (n = 24 central and n = 24 trigeminal), IMMPACT 3/6, and PEDro 6/10	80% RMT, F8, orientation NR, hand M1, 20 Hz, 2000 p, and 5 consecutive sessions + pharmacological	End of 5 sessions: >30% active vs <30% sham* 2 weeks of follow-up: >30% active vs <30% sham*	Decrease in pain intensity after the end of 5 sessions and follow-up	Moderate benefit at the end of sessions and follow-up
Ma et al., 2015[67]	III	RCT parallel (n = 24 active and n = 25 sham), IMMPACT 6/6, and PEDro 3/10	80% RMT, circular coil, posteroanterior, M1 representation of the contralateral painful area, 10 Hz, 1500p, and 10 consecutive sessions + pharmacological	End of 10 sessions: <30% active vs <30% sham* 3 months of follow-up: <30% active vs <30% sham*	Decrease in pain intensity after 10 sessions and follow-up (1 and 3 months) Increase in quality of life	Low benefit at the end of sessions and 1 and 3 months of follow-up
Central pain after spinal cord injury/Kang et al., 2009[50]	III	RCT crossover (n = 11), IMMPACT 3/6, and PEDro 9/10	80% RMT, F8, M1, 10 Hz, and 5 consecutive sessions + pharmacological	End of 5 sessions: no differences between groups, NS 7 weeks of follow-up: no differences between groups, NS	No statistically significant differences in mean pain between groups were observed	Without benefit at the end of sessions and follow-up

Table 4 *(continued)*

High-frequency rTMS over M1 (C3/4) efficacy.

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, coil type and orientation, frequency, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Phantom limb pain						
Ahmed et al., 2011[1]	II	RCT parallel (n = 17 active and n = 10 sham), IMMPACT 3/6, and PEDro 8/10	80% RMT, F8, orientation NR, M1-stump muscle of the painful side, 20 Hz, 4000p, and 5 consecutive sessions, pharmacological NR	End of 5 sessions: >50% active vs <30% sham* 2 months of follow-up: >30% active <30% sham*	Decrease in pain intensity at the end of 5 sessions and follow-up. Increase in serum beta-endorphin concentration	High benefit at the end of sessions and 1 month after treatment. Moderate benefit at 2 months of follow-up
Malavera et al., 2016[69]	I	RCT parallel (n = 27 active and n = 27 sham), IMMPACT 4/6, and PEDro 9/10	90% RMT, F8, orientation NR, hand M1 contralateral to the side of pain, 10 Hz, 1200p, and 10 consecutive sessions + pharmacological	15 days after stimulation: >50% active vs >50% sham* 30 days of follow-up: no differences between groups, NS	Decrease in pain intensity at 15 days after finishing the treatment. No differences between groups to the scores of the depression and anxiety scales.	High benefit at 15 days after stimulation, but not at 30 days of follow-up.
Myofascial pain syndrome						
Dall'Agnol et al., 2014[22]	II	RCT parallel (n = 12 active and n = 12 sham), IMMPACT 5/6, and PEDro 9/10	80% RMT F8, orientation NR, left M1, 10 Hz, 1600p, and 10 consecutive sessions + pharmacological	End of 10 sessions: >50% active vs <30% sham* 12 weeks of follow-up: >30% active vs <30% sham*	Decrease in pain intensity, analgesic use, and improved sleep quality. Reductions of the ICF, enhancement of the corticospinal inhibitory system, and increments in the BDNF secretion	High benefit at the end of sessions. Moderate benefit at 12 weeks of follow-up.
Medeiros et al., 2016[73]	II	RCT factorial design, (n = 11 rTMS and DIMST, n = 12 rTMS and sham-DIMST, n = 12 sham-rTMS and DIMST, and n = 11 sham-rTMS and sham-DIMST), IMMPACT 5/6, and PEDro 9/10	80% RMT, F8, orientation NR, left M1, 10 Hz, 600p, and 10 consecutive sessions + pharmacological	Immediately after at first and second day intervention was different from the ninth day, but not last day: >50% active vs <30% sham* No follow-up	Decrease in pain intensity immediately after the first and second day intervention was different from the ninth day (rTMS and DIMST). No peripheral biomarkers reflected the analgesic effect of both techniques	High benefit at the end of sessions
Other pain syndromes						
Mild traumatic brain injury (MTBI)-related headache. Leung et al., 2016[64]	II	RCT parallel (n = 15 active and n = 16 sham), IMMPACT 5/6, and PEDro 6/10	80% RMT, F8, orientation NR, left M1, 10 Hz (2000 p), and 3 consecutive sessions + pharmacological; neuronavigation-guided rTMS study	End of 1 week: >50% active vs <30% sham* 4 weeks of follow-up: no differences between groups, NS	Decrease in pain intensity (persistent headache intensity) after 3 sessions of rTMS. No difference in quality of life and depression.	High benefit at the end of sessions, but not at 4 weeks of follow-up
Chronic orofacial pain. Fricová et al., 2013[35]	II	RCT parallel (n = 13 active and n = 10 sham), IMMPACT 3/6, and PEDro 8/10	95% RMT, F8, M1 contralateral to the painful side, 20 Hz, 720p, and 5 consecutive sessions + pharmacological	End of each session: <30% active vs <30% sham* 2 weeks of follow-up: <30% active vs <30% sham*	Decrease in pain intensity The authors also compared this result with previous data from their pilot project using 10-Hz stimulation: 20-Hz stimulation had significantly stronger effect than 10 Hz.	Low benefit at the end of session and follow-up
Complex regional pain syndrome (CRPS type I). Picarelli et al., 2010[87]	II	RCT parallel (n = 12 active and n = 11 sham), IMMPACT 5/6, and PEDro 6/10	90% RMT, F8, posterior–anterior, M1 contralateral to the painful upper limb, 10 Hz, 2500p, and 10 consecutive sessions + pharmacological	End of 10 sessions: >30% active vs <30% sham* 3 months of follow-up: no differences between groups, NS	Decrease in pain intensity after the end of 10 sessions, but not at 1 and 3 months of follow-up. Positive changes in affective aspects of pain in CRPS patients during the period of stimulation and correlated with improvement in the affective and emotional subscores of the MPQ and SF-36.	Moderate benefit at the end of session, but not at follow-up
Migraine. Misra et al., 2013[77]	II	RCT parallel (n = 50 active and n = 50 sham), IMMPACT 4/6, and PEDro 7/10	70% RMT, F8, orientation NR, M1 (hand), 10 Hz, 600p, 3 consecutive sessions + pharmacological	Severity of headache: End of sessions: >50% active vs >30% sham* 4 weeks of follow-up: >50% active vs <30% sham*	Decrease in pain intensity and functional disability	High benefit at the end of session and 1 month of follow-up

* Statistically different at $P < 0.05$.
BDI, Beck Depression Inventory; BDNF, brain-derived neurotropic factor; BPI, Brief Pain Inventory; CRPS, complex regional pain syndrome; DIMST, deep intramuscular stimulation therapy; FIQ, Fibromyalgia Impact Questionnaire; F8, figure-of-8 coil; ICF, intracortical facilitation; NeP, neuropathic pain; NPSI, Neuropathic Pain Symptom Inventory; NR, not reported; NS, nonsignificant statistical difference; p, pulses; PCS, Pain Catastrophizing Scale; PGIC, patients global impression of change; RCT, randomized controlled trial; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SF-36, Short-Form 36 Questionnaire; SF-MPQ, Short-Form McGill Pain Questionnaire; tDCS, transcranial direct current stimulation; VAS, Visual Analogue Scale.

