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The analgesic effect of EEG neurofeedback for people with chronic pain: A systematic review and meta-analysis

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ABSTRACT
Electroencephalographic (EEG) neurofeedback has been utilised to regulate abnormal brain activity associated with chronic pain.

In this systematic review, we synthesised the evidence from randomised controlled trials (RCTs) to evaluate the effect of EEG neurofeedback on chronic pain using random effects meta-analyses. Additionally, we performed a narrative review to explore the results of non-randomised studies. The quality of included studies was assessed using Cochrane risk of bias tools, and the GRADE system was used to rate the certainty of evidence.

Ten RCTs and 13 non-randomised studies were included. The primary meta-analysis on nine eligible RCTs indicated that although there is low confidence, EEG neurofeedback may have a clinically meaningful effect on pain intensity in short-term. Removing the studies with high risk of bias from the primary meta-analysis resulted in moderate confidence that there remained a clinically meaningful effect on pain intensity. We could not draw any conclusion from the findings of non-randomised studies, as they were mostly non-comparative trials or explorative case series. However, the extracted data indicated that the neurofeedback protocols in both RCTs and non-randomised studies mainly involved the conventional EEG neurofeedback approach, which targeted reinforcing either alpha or sensorimotor rhythms and suppressing theta and/or beta bands on one brain region at a time. A post-hoc analysis of RCTs utilising the conventional approach resulted in a clinically meaningful effect estimate for pain intensity.

Although there is promising evidence on the analgesic effect of EEG neurofeedback, further studies with larger sample sizes and higher quality of evidence are required.

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INTRODUCTION

Chronic pain is a common and heterogenous condition\textsuperscript{1,2}, which is estimated to affect about half of the adult population\textsuperscript{3}. Chronic pain may result from a wide variety of pathophysiological conditions\textsuperscript{2} such as damage to the central (e.g., spinal cord injury and traumatic brain injury) or peripheral nervous system (e.g., neuropathy), tissue injury (e.g., arthritis), or other pain syndromes with unknown pathologies such as primary headache and fibromyalgia. In addition to physical limitations, chronic pain is often accompanied by psychosocial problems affecting emotional, cognitive, and social functioning\textsuperscript{4}. Thus, it is essential to evaluate the psychosocial factors in addition to pain outcomes in pain management studies.

Generally, chronic pain conditions are treated pharmacologically\textsuperscript{5}, however, evidence for the effect of analgesic medications on chronic pain is limited and typically of low quality\textsuperscript{6}. Accumulating evidence shows an increased risk of abuse, overdose, and myocardial infarction associated with long-term opioid therapy\textsuperscript{7}. Severe side effects of pharmacological treatments signify the need for nonpharmacological pain therapies. Understanding the pathophysiological mechanisms of pain development and chronicity has led researchers to explore nonpharmacological interventions which target brain activity. Non-invasive brain stimulation techniques including repetitive transcranial magnetic stimulation, cranial electrotherapy stimulation, and transcranial direct current stimulation aim to directly alter abnormal brain activity and thereby reduce pain\textsuperscript{8}. However, high-quality evidence to support the effectiveness of such techniques for chronic pain is lacking\textsuperscript{8,9}. In the past few decades, neurofeedback using electroencephalography (EEG) techniques has been used to reduce pain by aiming to modulate the electrical brain activity associated with chronic pain\textsuperscript{10,11}.

EEG neurofeedback aims to regulate the abnormal EEG frequencies thought to be responsible for the ongoing experience of pain\textsuperscript{10,12-14}. In the conventional EEG neurofeedback approach, surface EEG is recorded from one or more electrode sites, depending on the type or localisation of pain\textsuperscript{15}, often from the sensorimotor cortex\textsuperscript{16}. The targeted frequency bands are extracted and processed in real-time, then their calculated power is presented to the individual as a form of positive or negative reinforcement\textsuperscript{11,17}. Examples of such reinforcement include advancement or setbacks in a video game, and positive/negative visual and auditory feedback\textsuperscript{18,19}. Different EEG neurofeedback techniques train individuals with chronic pain to gain control over their abnormal brain activity, which ultimately leads to pain reduction\textsuperscript{20,21}.

Previous reviews on the effect of EEG neurofeedback on chronic pain mainly focus on specific pain conditions such as fibromyalgia\textsuperscript{22,23} or cancer-related pain\textsuperscript{24}. The results of these systematic
reviews are unable to address the question of whether EEG neurofeedback is effective for different pain conditions. Although a recent systematic review by Patel and colleagues found a medium effect size of pain reduction favouring neurofeedback treatments for chronic pain compared to control groups, the review was not exclusive to EEG neurofeedback. Further, they included studies involving functional magnetic resonance imaging (fMRI) neurofeedback and one study that investigated EEG neurofeedback in the same sample who underwent other treatments. Combining two or more different treatment paradigms makes it difficult to evaluate the effect of one specific intervention, and the review authors did not perform a subgroup analysis for the two types of neurofeedback. Thus, evidence for the analgesic effects of EEG neurofeedback in chronic pain populations remains unclear.

Here we report a systematic review and meta-analysis to evaluate the evidence from randomised controlled trials (RCTs) for the analgesic effect of EEG neurofeedback interventions for people with chronic pain compared to control or other treatment groups. We also synthesised evidence for the effects of EEG neurofeedback on pain-related psychological symptoms and resting-state brain activity from RCTs. Further, we explored the results of non-randomised studies in a narrative review, and summarised the details of the neurofeedback protocols and evidence for adverse events related to EEG neurofeedback interventions from all eligible clinical trials.

METHODS
We conducted this systematic review according to the Cochrane Handbook and reported it in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 Guidelines. The PRISMA checklist is provided in Appendix. We registered the protocol of this systematic review in PROSPERO (CRD42020177608) and the published protocol can be found here.

Criteria for the eligible studies

Types of studies
We included RCTs that compared EEG neurofeedback with a control group (i.e., sham, no treatment, and waitlist) or another treatment group. In addition, non-randomised studies, including any single-arm interventional studies, were included for a narrative review. The findings of these studies are reported for substantiating evidence on different EEG neurofeedback...
protocols and adverse effects. Studies that investigated EEG neurofeedback in conjunction with other interventions were excluded.

**Types of participants**

We included studies that involved individuals with any type of chronic pain, defined as persistent or recurrent pain lasting for at least three months\(^2\). Studies that involved participants with migraines and recurrent headaches were included as these conditions are also considered as chronic pain. There was no restriction on sex or age of the participants. We excluded studies that involved individuals experiencing pain for less than three months and individuals with experimentally induced pain. Participants in the included studies were allowed to take their medications as usual.

**Types of intervention**

We included studies that investigated the EEG neurofeedback intervention for people with chronic pain, regardless of the number and duration of treatment sessions, the neurofeedback protocol, and the targeted brain areas.

**Types of outcome measures**

The primary outcome was pain intensity, assessed using a self-report rating scale such as the visual analogue scale (VAS) or the numeric rating scale (NRS). The secondary outcome measures were self-reported fatigue, sleep quality, pain interference, depressive and anxiety symptoms, as well as calculated resting-state EEG power. Eligible studies were required to have outcomes measured on at least two occasions, one before/at the beginning of the intervention and one after/at the end of the intervention. Studies were not excluded if they used different rating scales for the extracted outcomes. The reports of negative side effects and adverse events were also extracted and summarised.

**Search strategy for studies identification**

We searched five electronic databases (Cochrane CENTRAL, MEDLINE, Embase, PsycInfo, and CINAHL) for published studies and clinical trial registries (e.g., ClinicalTrials.gov and WHO Clinical Trial Registry) for completed unpublished studies\(^{28}\). Only studies on humans and in
English language were included, with no restriction on the publication years. The initial search (July 2020) was updated in January 2021. Search strategies were established using a combination of different keywords for pain, EEG, and neurofeedback to identify the relevant literature. The search syntax for the Cochrane CENTRAL is included in Appendix 2 and it was customised for each database. While the review was in progress, we used a citation alert on Google Scholar to receive the recent relevant studies as they were published. Additionally, we examined reference lists of relevant reviews to identify any previously missed studies.

**Data collection**

**Study selection**

Duplicate records were identified and removed when storing the search results in EndNote (Version 9) and when importing to Covidence\(^3^0\) for managing the systematic review. Next, two review authors independently assessed the title and abstract of each record against the eligibility criteria, then screened the full-text of studies for eligibility. Any uncertainty was discussed between the two authors and resolved by consensus.

**Data extraction**

Two review authors independently conducted data extraction using a customised spreadsheet. In cases of inconsistency, a third review author was consulted to resolve the discrepancies.

We extracted the following information from the eligible studies: *study characteristics; participants characteristics; interventions;* and *outcome measures*, including measures of the primary and secondary outcomes at post-intervention timepoints. The post-intervention measures were grouped into three categories: short-term for less than one week, mid-term for one to six weeks, and long-term for more than six weeks follow-up assessments. When a study reported more than one measure of pain intensity, we extracted only a single measure, prioritising in this order: 100-mm/10-cm VAS, 11-point NRS, and then pain intensity rating from composite scales\(^3^1\). In this manuscript, the 'short-term follow-up' measure will be called 'post-treatment' measure.