Neuropathic pain and fibromyalgia were the pain syndromes more frequently assessed in all studies, and the effects of stimulation were overall moderate to high at the end of treatment, decreasing pain intensity and improving other pain-related factors such as fatigue, catastrophism,[76] and quality of life.[15] Patients with central neuropathic pain (mostly SCI and central poststroke pain) were more frequently mixed with neuropathic pain of peripheral origin[44] in most trials. Trials with exclusive central neuropathic pain patients were the exception.[23] Other (prevalent) pain syndromes such as musculoskeletal pain, migraine, and CRPS were underrepresented in rTMS studies. These studies suggest that the analgesic effects could be maintained in the long term with intermittent (ie, weekly; fortnightly) sessions of treatment, as evidenced in the treatment of major depression. Interestingly, the sham effect of rTMS was relatively low in most CP studies, being usually below 15% pain reduction, which is different from rTMS studies for major depression where both pharmacological and neuromodulatory treatments had significant placebo effects.[18]

Based on the data methodological steps above, the consensus panel provided specific recommendations for NIBS for CP. Details are shown in Boxes 1 and 2.

4. Discussion

4.1. General recommendations

This study involves a consensus-based recommendation for the use of tDCS and rTMS in the control of CP. The consensus panel involved pain and/or neuromodulation specialists in LA and Caribbean region that voted in 2 rounds of discussion based on a systematic review of the literature and elaboration of recommendations based on the European Federation of Neurological Societies criteria for guidelines elaboration.[16]

According to these results, this consensus made a level A recommendation for efficacy of induction sessions (n = 5–10) of anodal tDCS, with 2-mA intensity over M1 (C3 and C4 of the 10/20 EEG international system or neuronavigated), with the cathode over the contralateral supraorbital area (Fp1 or Fp2 of the 10/20 EEG international system). Transcranial DCS might be used as an add-on analgesic treatment of patients who remain symptomatic, despite pharmacological and nonpharmacological treatment. These results are in agreement with previous reviews,[45,59,70,119] and include not only the control of pain, but also increase in many aspects of quality of life, as well. A recent guideline[60] made a level B recommendation for the use of anodal M1 tDCS, and this discrepancy is apparently due to the fact that they considered that trials coming from the same research group would be counted as one study. However, if we had followed the same criteria, we would again have 2 level II trials, which would increase the recommendation from level B to level A. It is important to highlight that although we input the higher level of recommendation to the use of tDCS in this condition, clinicians would expect only low (20%–30%) to moderate (30%–50%) pain intensity reduction.

Our results showed that the tDCS analgesic effects are somewhat less marked for patients with neuropathic pain, consistent with the guideline published by Lefaucheur et al.[60] We did not classify HTLV-related pain[105] as purely neuropathic, as those patients generally suffer from a mixture of nociceptive (low back) and neuropathic pain (lower limbs), and many of them have diffuse pain.[95] Consequently, we included only 4 neuropathic pain studies,[8,41,54,104] and only one of them[54] showed a >30% reduction in pain intensity (**Tables 1 and 2**). This study involved 40 participants with diabetic polyneuropathy and showed a decrease in pain intensity and increase in pressure pain

Table 5

rTMS efficacy over dorsolateral prefrontal cortex.

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, coil type and orientation, frequency, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/ last follow-up)	Main clinical findings	Recommendation of benefit/harm
Fibromyalgia Short et al., 2011[103]	II	RCT parallel (n = 10 active and n = 10 sham), IMMPACT 5/6, and PEDro 9/10	120% RMT, F8, orientation NR, left DLPFC, 10 Hz, 4000p, and 10 consecutive sessions + pharmacological	End of 10 sessions: no differences between groups, NS 2 weeks of follow-up: no differences between groups, NS	No statistically significant differences in mean pain between groups were observed	Without benefit at the end of sessions and follow-up
Central poststroke pain[20] de Oliveira et al., 2014[23]	II	RCT parallel (n = 12 active and n = 11 sham), IMMPACT 5/6, and PEDro 8/10	120% RMT. F8, anterior–posterior, left DLPFC/PMC, 10 Hz (1250p), and 10 consecutive sessions + pharmacological	End of 10 sessions: no differences between groups, NS 4 weeks of follow-up: no differences between groups, NS	No differences between groups in intensity of pain, anxiety, and depression.	Without benefit at the end of sessions and follow-up
Other pain syndromes Mild traumatic brain injury (MTBI)-related headache. Leung et al., 2017[63]	II	RCT, parallel (n = 14 active and n = 15 sham), IMMPACT 5/6, and PEDro 7/10	80% RMT, F8, orientation NR, left DLPFC, 10 Hz 2000 p, 4 sessions + pharmacological; and neuronavigation-guided rTMS study	End of 1 week: <30% active vs <30% sham* 4 weeks of follow-up: <30% active vs <30% sham*	Decrease in pain intensity (daily persistent headache intensity) after 4 sessions and follow-up. Improvement of depressive symptoms after 1 week posttreatment	Low benefit at the end of session and follow-up

DLPFC, dorsolateral prefrontal cortex; NR, not reported; NS, nonsignificant statistical difference; p, pulses; PMC, premotor cortex; RCT, randomized controlled trial; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation.* *P* <0.05.

Table 6

rTMS efficacy in other cortical areas.

Condition/authors	Study class	Study design, sample size/group, IMMPACT score (X/6), and PEDro scale (x/10)	Characteristics of the intervention (amplitude, coil type and orientation, frequency, no. of sessions, and combined intervention)	% Improvement in pain intensity active × sham (end of sessions/last follow-up)	Main clinical findings	Recommendation of benefit/harm
Diabetic neuropathy. Onesti et al., 2013[84]	III	RCT crossover (n = 13 active + sham and n = 12 sham + active), IMMPACT 5/6, and PEDro 5/10	100% RMT, H coil, vertex, 20 Hz (1500p), and 5 consecutive sessions + pharmacological	End of 5 sessions: >50% active vs sham* 3 weeks of follow-up: >30% active vs sham*	Decrease in pain intensity after sessions and follow-up	High benefit at the end of sessions and moderate benefit at 3 weeks of follow-up
Neuropathic pain. Shimizu et al., 2017[101]	II	RCT crossover (n = 18) sham (H coil), active H coil and active F8, IMMPACT 6/6, and PEDro 9/10	90% RMT, H coil and F8, lower limb region of the M1 (1 cm lateral and 1 cm posterior from Cz), 5 Hz (500p), and 5 consecutive sessions each + pharmacological	H coil: immediately after stimulation: active vs sham* 1 hour after stimulation: active vs sham* F8: immediately after stimulation: no differences between groups, NS 1 hour after stimulation: no differences between groups, NS.	Decrease in pain intensity immediately after and 1 hour after stimulation in active H coil. No differences in pain intensity between active F8 and sham groups. No significant effects (end of 5 sessions) on VAS scores	No recommendation. Percentage of pain improvement not reported.