When a study used two rating scales for the secondary outcomes (Kayiran et al. reported scores from both Hamilton and Beck Depression Scales), we extracted both outcomes and combined the effect sizes, noting dependence for related outcomes, by assuming a correlation between scales.
The combined effect size was calculated using the combined mean and variance from the following equations:

\[
\overline{M} = \frac{1}{2}(M_1 + M_2) \quad (1)
\]

\[
V_{\overline{M}} = \frac{1}{4}(V_{M1} + V_{M2} + 2r\sqrt{V_{M1}V_{M2}}) \quad (2)
\]

where \( M_1 \) and \( M_2 \) are the mean scores, \( V_{M1} \) and \( V_{M2} \) are the mean variances, and the \( \overline{M} \) and \( V_{\overline{M}} \) are the combined mean and variance, respectively.

**Risk of bias assessment**

Two review authors independently assessed the ‘risk of bias’ of the eligible studies using the Cochrane Risk of Bias (RoB 1.0) tool for RCTs and the Cochrane Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool for non-randomised studies. Disagreements were discussed and resolved through consensus. We used the Cochrane RoB 1.0 tool to assess risk of bias in participant selection, trial performance, detection, attrition, and reporting outcomes. The ROBINS-I tool covers confounding and participant selection (pre-intervention), intervention classification (during intervention), deviations, missing data, measurements and selection of reported results (post-intervention).

**Data synthesis**

**Meta-analysis**

We quantitatively synthesised the data from RCTs by meta-analyses in R (R version 4.0.4) using the ‘metafor’ package. Meta-analyses were conducted using a random-effects model and ‘restricted maximum-likelihood estimator’ to calculate the pooled mean difference and 95% confidence interval (CI). In addition, we estimated the 95% prediction interval for the pooled effect.

The primary and secondary outcome data were converted to a 0-100 point scale (mean and standard deviation). We used the same approach for the numerical and Likert scales in dividing the final scale scores by the range of that scale and then multiplying the result by 100. We defined the minimal clinically important effect of the intervention on pain intensity by a threshold of 10 points on the 0-100 point scale. Further, we adopted a 10-point threshold as the minimal
clinically meaningful change for depressive symptoms, anxiety symptoms, fatigue, and sleep quality.

Heterogeneity was considered significant when \( p<0.1 \) in \( \chi^2 \) test\(^{26} \). We also quantified the degree of heterogeneity using the \( I^2 \) statistic, which was considered small (<25%), moderate (25%-74%), or large (≥75%).

**Subgroup and sensitivity analysis**

We conducted three post-hoc subgroup analyses on RCTs according to: 1) the type of chronic pain, 2) the EEG neurofeedback type, and 3) the blinding of participants. Further, we assessed the impact of studies with high risk of bias on the primary outcome by rerunning the analysis with those studies excluded.

**Meta-regression**

As the mean age differed across the included RCTs (see Table.S1, Appendix-4), we performed a post-hoc meta-regression to explore whether there was an association between the effect of EEG neurofeedback and the participants age. Two RCTs\(^{38,39} \) did not report data on age, so seven trials were included in the meta-regression.

**Certainty of evidence**

We applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating\(^{40} \) to estimate the certainty of the intervention effect on the primary and secondary outcomes. There are four levels of certainty within the GRADE rating: very low, low, moderate, and high. To assign one of the four levels of certainty to the outcomes, we considered five factors including (1) risk of bias: when there was a high risk of bias for >25% and <50% of the included studies participants, we downgraded two levels, and when >50% of participants were from high risk of bias studies, we downgraded one level\(^{41} \); (2) imprecision: when the total number of participants was <400 for continuous data and <300 for dichotomous data, we downgraded one level\(^{42} \); (3) inconsistency: if there was significant heterogeneity (\( p<0.1 \)) in the study populations we downgraded one level\(^{43} \); (4) indirectness: when the conventional EEG neurofeedback was not applied to >50% of participants, we downgraded by one\(^{44} \), some included studies were targeted only at specific populations within the target population e.g. fibromyalgia, reducing confidence that their effect extended beyond those specific populations, but this was not regarded as a
sufficient concern to require downgrading; and (5) publication bias: if a publication bias was detected, we downgraded by one\textsuperscript{45}. We evaluated the publication bias using visual inspection of funnel plot asymmetry.

RESULTS

Search results

The search results are summarised in a PRISMA flow diagram (Figure 1). Electronic database searches identified 400 potentially eligible articles, while 11 studies were added manually during the review process. After removing duplicates, we screened the title and abstract of 340 articles, from which 75 full-text articles were retrieved to assess for eligibility. Finally, 48 articles were excluded for the reasons detailed in Figure 1, while four other articles were excluded after data extraction due to overlapped population. Thus, a total of 23 articles were included in the review, consisting of 10 RCTs and 13 non-randomised studies.

Randomised controlled trials

Details of included studies

The included RCTs examined 186 individuals in the neurofeedback group and 167 individuals in the control and other treatment groups, combined. Four studies compared the intervention with sham treatment\textsuperscript{12,46-48}, one with no treatment\textsuperscript{39}, one with waitlist\textsuperscript{21}, and one with an attention-control condition\textsuperscript{49}. One study included both a control group and another treatment (transcutaneous electrical nerve stimulation) group\textsuperscript{50}, however, we only included the control group in the meta-analysis, because we only included other treatment groups in the meta-analysis when there was no control group. Two other studies had other treatments as comparisons: one trial\textsuperscript{51} compared neurofeedback with taking Escitalopram; and the other trial\textsuperscript{38} randomised participants into three groups of alpha biofeedback, electromyographic biofeedback, and temperature biofeedback. Four chronic pain conditions were investigated; five studies on fibromyalgia\textsuperscript{46,47,49,51,52}, three on migraine/headache\textsuperscript{38,39,50}, one on peripheral neuropathy\textsuperscript{21}, and one unpublished study on knee osteoarthritis-related pain\textsuperscript{48}.

We contacted the authors of a trial\textsuperscript{47} to provide potential post-treatment measures of their secondary outcomes, however, they were not measured. Nelson et al.\textsuperscript{52} measured but did not report post-treatment pain intensity scores and the authors were not able to provide the data.
However, this study provided measures of fatigue, sleep quality, and depression, and these data were included in the meta-analyses for the secondary outcome measures. Thus, up to nine RCTs were included in the meta-analyses for the effect of EEG neurofeedback on primary and secondary outcomes.

**Risk of bias**

Four RCT studies were assessed as high risk, five as moderate, and one as low risk of bias. The detailed assessment is reported in Table 1. When deciding on an overall risk of bias judgment for each RCT, the selection bias and performance bias were considered more important compared to the detection, attrition, reporting, and other biases. Considering the review topic, the randomisation process and allocation concealment (i.e., selection bias), as well as blinding the participants and personnel (i.e., performance bias) had higher value in assessing the risk of bias. On the other hand, blinding the assessor (i.e., detection bias) was assigned lower value because the primary and most of the secondary outcomes were measured by self-reported scales.

**Certainty of evidence**

The assessment of certainty of evidence using the GRADE rating is reported in Appendix.3 and reported in the following results.

**Outcomes**

**Primary outcome: pain intensity**

Nine of the 10 included RCTs reported pain intensity at post-treatment. One study included both mid-term and long-term follow-up measures, while two other studies included a long-term follow-up measure. One study did not report standard deviation for pain intensity at post-treatment and long-term follow-up; therefore, we imputed the largest standard deviation values (the most conservative approach) from other studies (47 for post-treatment and 21 for long-term follow-up).

There is low confidence that EEG neurofeedback may offer a clinically meaningful reduction in post-treatment pain intensity by 12.6 points on a 100-point scale (95% CI 7.6 to 17.6, I²=35.0%, p=0.19) compared to control/other treatments (Figure 2 and Analysis.S1, Appendix.3). There is very low confidence that EEG neurofeedback does not reduce pain intensity at long-term follow-
up. The pooled effect size of this comparison was -12.4 (95%.CI -29.7 to 5.0, \( I^2 =82.0\% \), \( p<0.01 \)) (Analysis.S2, Appendix.3).

Visual interpretation of funnel plot for post-treatment pain intensity did not indicate publication bias. We did not conduct Egger’s regression test because only nine studies were available. Funnel plots for other outcomes are available in Appendix.3, but we refrain from making inferences about publication bias due to limited study numbers in each analysis.

**Secondary outcomes**

**Fatigue**

Four RCTs measured post-treatment fatigue on the VAS, the Brief Fatigue Inventory, or a 1-10 point scale, and two of them also reported long-term follow-up measures. There is very low confidence that EEG neurofeedback does not reduce post-treatment fatigue (-2.8 [95%.CI -17.1 to 11.4], \( I^2 =85.4\% \), \( p<0.01 \)) or long-term follow-up (-20.3 [95%.CI -43.0 to 2.5], \( I^2 =87.3\% \), \( p=0.01 \)) compared to control (Analysis.S3 and S4, Appendix.3).