NS, nonsignificant statistical difference; p, pulses; RCT, randomized controlled trial; RMT, resting motor threshold; VAS, Visual Analogue Scale.* $P < 0.05$.

thresholds after consecutive sessions, but not at 1-month follow-up. Another study involving SCI pain showed <30% pain reduction,[104] in accordance with recent meta-analyses.[65,74] Even if the HTLV-related pain study has been included as a neuropathic pain study, the level of evidence for tDCS efficacy in neuropathic pain would not have increased, as there were no statistical differences between active and

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Box 1. tDCS recommendations for chronic pain relief.

Electrode position:
- Unilateral pain or bilateral pain with unilateral predominance—anode over the contralateral M1 and cathode over the ipsilateral supraorbital area.

Electrodes' characteristics:
- 5 × 5 or 5 × 7 cm;
- Sponge electrodes embedded with saline solution.

Amplitude:
- 2 mA.

Duration of stimulation and number of induction sessions:
- 20 to 30 minutes;
- 5 to 10 consecutive sessions (once daily).

Indications:
- Low to moderate benefit to decrease pain intensity, without substantial risk of serious adverse event: anodal M1 tDCS for fibromyalgia;
- Potential but still uncertain benefit, without substantial risk of serious adverse event: Anodal M1 tDCS for peripheral neuropathic pain, chronic abdominal pain, and migraine; bifrontal tDCS (anode F3 and cathode F4) and M1 HD-tDCS for fibromyalgia; Oz (cathode)/Cz (anode) tDCS for migraine.

Secondary benefits:
- Possible improvement in quality of life aspects, anxiety, and pressure pain threshold.

Potential adverse events:
- Itching, tingling, skin redness, somnolence, concentration issues, headache, fatigue, light headedness, and skin burning under the electrode (rare).

Precautions:
- Prescription and follow-up by trained staff;
- History of seizures;
- Cranial bone defect;
- Cranial skin scars.

Contraindications:
- Head implants;
- Tumor below the electrodes;
- Hypertrophic skin scars below the electrodes.

Box 2. rTMS tDCS recommendations for chronic pain relief.

Coil type and positioning:
- Figure-of-eight coil placed at M1, with the handle pointing forward or backwards to the sagittal plane.

Intensity:
- 80% to 90% RMT (when using 90%, refer to safety guidelines[88]).

Frequency:
- 10 to 20 Hz.

Number of pulses:
- 1500 to 3000 per session.

Interval between trains:
- 10 to 25′.

Number of induction sessions:
- 3 to 10.

Indications:
- Low to moderate benefit, without substantial risk of serious adverse event: HF rTMS over M1 for fibromyalgia and neuropathic pain;
- Potential but still uncertain benefit, but without substantial risk of serious adverse event: HF rTMS over M1 for myofascial or musculoskeletal pain, complex regional pain syndrome, and migraine;
- So far without clear benefit: HF rTMS over left dorsolateral prefrontal cortex.

Potential adverse events:
- Headache (up to 30% of patients report neck or head pain, usually after the first session of rTMS, which is usually mitigated by a proper and comfortable patient positioning during sessions);
- Seizure (very rare when following the above recommendations; frequency <1/1000).

Precautions:
- Prescription and follow-up by trained staff;
- History of seizures;
- Cranial bone defect;
- History of substance abuse;
- History of sleep deprivation.

Contraindications:
- Intracranial metallic implants/electrodes (eg, cochlear implants and deep brain stimulation);
- Presence of uncontrolled epilepsy.

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control groups in this study. Consequently, based on the diabetic polyneuropathy study, our level B recommendation for the use of tDCS in neuropathic pain only applies for peripheral neuropathy–related pain. Future studies should be developed to investigate efficacy of this approach, and clinicians would only expect a moderate decrease of pain.

Anodal tDCS over M1 was recommended as a level B in the treatment of chronic abdominal pain and migraine, as both have one class II study showing moderate benefits. We could not compare the results of the chronic abdominal pain study with other recommendations or meta-analyses. Our recommendation for migraine is supported by a meta-analysis[102] showing that anodal M1 tDCS has a moderate to high effect size in the decrease of pain and reduction of pain killers intake. Two of the articles included in this study[3,7] were also included in our review, but one of them is a class III study using cathodal tDCS over the visual cortex.[3] The same recommendation was also achieved for bifrontal tDCS in the treatment of fibromyalgia, with one class II study. These approaches may be further investigated, as they involve unusual electrode montages that seem to be useful in the control of pain.

Regarding the position of the anode over the motor cortex, a location on the hemisphere contralateral to pain should be recommended for unilateral pain (C3 or C4). If pain is bilateral or diffuse, one may consider positioning the anode over the dominant hemisphere or contralateral to the worst pain. For axial or lower limbs pain, a reasonable position for the active electrode should be at the vertex (Cz). However, there is no study

comparing these montages, which are being recommended based only on neuroanatomical characteristics of the M1.

A level A recommendation against the use of anodal tDCS over M1 was provided for LBP as a stand-alone treatment or when associated with cognitive behavioral therapy, as none of the included studies could show minimum benefits with tDCS only. It has to be highlighted that this recommendation was based on 2 class I studies, which reinforces this statement. A recent study suggested that patients with LBP do not respond to tDCS M1 stimulation.[96] However, associating this approach with PES[43] or exercises[107] has been shown to be effective, but the exact mechanisms by which this additive effect happens are not known.

A recent comprehensive meta-analysis assessed efficacy of tDCS in the control of CP conditions,[81] showing that the effects are below the clinical relevant analgesic effect (overall 17% decrease), but significant in the increase of quality of life. Although they compared studies across their 95% confidence intervals, which is a potentially better approach than ours, comparing ranges of decrease in pain intensity (<30%, >30%, and >50%), they did not involve a subgroup analysis by pain syndromes. They pooled the studies into neuropathic and non-neuropathic pain, which can hide specificities of different pain types. Also, they did not include migraine studies, nor did consider pain satisfaction or disability measures such as timed-up-and-go and mouth opening in temporomandibular joint pain participants. Another potential limitation was to consider all 2-mA studies at high risk of bias in the blinding assessment, an assumption that is subject to

criticism given the literature showing that blinding can be effective in this setting, especially in parallel studies.[19,20]

Regarding rTMS, we recommended that high-frequency (10–20 Hz) rTMS should be used over the motor cortex area, using a figure-of-eight coil, with the handle pointing forward or backward to the sagittal plane, with intensities ranging from 80% to 90% of the resting motor threshold, 1500 to 3000 pulses per session, and intertrain interval of 10 to 25 seconds. Induction sessions would range from 3 to 10. The use of maintenance sessions is desirable, but there is still not a consensus on its effectiveness. This approach was recommended as an A level (low to moderate benefit) for the use of rTMS in the control of pain associated with fibromyalgia and neuropathic pain, and a level B recommendation for the treatment of myofascial pain, musculo-skeletal pain, CRPS, and migraine. A level B recommendation was made to avoid the use of DLPFC rTMS in the control of pain.

The level A recommendation for the use of HF rTMS at M1 in the treatment of fibromyalgia is in accordance with recent studies showing that this approach may potentially decrease pain intensity and increase quality of life. Hou et al.[45] demonstrated that HF rTMS over M1 could reduce pain, and fatigue, and improve general health and function. Their findings also show that HF rTMS over DLPFC could have the same effects but additionally influencing positively depression and sleep disturbances. In this study, rTMS and using M1 as a target yielded greater effect sizes than tDCS and using DLPFC as a target. This consensus' recommendations differ from those of Lefaucheur et al.,[57] which did not recommend the use of rTMS in patients with fibromyalgia probably likely because 3 RCTs[13,76,85] came from the same research group. However, we did not use such restraint that hindered us 2 positive and one negative class II RCT. Consequently, a level A recommendation was achieved but, again, clinicians should bear in mind that low to moderate decrease in pain intensity was provided by using HF rTMS at M1 as an add-on therapy, which was associated with improvement in quality of life, mood, and catastrophism. The attribution of a level A recommendation for the use of HF rTMS at M1 in the treatment of neuropathic pain was made taking into account 3 class III,[50,53,67] 3 class II,[1,6,52] and 2 class I[44,69] studies, showing low to moderate benefit in the decrease of pain and 1 class I study. This result is one of the most consistent and involves patients with central and peripheral neuropathic pain. It is consistent with a meta-analyses showing that HF rTMS to M1 is effective in the control of neuropathic pain,[62] although they proposed that the central origin of pain was more prone to have better results, something that we could not observe in the current available data. The same recommendation has been attributed in a consensus guideline including quite different studies.[57] However, this recommendation is in disagreement with 2 meta-analysis showing that rTMS is not effective in SCI neuropathic pain[38] or in neuropathic pain in general.[81] This last comprehensive meta-analysis made subgroup analysis separating non-neuropathic from neuro-pathic pain and showed that HF rTMS to M1 has a small but significant effect size in decreasing neuropathic pain, irre-spective of its peripheral or central origin. Considering all these results, clinicians should expect low to moderate benefit of using HF rTMS to M1 in the control of neuropathic pain due to central or peripheral origin.

This consensus made a level B recommendation for the use of HF rTMS to M1 in the control of myofascial, musculoskeletal, CRPS, and migraine because for each type of pain, yielded at least a class II study. These pain syndromes were less frequently studied, had trials with smaller effect sizes, or represented studies that so far have not been widely replicated by different research groups.

4.2. Combination of neuromodulatory approaches

Among the studies reviewed for this consensus guideline, some tDCS studies investigated the association of NIBS with other nonpharmacological interventions such as PES,[42] standardized physiotherapy,[94] exercise,[75,83,110] manual therapy,[83] or visual illusion.[96,104] These studies usually showed an additive effect, which raises the question of the clinical value of these combined strategies and their underlying mechanisms. For example, anodal tDCS of M1 has been beneficially combined with PES in individuals with chronic LBP,[42] while the supposed effects of these procedures on cortical excitability are opposite, tDCS being excitatory and PES inhibitory. Noninvasive brain stimulation techniques could also be combined with cognitive training, such as mental practice and go-no-go tasks, which are known to be potentially beneficial to individuals with CP. The combination of NIBS techniques with other therapies is believed to be able to promote a variety of neural mechanisms related to synaptic plasticity such as metaplasticity (ie, the plasticity of synaptic plasticity).[79]

4.3. Relationship between benefits and harms and adverse events

The present estimation of the relationship between benefits and harms was based on the IMMPACT recommendations, which is a potential flaw of previous studies. Benefit was expressed in terms of percentage of pain relief in the active vs sham groups. Although our classification took into account a comparison between high (>50%), moderate (>30%), or small (<30%) pain relief in the active and control groups, we considered to only assume this difference if it was statistically different. This method could have a potential limitation because it did not take into account the net difference between the active and sham arms. For example, 2 studies with >50% pain reduction in the active arms, but one with sham effect <10% and the other with sham effect >30% would be both considered as "high benefit" given this difference was statistically different, and both would be scored as having a "high" treatment effect. However, considering the induction period, this type of situation only occurred for one study,[77] where real rTMS caused significant >50% pain relief compared with sham, but the sham arm provided >30% pain relief. Except for this case, all other rTMS studies (n = 9) and all tDCS studies (n = 9) included in the present analysis provided sham effects that were <30% pain relief compared with baseline suggesting that the scoring system we used was minimally influenced by this potential classification bias. In fact, several reviews have shown that different from intuitive thinking, NIBS techniques have relatively low placebo effects in pain and depression trials.

Harm was assessed independently but scored together with benefits in our classification according to IMMPACT-based approach, which may also be another limitation. None of the included studies presented serious harmful effects for the participants, except a case of seizure, which is discussed below. This study did not involve an accurate reliability study of the benefits, but this aspect was indirectly approached through the regional experts' opinions, which also included availability of equipment and trained staff. In most of the tDCS

and rTMS studies, adverse events had statistically equal frequency after active and sham sessions. Some tDCS studies did report adverse events in active groups.[78,83,94,104,113] Only 2 rTMS[1,50] and one tDCS studies failed to mention adverse events. In one tDCS study, it was not possible to state whether the adverse events were in the active or sham group.[42] Treatments with tDCS were generally safe and well-tolerated, and there were no severe adverse events reported. The most frequent adverse events were itching, tingling, and skin redness. Somnolence, concentration issues, fatigue, light headedness, headache, and one little burning below the cathode were also reported,[83] but participants nevertheless completed the studies. The use of rTMS is commonly associated with higher risks, but these were not seen in the results of the revised studies. Headache and neck pain can happen in around 30% of the patients and might be managed by properly positioning in the stimulation chair. A checklist of potential contraindications is available[91] and should be used in the screening to rTMS utilization.