**Sleep**

Three RCTs measured post-treatment sleep quality using the Medical Outcomes Study-Sleep Scale or the Pittsburgh Sleep Quality Index. There is low confidence that EEG neurofeedback does not improve sleep quality (3.9 [95%.CI -2.3 to 10.2], \( I^2 =13.7\% \), \( p=0.45 \)) compared to control (Analysis.S5, Appendix.3).

**Pain interference**

Three studies measured pain interference, assessed by the Brief Pain Inventory, at post-treatment. There is low confidence that EEG neurofeedback may offer a minimally important reduction in pain interference by 11.5 points on a 100-point scale (95%.CI 3.4 to 19.7, \( I^2 =0.0\% \), \( p=0.75 \)) compared to control/other treatments (Analysis.S6, Appendix.3).

**Depression**

Three RCTs reported depressive symptoms using the Hamilton depression scale, Beck depression scale, Patient Health Questionnaire-9, or a 1-10 point scale at post-treatment. One
study had used both Hamilton and Beck depression scales, so we calculated the combined effect sizes using equations 1 and 2 and assuming a conservative correlation of 0.5 between scales. There is very low confidence that EEG neurofeedback does not reduce depressive symptoms (-1.1 [95%.CI -9.1 to 6.9], I²=60.6%, p=0.07) compared to control (Analysis.S7, Appendix.3).

**Alpha power**

Two RCTs measured resting-state alpha power at post-treatment. There is very low confidence that EEG neurofeedback does not change alpha power (3.2 [95%.CI -5.2 to 11.6], I²=82.2%, p=0.02) compared to control (Analysis.S8, Appendix.3).

**Subgroup and sensitivity analysis**

No heterogeneity was detected for the primary outcome at post-treatment. However, we conducted a post-hoc subgroup analysis on three studies for headache and four studies for fibromyalgia to provide condition-specific effect estimates. There is low confidence that EEG neurofeedback may offer a clinically meaningful reduction in post-treatment pain intensity by 15.3 points on a 100-point scale (95%.CI 8.3 to 22.4, I²=0.0%, p=0.60) for people with headache. Also, there is very low confidence that EEG neurofeedback does not improve pain intensity for people with fibromyalgia (-8.6 [95%.CI -17.3 to 0.1], I²=57.5%, p=0.07) (Figure 3 and Analysis.S9, Appendix.3). Furthermore, we conducted a post-hoc subgroup analysis on seven RCTs that used the conventional approach of EEG neurofeedback, in which the participants were required to learn how to control their brain activity. The result shows that there is low quality of evidence that the conventional EEG neurofeedback may offer a clinically meaningful effect on post-treatment pain intensity by 13.7 points (95%.CI 8.8 to 18.5, I²=27.0%, p=0.33) (Figure 4 and Analysis.S10, Appendix.3). We performed another post-hoc subgroup analysis on two trials that had their participants blinded versus those with non-blinded participants to assess the impact of a possible placebo effect. There is low confidence that EEG neurofeedback does not improve pain intensity at post-treatment in trials with blinded participants (-8.4 [95%.CI -31.5 to 14.6], I²=56.2%, p=0.13) (Analysis.S12, Appendix.3). In addition, there is low confidence that this intervention may offer a clinically important reduction in post-treatment pain intensity in non-blinded participants (-13.7 [95%.CI -18.5 to -8.8], I²=27.0%, p=0.33) (Analysis.S12, Appendix.3).
For sensitivity analysis, we repeated the meta-analysis for post-treatment pain intensity, excluding the four studies with high risk of bias; there is moderate confidence that EEG neurofeedback may offer a minimally important pain reduction at post-treatment (-10.4 [95%CI -18.2 to -2.6], I²=49.0%, \( p=0.10 \)) (Figure 5 and Analysis.S11, Appendix.3).

**Meta-regression**

The meta-regression did not find evidence of an association between mean age of participants and the effect size on post-treatment pain intensity (\( \beta=-0.06 [95\% CI -0.69 to 0.5], p=0.86 \)).

**Non-randomised studies**

**Details of included studies**

The non-randomised studies included nine single-arm trials\(^{10,12-14,18,54-57}\) and three case series\(^{15,58,59}\), while only one study\(^{20}\) compared their intervention group with a subgroup (\( n=63 \)) of a nationally collected fibromyalgia patient group (\( n=583 \)). The included non-randomised studies involved 181 patients with several types of chronic pain including chronic pain related to neurological disorders such as spinal cord injury (SCI) or traumatic brain injury (TBI), fibromyalgia, complex regional pain syndrome, chronic low back pain, and headache.