Transcranial DCS- and rTMS-related adverse events tended to resolve in minutes to hours after the end of sessions. Although the use of NIBS does not require advanced clinical facilities and specific cardiopulmonary resuscitation apparel, a trained staff is necessary to ensure proper use of equipment, electrode and coil positioning, and respect of indications, contraindications, and precautions of use. For results on the cost-estimation analysis, target population preferences, and views, please refer to supplementary file 2 (S2), available at http://links.lww.com/PR9/A35.

4.4. What is needed in a noninvasive brain stimulation facility?

This consensus work supports the use of NIBS neuromodulation for therapeutic purpose in patients with various CP syndromes using both tDCS and rTMS. For a detailed description on the recommendations of the infrastructure necessary to an NIBS facility, please refer to supplementary file 1 (S1), available at http://links.lww.com/PR9/A35.

4.5. Facilitators and barriers to application

Neuromodulation through tDCS or rTMS seems to be a fair option in the control of certain CP syndromes, as the benefits of those techniques are clearly higher than the risks. Potential facilitators to the implementation of NIBS approaches in the clinical setting also include the relative ease of training in low-complexity techniques and the possibility of combination and association with a variety of other pharmacological and nonpharmacological treatments. However, this implementation faces some important barriers that should be properly addressed in the way of further developing NIBS applications in clinical practice. Internal validity of included randomized clinical trials was good regarding selection, reporting, detection, and attrition bias, which was indirectly represented by high grades in PEDro score. However, internal validity was often compromised by the relatively low sample size of the studies, which is partially explained by difficulties in allocating participant of certain infrequent but important diseases, such as central pain syndromes. Hence, bigger studies should be encouraged, such as those with peripheral neuropathic pain, musculoskeletal pain, and migraine, which are more frequent in the population. Future studies need to address this problem through larger (>200) samples, including multicentric trials.

The cost of the devices, including maintenance, and the necessity of skilled supervision during treatment increase the requirements to set up neuromodulation clinical facilities. One can estimate approximately 40 minutes to perform a tDCS session, and up to 1 hour to perform an rTMS session, which will lead to approximately 10 to 15 patients/day using a single machine. As there is need of 5 to 10 daily sessions for each patient during the induction phase of treatment, this drastically reduces the number of patients that can be allocated to the practice of NIBS in a given center, unless several machines and a proper staff number are available. Regulatory policies are another issue in NIBS neuromodulation, regardless the amount of clinical and scientific evidence provided in this area[57,60,82] because most countries have not so far officially regulated its use for pain relief.[34]

5. Summary of recommendations

This is the first regional consensus recommendation for the use of NIBS techniques for pain relief in LA and Caribbean region. This is an updated guideline supporting the use of tDCS and rTMS for pain and recommendations based on gathered scientific knowledge behind the use of these techniques. Based on this work, level A recommendation (low to moderate benefit) was provided for the use of anodal tDCS over M1 in the control of pain in fibromyalgia, and level B (potential, but still uncertain benefit) recommendation for its use in peripheral neuropathic pain, abdominal pain, and migraine. Bifrontal (F3/F4) tDCS has also received a level B recommendation for the treatment of fibromyalgia, as well as M1 HD-tDCS. A level B recommendation has also been attributed to Oz/Cz tDCS for migraine and for secondary benefits such as improvement in quality of life, decrease in anxiety, and increase in pressure pain threshold. Regarding rTMS, level A recommendation (low to moderate benefit) was provided for HF rTMS over M1 for fibromyalgia and neuropathic pain, and a level B recommendation (potential, but still uncertain benefit) for myofascial or musculoskeletal pain, CRPS, and migraine. Level A recommendation against the use of M1 tDCS for LBP and a level B recommendation against the use of HF rTMS over the left DLPFC in the control of CP were also recommended.

There are some limitations to this study. First, we did not perform a meta-analysis. Instead, we used guidelines to classify the evidence of studies. As yet, the number of studies is still low. In future, when number of studies has increased, a meta-analysis may be considered as part of our work to address our research question. Second, as in previous studies, studies with at least 25 participants receiving active treatment were classified as sufficiently statistically powered, considering previous recommendations. However, future studies or revision of this study may consider power calculations, instead. Classification of studies may also consider other instruments such as the GRADE system and also the problem of publication bias.

6. Conclusions

This study supports the use of tDCS and rTMS, but not other forms of NIBS, in the treatment of patients with certain CP conditions. Also, this is one of the few recommendations to argue against the use of some NINS techniques for some specific types of CP. We have also covered, in a systematic and AGREE-compliant manner, several crucial points that are frequently overlooked such as facilitators and barriers to the implementation of the recommendations. Likewise, we reported the first effort to provide a cost-estimation analysis

for the use of NIBS techniques for pain in clinical practice in LA and Caribbean region. As all guideline recommendations, time will refine the current concepts and correct potential misinterpretations present in the actual study and, thus, periodic refreshing of this work will be scheduled.

Disclosures

Acknowledgments

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A35.

References

[1] Ahmed MA, Mohamed SA, Sayed D. Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. Neurol Res 2011;33: 953–8.

[2] Angulo J, Gonzalez R, Hernandez L, Hernandez-Ortiz A, Jaque J, Lara-Solares A, Robles San Roman M, Vacas J. Musculoskeletal chronic pain: Latin-American expert panel review based on scientific evidence [in Spanish]. Drugs Today (Barc) 2011;47(suppl C):1–31.

[3] Antal A, Kriener N, Lang N, Boros K, Paulus W. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia 2011;31:820–8.

[4] Antal A, Terney D, Kuhnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manage 2010;39: 890–903.

[5] Araujo LQ, Macintyre CR, Vujacich C. Epidemiology and burden of herpes zoster and post-herpetic neuralgia in Australia, Asia and South America. Herpes 2007;14(suppl 2):40–4.

[6] Attal N, Ayache SS, Ciampi De Andrade D, Mhalla A, Baudic S, Jazat F, Ahdab R, Neves DO, Sorel M, Lefaucheur JP, Bouhassira D. Repetitive transcranial magnetic stimulation and transcranial direct-current stimulation in neuropathic pain due to radiculopathy: a randomized sham-controlled comparative study. PAIN 2016;157:1224–31.

[7] Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, Punjaruk W, Thinkhamrop B, Auvichayapat N. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. J Med Assoc Thai 2012;95:1003–12.

[8] Ayache SS, Palm U, Chalah MA, Al-Ani T, Brignol A, Abdellaoui M, Dimitri D, Sorel M, Creange A, Lefaucheur JP. Prefrontal tDCS decreases pain in patients with multiple sclerosis. Front Neurosci 2016;10:147.

[9] Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. J Neurosci 2011;31:13981–90.

[10] Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006;26:12165–73.

[11] Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. PLoS One 2011;6:e26010.

[12] Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010; 9:807–19.

[13] Baudic S, Attal N, Mhalla A, Ciampi de Andrade D, Perrot S, Bouhassira D. Unilateral repetitive transcranial magnetic stimulation of the motor cortex does not affect cognition in patients with fibromyalgia. J Psychiatr Res 2013;47:72–7.

[14] Boulanger A, Clark AJ, Squire P, Cui E, Horbay GL. Chronic pain in Canada: have we improved our management of chronic noncancer pain? Pain Res Manag 2007;12:39–47.

[15] Boyer L, Dousset A, Roussel P, Dossetto N, Cammilleri S, Piano V, Khalfa S, Mundler O, Donnet A, Guedj E. rTMS in fibromyalgia: a randomized trial evaluating QoL and its brain metabolic substrate. Neurology 2014;82:1231–8.

[16] Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. Eur J Neurol 2004;11:577–81.

[17] Brietzke AP, Rozisky JR, Dussan-Sarria JA, Deitos A, Laste G, Hoppe PF, Muller S, Torres IL, Alvares-da-Silva MR, de Amorim RF, Fregni F, Caumo W. Neuroplastic effects of transcranial direct current stimulation on painful symptoms reduction in chronic hepatitis C: a phase II randomized, double blind, sham controlled trial. Front Neurosci 2015;9: 498.

[18] Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F. Placebo response of non-pharmacological and pharmacological trials in major depression: a systematic review and meta-analysis. PLoS One 2009;4:e4824.

[19] Brunoni AR, Schestatsky P, Lotufo PA, Bensenor IM, Fregni F. Comparison of blinding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial. Clin Neurophysiol 2014;125:298–305.

[20] Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, Boggio PS, Lotufo PA, Bensenor IM, Fregni F. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 2013;70: 383–91.

[21] Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W, Taylor R, Tronnier V, Truini A, Attal N. EAN guidelines on central neurostimulation therapy in chronic pain conditions. Eur J Neurol 2016;23:1489–99.

[22] Dall'Agnol L, Medeiros LF, Torres IL, Deitos A, Brietzke A, Laste G, de Souza A, Vieira JL, Fregni F, Caumo W. Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: an explanatory double-blinded, randomized, sham-controlled trial. J Pain 2014;15: 845–55.

[23] de Oliveira RA, de Andrade DC, Mendonca M, Barros R, Luvisoto T, Myczkowski ML, Marcolin MA, Teixeira MJ. Repetitive transcranial magnetic stimulation of the left premotor/dorsolateral prefrontal cortex does not have analgesic effect on central poststroke pain. J Pain 2014; 15:1271–81.

[24] Donnell A, D Nascimento T, Lawrence M, Gupta V, Zieba T, Truong DQ, Bikson M, Datta A, Bellile E, DaSilva AF. High-definition and non-invasive brain modulation of pain and motor dysfunction in chronic TMD. Brain Stimul 2015;8:1085–92.

[25] Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. PAIN 2010;149:338–44.

[26] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. PAIN 2005;113:9–19.

[27] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.

[28] Dy SM, Bennett WL, Sharma R, Zhang A, Waldfogel JM, Nesbit SA, Yeh HC, Chelladurai Y, Feldman D, Wilson LM, Robinson KA. Preventing complications and treating symptoms of diabetic peripheral neuropathy. Rockville, MD: Agency for Healthcare Research and Quality (US), 2017.

Report No.: 17-EHC005-EF.AHRQ Comparative Effectiveness Reviews.

[29] Fagerlund AJ, Hansen OA, Aslaksen PM. Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. PAIN 2015;156:62–71.

[30] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.

[31] Flor H. Cortical reorganisation and chronic pain: implications for rehabilitation. J Rehabil Med 2003(41 suppl):66–72.

[32] Flor H. Maladaptive plasticity, memory for pain and phantom limb pain: review and suggestions for new therapies. Expert Rev Neurother 2008; 8:809–18.

[33] Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, Bravo R, Rigonatti SP, Freedman SD, Nitsche MA, Pascual-Leone A, Boggio PS. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum 2006;54:3988–98.

[34] Fregni F, Nitsche MA, Loo CK, Brunoni AR, Marangolo P, Leite J, Carvalho S, Bolognini N, Caumo W, Paik NJ, Simis M, Ueda K, Ekhitari H, Luu P, Tucker DM, Tyler WJ, Brunelin J, Datta A, Juan CH, Venkatasubramanian G, Boggio PS, Bikson M. Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. Clin Res Regul Aff 2015;32:22–35.

[35] Fricova J, Klirova M, Masopust V, Novak T, Verebova K, Rokyta R. Repetitive transcranial magnetic stimulation in the treatment of chronic orofacial pain. Physiol Res 2013;62(suppl 1):S125–S134.

[36] Gabis L, Shklar B, Baruch YK, Raz R, Gabis E, Geva D. Pain reduction using transcranial electrostimulation: a double blind "active placebo" controlled trial. J Rehabil Med 2009;41:256–61.

[37] Galhardoni R, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziyama HH, Marcolin MA, Bouhassira D, Teixeira MJ, de Andrade DC. Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. Arch Phys Med Rehabil 2015;96(4 suppl):S156–S172.

[38] Gao F, Chu H, Li J, Yang M, Du L, Li J, Chen L, Yang D, Zhang H, Chan C. Repetitive transcranial magnetic stimulation for pain after spinal cord injury: a systematic review and meta-analysis. J Neurosurg Sci 2017;61: 514–22.

[39] Garcia JB, Hernandez-Castro JJ, Nunez RG, Pazos MA, Aguirre JO, Jreige A, Delgado W, Serpentegui M, Berenguel M, Cantemir C. Prevalence of low back pain in Latin America: a systematic literature review. Pain Physician 2014;17:379–91.

[40] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388: 1545–602.

[41] Hagenacker T, Bude V, Naegel S, Holle D, Katsarava Z, Diener HC, Obermann M. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. J Headache Pain 2014;15:78.

[42] Hazime FA, Baptista AF, de Freitas DG, Monteiro RL, Maretto RL, Hasue RH, Joao SMA. Treating low back pain with combined cerebral and peripheral electrical stimulation: a randomized, double-blind, factorial clinical trial. Eur J Pain 2017;21:1132–43.

[43] Hazime FA, da Cunha RA, Soliaman RR, Romancini ACB, Pochini AC, Ejnisman B, Baptista AF. Anodal transcranial direct current stimulation (Tdcs) increases isometric strength of shoulder rotators muscles in handball players. Int J Sports Phys Ther 2017;12:402–7.

[44] Hosomi K, Shimokawa T, Ikoma K, Nakamura Y, Sugiyama K, Ugawa Y, Uozumi T, Yamamoto T, Saitoh Y. Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. PAIN 2013; 154:1065–72.

[45] Hou WH, Wang TY, Kang JH. The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials. Rheumatology (Oxford) 2016;55:1507–17.