**Risk of bias**

Two non-randomised studies were assessed as high, five as moderate and the other six studies had low risk of bias. The detailed assessment for these studies is reported in Table.S2, Appendix.4.

**Outcomes**

We summarised the findings from non-randomised studies in Table 2. Two studies from the same team\(^{54,55}\) involved people with central neuropathic pain following SCI and both reported pain reduction (32.4%, \( n=15^{54}; \) 35.1%, \( n=5^{55} \)) comparing before and after daily sessions. Two studies included people with chronic pain after SCI\(^{10,57}\), but there was no change in pain intensity in pre-to post-session comparisons (\( n=30 \)) for one study\(^{57}\) and at post-treatment and 3-month follow-up (\( n=10 \)) for the other study\(^{10}\). Two studies included people with chronic pain after TBI\(^{14,18}\). One of
these studies found improvement in post-treatment pain intensity, depression, sleep, and pain interference, while the other found no change in post-treatment and 3-month follow-up pain intensity, but resulted in improvement in depression and sleep at 3-month follow-up. Furthermore, two studies involved individuals with fibromyalgia and the results showed reduction in post-treatment pain intensity (39.1%, n=15; 54.8%, n=3), while Caro and Winter also reported improvement in fatigue. Mayaud et al. investigated the effect of EEG neurofeedback on 16 females with chronic low back pain and found only an improvement in anxiety at 12-month follow-up. Nelson et al. used EEG neurofeedback for nine individuals with headache, resulting in 34.2% reduction in pain intensity. Jensen et al. examined EEG neurofeedback on 16 persons with type 1 complex regional pain syndrome and found 41.9% pre- to post-session pain reduction. The remaining studies explored EEG neurofeedback on different types of chronic pain in two case series and reported improvements in pain intensity.

**Neurofeedback protocols**

The neurofeedback protocols used in five RCTs and nine non-randomised studies aimed to either reinforce alpha (~8-12 Hz) or sensorimotor (~12-15 Hz) rhythms and suppress a combination of theta (~4-8 Hz) and/or beta (~13-30 Hz) rhythms, while two RCTs focused only on alpha reinforcement. All these studies were targeting one specific area of brain at a time.

Additionally, one recent unpublished study modulated the slow-wave rhythms (<0.1 Hz) on three different brain regions. Two RCTs and two non-randomised studies used variants of EEG neurofeedback, which, unlike the conventional approach, did not require active effort from participants. The neurotherapy system used by Kravitz et al. conducted imperceptible photic stimulation to alter brain activity, while Hershaw et al. used a system called live z-score training, which provides automated feedback by comparing the real-time EEG with a normative database in an attempt to normalise the participants' brain activity. Further, in two studies by Nelson et al., the neurotherapy system compared the obtained EEG with pre-specified parameters to conduct pulses of electromagnetic stimulation via the EEG electrodes. The details of neurofeedback protocols for all reviewed studies are reported in *Table 3*.

The number of neurofeedback sessions in RCTs ranged from 7 to 24, with a duration of 20 to 45 minutes, while the number of sessions varied considerably in the included non-randomised studies, from only one session to a mean of 58 sessions across participants, and the
sessions duration ranged from a few minutes in the EEG-based electromagnetic stimulation method\textsuperscript{12} to a maximum of 45 minutes\textsuperscript{15,55}.

**Side effects or adverse events**

Most RCTs did not report any information about adverse events, two studies\textsuperscript{21,52} reported that there were no significant adverse events, and one study\textsuperscript{46} stated that 31 (of 59 participants) experienced at least one side effect during the trial. The side effects included fatigue, headache, drowsiness, change in sleep patterns, stiffness, or muscle spasm. They reported that most side effects in earlier sessions did not affect function, but in later sessions, they were severe enough to interfere with function. No participant dropped out of the study because of the treatment-related side effects; in a few cases, the neurofeedback sessions were postponed for a few days\textsuperscript{46}.

Only five of the included non-randomised studies reported side effects/adverse events. Al-Taleb et al.\textsuperscript{54} reported side effects including occasional headache and hypersensitivity in the feet, but did not mention the number of participants experiencing them. Hassan et al.\textsuperscript{55} stated that three (out of five) individuals experienced strong spasm which was appeared as uncontrollable leg movements. Nelson et al.\textsuperscript{12} reported that a few of participants experienced minor intensification of their headache after a neurofeedback session, followed by more evident improvement in pain intensity. Elbogen et al.\textsuperscript{14} (n=41), reported the number of participants who experienced different side effects such as headset discomfort (n=14), drowsiness (n=13), irritability (n=6), headache (n=3), dizziness (n=1), vibrating/buzzing (n=1), and muscle twitching (n=1). Finally, two (out of 38) of the participants in Hershaw et al.\textsuperscript{18} dropped out due to nausea and intensification of their pre-existing headache, two more were pulled out by the investigators due to an increase in their pre-existing migraines.