[46] Hubbard CS, Khan SA, Keaser ML, Mathur VA, Goyal M, Seminowicz DA. Altered brain structure and function correlate with disease severity and pain catastrophizing in migraine patients. eNeuro 2014;1:e20.14.

[47] Itz CJ, Geurts JW, van Kleef M, Nelemans P. Clinical course of non-specific low back pain: a systematic review of prospective cohort studies set in primary care. Eur J Pain 2013;17:5–15.

[48] Johnson MI, Elzahaf RA, Tashani OA. The prevalence of chronic pain in developing countries. Pain Manag 2013;3:83–6.

[49] Jutzeler CR, Curt A, Kramer JL. Relationship between chronic pain and brain reorganization after deafferentation: a systematic review of functional MRI findings. Neuroimage Clin 2015;9:599–606.

[50] Kang BS, Shin HI, Bang MS. Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury. Arch Phys Med Rehabil 2009;90:1766–71.

[51] Kang EK, Baek MJ, Kim S, Paik NJ. Non-invasive cortical stimulation improves post-stroke attention decline. Restor Neurol Neurosci 2009; 27:645–50.

[52] Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Long lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005;76:833–8.

[53] Khedr EM, Kotb HI, Mostafa MG, Mohamad MF, Amr SA, Ahmed MA, Karim AA, Kamal SM. Repetitive transcranial magnetic stimulation in neuropathic pain secondary to malignancy: a randomized clinical trial. Eur J Pain 2015;19:519–27.

[54] Kim YJ, Ku J, Kim HJ, Im DJ, Lee HS, Han KA, Kang YJ. Randomized, sham controlled trial of transcranial direct current stimulation for painful diabetic polyneuropathy. Ann Rehabil Med 2013;37:766–76.

[55] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–56.

[56] Leao Ferreira KA, Bastos TR, Andrade DC, Silva AM, Appolinario JC, Teixeira MJ, Latorre MD. Prevalence of chronic pain in a metropolitan area of a developing country: a population-based study. Arq Neuropsiquiatr 2016;74:990–8.

[57] Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipovic SR, Hummel FC, Jaaskelainen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schonfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:2150–206.

[58] Lefaucheur JP, Andre-Obadia N, Poulet E, Devanne H, Haffen E, Londero A, Cretin B, Leroi AM, Radtchenko A, Saba G, Thai-Van H, Litre CF, Vercueil L, Bouhassira D, Ayache SS, Farhat WH, Zouari HG, Mylius V, Nicolier M, Garcia-Larrea L. French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications [in French]. Neurophysiol Clin 2011;41: 221–95.

[59] Lefaucheur JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimul 2008;1:337–44.

[60] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P, Mylius V, Nitsche MA, Padberg F, Palm U, Poulet E, Priori A, Rossi S, Schecklmann M, Vanneste S, Ziemann U, Garcia-Larrea L, Paulus W. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol 2017; 128:56–92.

[61] Lembke A. Why doctors prescribe opioids to known opioid abusers. N Engl J Med 2012;367:1580–1.

[62] Leung A, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, Saitoh Y, Andre-Obadia N, Rollnik J, Wallace M, Chen R. rTMS for suppressing neuropathic pain: a meta-analysis. J Pain 2009;10:1205–16.

[63] Leung A, Metzger-Smith V, He Y, Cordero J, Ehlert B, Song D, Lin L, Shahrokh G, Tsai A, Vaninetti M, Rutledge T, Polston G, Sheu R, Lee R. Left dorsolateral prefrontal cortex rTMS in alleviating MTBI related headaches and depressive symptoms. Neuromodulation 2018;21: 390–401.

[64] Leung A, Shukla S, Fallah A, Song D, Lin L, Golshan S, Tsai A, Jak A, Polston G, Lee R. Repetitive transcranial magnetic stimulation in managing mild Traumatic brain injury-related headaches. Neuromodulation 2016;19:133–41.

[65] Luedtke K, Rushton A, Wright C, Geiss B, Juergens TP, May A. Transcranial direct current stimulation for the reduction of clinical and experimentally induced pain: a systematic review and meta-analysis. Clin J Pain 2012;28:452–61.

[66] Luedtke K, Rushton A, Wright C, Jurgens T, Polzer A, Mueller G, May A. Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial. BMJ 2015;350: h1640.

[67] Ma SM, Ni JX, Li XY, Yang LQ, Guo YN, Tang YZ. High-frequency repetitive transcranial magnetic stimulation reduces pain in postherpetic neuralgia. Pain Med 2015;16:2162–70.

[68] Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 2003;83:713–21.

[69] Malavera A, Silva FA, Fregni F, Carrillo S, Garcia RG. Repetitive transcranial magnetic stimulation for phantom limb pain in land mine victims: a double-blinded, randomized, sham-controlled trial. J Pain 2016;17:911–18.

[70] Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. Pain Pract 2013;13: 131–45.

[71] Masse-Alarie H, Beaulieu LD, Preuss R, Schneider C. The side of chronic low back pain matters: evidence from the primary motor cortex excitability and the postural adjustments of multifidi muscles. Exp Brain Res 2017;235:647–59.

[72] Masse-Alarie H, Schneider C. Revisiting the corticomotor plasticity in low back pain: challenges and perspectives. Healthcare (Basel) 2016;4: 67.

[73] Medeiros LF, Caumo W, Dussan-Sarria J, Deitos A, Brietzke A, Laste G, Campos-Carraro C, de Souza A, Scarabelot VL, Cioato SG, Vercelino R, de Castro AL, Araujo AS, Bello-Klein A, Fregni F, Torres IL. Effect of deep intramuscular stimulation and transcranial magnetic stimulation on neurophysiological biomarkers in chronic myofascial pain syndrome. Pain Med 2016;17:122–35.

[74] Mehta S, McIntyre A, Guy S, Teasell RW, Loh E. Effectiveness of transcranial direct current stimulation for the management of neuropathic pain after spinal cord injury: a meta-analysis. Spinal Cord 2015;53:780–5.

[75] Mendonca ME, Simis M, Grecco LC, Battistella LR, Baptista AF, Fregni F. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: a randomized placebo-controlled clinical trial. Front Hum Neurosci 2016;10:68.

[76] Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. PAIN 2011; 152:1478–85.

[77] Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. J Neurol 2013;260:2793–801.

[78] Morin A, Leonard G, Gougeon V, Cyr MP, Waddell G, Bureau YA, Girard I, Morin M. Efficacy of transcranial direct-current stimulation in women with provoked vestibulodynia. Am J Obstet Gynecol 2017;216: 584.e1–584.e11.

[79] Muller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. Neuroscientist 2015;21:185–202.

[80] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basanez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fevre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gonzalez-Medina D, Gosselin R, Grainger R, Grant B, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N,

Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Laden F, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Levinson D, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mock C, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA III, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leon FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiebe N, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, AlMazroa MA, Memish ZA. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197–223.

[81] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018;4:CD008208.

[82] O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2014:CD008208.

[83] Oliveira LB, Lopes TS, Soares C, Maluf R, Goes BT, Sa KN, Baptista AF. Transcranial direct current stimulation and exercises for treatment of chronic temporomandibular disorders: a blind randomised-controlled trial. J Oral Rehabil 2015;42:723–32.

[84] Onesti E, Gabriele M, Cambieri C, Ceccanti M, Raccah R, Di Stefano G, Biasiotta A, Truini A, Zangen A, Inghilleri M. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. Eur J Pain 2013;17:1347–56.

[85] Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007;130:2661–70.

[86] Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. Eur J Pain 2014;18: 1067–80.

[87] Picarelli H, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT, Fonoff ET, Pridmore S, Marcolin MA. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. J Pain 2010; 11:1203–10.

[88] Queiroz LP, Silva Junior AA. The prevalence and impact of headache in Brazil. Headache 2015;55(suppl 1):32–8.

[89] Reidler JS, Mendonca ME, Santana MB, Wang X, Lenkinski R, Motta AF, Marchand S, Latif L, Fregni F. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. J Pain 2012;13:450–8.

[90] Riberto M, Marcon Alfieri F, Monteiro de Benedetto Pacheco K, Dini Leite V, Nemoto Kaihami H, Fregni F, Rizzo Battistella L. Efficacy of transcranial direct current stimulation coupled with a multidisciplinary rehabilitation program for the treatment of fibromyalgia. Open Rheumatol 2011;5:45–50.

[91] Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.

[92] Sa KN, Baptista AF, Matos MA, Lessa I. Chronic pain and gender in Salvador population, Brazil. PAIN 2008;139:498–506.

[93] Sa KN, Pereira Cde M, Souza RC, Baptista AF, Lessa I. Knee pain prevalence and associated factors in a Brazilian population study. Pain Med 2011;12:394–402.

[94] Sakrajai P, Janyacharoen T, Jensen MP, Sawanyawisuth K, Auvichayapat N, Tunkamnerdthai O, Keeratitanont K, Auvichayapat P. Pain reduction in myofascial pain syndrome by anodal transcranial direct current stimulation combined with standard treatment: a randomized controlled study. Clin J Pain 2014;30:1076–83.

[95] San-Martin DL, Santos DN, Baptista AF; Pain Study Group. Pain prevalence, characteristics and associated factors in human T-cell lymphotropic virus type 1 infected patients: a systematic review of the literature. Braz J Infect Dis 2016;20:592–8.

[96] Schabrun SM, Burns E, Thapa T, Hodges P. The response of the primary motor cortex to neuromodulation is altered in chronic low back pain: a preliminary study. Pain Med 2018;19:1227–36.

[97] Schreiber KL, Loggia ML, Kim J, Cahalan CM, Napadow V, Edwards RR. Painful after-sensations in fibromyalgia are linked to catastrophizing and differences in brain response in the medial temporal lobe. J Pain 2017;18:855–67.

[98] Seifert F, Maihofner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. Cell Mol Life Sci 2009;66:375–90.

[99] Seifert F, Maihofner C. Functional and structural imaging of pain-induced neuroplasticity. Curr Opin Anaesthesiol 2011;24:515–23.

[100] Seymour B. The maladaptive brain: excitable pathways to chronic pain. Brain 2012;135:316–18.

[101] Shimizu T, Hosomi K, Maruo T, Goto Y, Yokoe M, Kageyama Y, Shimokawa T, Yoshimine T, Saitoh Y. Efficacy of deep rTMS for neuropathic pain in the lower limb: a randomized, double-blind crossover trial of an H-coil and figure-8 coil. J Neurosurg 2017;127:1172–80.

[102] Shirahige L, Melo L, Nogueira F, Rocha S, Monte-Silva K. Efficacy of noninvasive brain stimulation on pain control in migraine patients: a systematic review and meta-analysis. Headache 2016;56:1565–96.

[103] Short EB, Borckardt JJ, Anderson BS, Frohman H, Beam W, Reeves ST, George MS. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. PAIN 2011;152:2477–84.

[104] Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, Navarro X, Pascual-Leone A. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain 2010;133:2565–77.

[105] Souto G, Borges IC, Goes BT, de Mendonca ME, Goncalves RG, Garcia LB, Sa KN, Coutinho MR, Galvao-Castro B, Fregni F, Baptista AF. Effects of tDCS-induced motor cortex modulation on pain in HTLV-1: a blind randomized clinical trial. Clin J Pain 2014;30:809–15.

[106] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17:37–53.

[107] Straudi S, Buja S, Baroni A, Pavarelli C, Pranovi G, Fregni F, Basaglia N. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial. Clin Rehabil 2018;32:1348–56.

[108] To WT, James E, Ost J, Hart J Jr, De Ridder D, Vanneste S. Differential effects of bifrontal and occipital nerve stimulation on pain and fatigue using transcranial direct current stimulation in fibromyalgia patients. J Neural Transm (Vienna) 2017;124:799–808.

[109] Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 1991;52:137–9.

[110] Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, Boggio PS, Fregni F. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. J Pain Manag 2009;2:353–61.

[111] van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. PAIN 2014;155:654–62.

[112] Vieira AS, Baptista AF, Mendes L, Silva KS, Gois SC, Lima FM, Souza I, Sa KN. Impact of neuropathic pain at the population level. J Clin Med Res 2014;6:111–19.

[113] Volz MS, Farmer A, Siegmund B. Reduction of chronic abdominal pain in patients with inflammatory bowel disease through transcranial direct current stimulation: a randomized controlled trial. PAIN 2016;157:429–37.

[114] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basanez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fevre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA III, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leon FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163–96.

[115] Waldfogel JM, Nesbit SA, Dy SM, Sharma R, Zhang A, Wilson LM, Bennett WL, Yeh HC, Chelladurai Y, Feldman D, Robinson KA. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. Neurology 2017;88:1958–67.

[116] Wrigley PJ, Gustin SM, McIndoe LN, Chakiath RJ, Henderson LA, Siddall PJ. Longstanding neuropathic pain after spinal cord injury is refractory to transcranial direct current stimulation: a randomized controlled trial. PAIN 2013;154:2178–84.

[117] Xie YF, Huo FQ, Tang JS. Cerebral cortex modulation of pain. Acta Pharmacol Sin 2009;30:31–41.

[118] Young NA, Sharma M, Deogaonkar M. Transcranial magnetic stimulation for chronic pain. Neurosurg Clin N Am 2014;25:819–32.

[119] Zhu CE, Yu B, Zhang W, Chen WH, Qi Q, Miao Y. Effectiveness and safety of transcranial direct current stimulation in fibromyalgia: a systematic review and meta-analysis. J Rehabil Med 2017;49:2–9.

[120] Ziemann U, Siebner HR. Modifying motor learning through gating and homeostatic metaplasticity. Brain Stimul 2008;1:60–6.