**DISCUSSION**

We conducted a systematic review to synthesise the evidence for the effect of EEG neurofeedback on pain intensity for people with chronic pain. Although there is low confidence in the current evidence, the findings suggest that EEG neurofeedback may offer patients with chronic pain clinically meaningful benefits in short-term pain intensity and pain interference. At long-term (>6 weeks) follow-up, the evidence was assessed as very low confidence that EEG neurofeedback does not improve pain intensity. We were unable to evaluate mid-term effect, as there was only one study reporting pain intensity between 1- and 6-week follow-up. Furthermore,
the evidence with very low confidence indicates that EEG neurofeedback does not appear to reduce fatigue or depressive symptoms, or change the alpha power, additionally, there is low confidence that this intervention may not improve sleep quality.

The primary meta-analysis in this review included six more RCTs compared to the previous similar review by Patel et al.\textsuperscript{25} (n=233), and excluded the two studies on fMRI neurofeedback and another ineligible study. The larger sample of our review (n=353) helped to enhance the meta-analytic power. The previous review found a medium effect size ($d=-0.76$ [95%.CI -1.31 to -0.20]) according to Cohen’s $d$ criteria for a pooled effect of studies on both EEG and fMRI neurofeedback for people with chronic pain, and resulted in a high level of heterogeneity ($I^2=73\%$, $p=0.002$)\textsuperscript{25}. In our review, we found a clinically important reduction in pain intensity by -12.6 points on a 100-point scale ([95%.CI -17.6 to -7.6]). Although we included studies with different types of chronic pain, which increased the possibility of heterogeneity, the primary meta-analysis showed non-significant heterogeneity ($I^2=35.0\%$, $p=0.19$).

Although there was little evidence of heterogeneity for the post-treatment primary outcome, we conducted a post-hoc subgroup analysis to provide pain-specific effect estimates. We found a higher effect estimate for people with headache (three studies, n=74) compared to the pooled effect of all included pain conditions. In addition, we detected that post-treatment pain intensity did not improve in people with fibromyalgia (four studies, n=192) using EEG neurofeedback, which confirms the results from Glombiewski et al.\textsuperscript{23}. Their review showed that EEG neurofeedback did not have an effect on pain intensity in participants with fibromyalgia compared to control groups (three studies, n=127). Additionally, they indicated that the pooled effect of EEG and EMG (electromyography) biofeedback was significant on pain intensity in short-term, but not on fatigue, sleep problems, and depression in both short-term and long-term. Further, two narrative reviews for people with cancer pain\textsuperscript{24} and fibromyalgia\textsuperscript{22} concluded that there was initial evidence about the potential effect of EEG neurofeedback on pain intensity but could not speculate further.

Regardless of the type of chronic pain, the conventional neurofeedback approach was used in 16 (out of 23) included studies. Although the details of the protocols were different, there was a commonly used pattern, aiming to upregulate alpha/sensorimotor (8-15 Hz) rhythms, and/or downregulate theta (4-8 Hz) and/or beta (13-30 Hz) rhythms according to each individual’s resting-state EEG power. We were unable to draw any conclusion regarding the results of non-randomised studies, however, the pooled effect of RCTs that used the conventional EEG neurofeedback was estimated slightly higher than the overall effect of all included RCTs.
Although the aim of EEG neurofeedback is to alter the abnormal brain activity, most of the studies in this review (16 of 23) did not evaluate changes in brain activity. Additionally, noise/artefact removal both in real-time during the neurofeedback and later during the offline analysis was overlooked in 15 of the 23 included studies. There were inconsistencies across studies in reporting measures of brain activity; some compared pre- to post-treatment measures while some evaluated brain activity during the training sessions. Only two RCTs reported the same band power (alpha) for both intervention and control groups, and the result of our meta-analysis indicated no change across the two groups. Thus, the question about the underlying mechanism of how EEG neurofeedback might improve pain intensity and/or pain-related interference remains unanswered.

A recent systematic review on neurofeedback for pain management included studies on both EEG and fMRI neurofeedback, and considered studies combining neurofeedback with other treatments. Patients with all types of chronic pain, acute pain, and laboratory-induced pain were included and due to high heterogeneity of the included studies, the authors were not able to conduct a meta-analysis or to draw any conclusion regarding the effect of neurofeedback. In the current review, we focused on a single modality treatment to control for indirectness, however, some researchers have proposed multimodal treatments incorporating neurofeedback as possibly more effective for managing chronic pain.

**Strengths and limitations**

This is the first systematic review specifically evaluating the effect of EEG neurofeedback on chronic pain and it has several important strengths. Inclusion of a wide variety of pain conditions increased the likelihood of conclusive evidence about the analgesic effect of EEG neurofeedback. We followed our prospectively registered protocol and reported the review in line with the recommended guidelines. We undertook a comprehensive search by exploring relevant reviews, receiving alerts from Google Scholar, and searching trial registries. We used the Cochrane RoB and ROBINS-I tools, and assessed the certainty of evidence using the GRADE system.

However, the findings of this review are limited by the number of available RCTs, many of which included small sample sizes. As trials with smaller numbers of participants result in larger effect sizes, the effects found in this review must be interpreted with caution. The certainty of evidence was mainly rated as low/very low because of issues with inconsistency (i.e., heterogeneity),
The imprecision (i.e., overall sample size), and risk of bias. We assessed selection bias and performance bias of most RCTs as unclear or high risk of bias, which lowers the strength of evidence. By excluding the studies with overall high risk of bias in the sensitivity analysis, the quality of evidence improved but the effect estimate was decreased. Another limitation is that our search strategy was restricted to studies in English, making it possible that we overlooked additional eligible studies published in other languages.

**Recommendations**

Although there is reason for cautious optimism towards the analgesic effect of EEG neurofeedback, fully-powered and well-designed trials, particularly RCTs, on different pain conditions are required. To improve the quality of future clinical trials that generate more conclusive evidence in EEG neurofeedback for chronic pain, we propose a few recommendations. First, to account for a placebo effect, we recommend the inclusion of a sham treatment or placebo condition (targeting a brain region and frequency band not related to chronic pain)\(^6\), as an alternative to evaluating other treatments, no treatment, or waitlist as control condition. Second, to assess the impact of a possible placebo effect for self-reported outcome measures, we propose that blinding the participants is the only important blinding factor and needs to be considered. Third, future clinical trials should follow consensus guidelines regarding their design, implementation, analysis, and reporting such as CONSORT\(^8\) and TIDieR\(^8\). It is recommended for clinical trials to register their pre-planned protocol in the available platforms. A part of this pre-planning is to estimate the optimal sample size, to ensure sufficiency to detect an effect and to allow for potential missing data. Fourth, we recommend including a thorough description of the randomisation process, allocation concealment, and blinding participants, personnel, and assessors, as well as clearer reporting of all outcomes at different time points. Fifth, evaluating outcomes at mid- and long-term follow-up time points is critical to understand if changes in the outcome measures are sustained following the intervention. Finally, in future studies, measuring and reporting pre- and post-treatment resting-state EEG power for different bands will help to evaluate any treatment-induced change in brain activity. Mediation analyses could also determine the extent that treatment-induced changes in bands power mediates the effect favouring EEG neurofeedback compared to a control condition. Such insights enable a deeper investigation on whether improvement in pain intensity is related to/mediated by changes in brain activity (if any), which in turn may clarify for researchers, the underlying mechanisms responsible for effective EEG neurofeedback.
Availability of data and materials

All data and analyses code are publicly available on the Open Science Framework (https://osf.io/a2we5/).

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Author contributions

NHS acted as the first review author, implemented the search strategy, applied eligibility criteria, assessed studies, extracted data, and drafted the manuscript. WJC acted as the second review author, applied eligibility criteria, assessed studies, and extracted data. MW provided statistical advice, implemented the meta-analyses, and acted as the third review author for inconsistencies in data extraction and risk of bias assessment. All authors critically reviewed the manuscript and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Supplementary material

Appendix 1. PRISMA Checklist

Appendix 2. Search Strategy

Appendix 3. Meta-analyses Results

Appendix 4. Additional Tables
Figures

Figure 1. PRISMA flow diagram.

Figure 2. Forest plot of EEG neurofeedback effect on post-treatment pain intensity (0-100 scale) for people with chronic pain. Negative values of mean difference indicate that effect favours the intervention compared to control/other treatment.

Figure 3. Forest plot of sub-analyses of EEG neurofeedback effect on post-treatment pain intensity (0-100 scale) for people with fibromyalgia and headache, separately. Negative values of mean difference indicate that effect favours the intervention compared to control/other treatment.

Figure 4. Forest plot of sub-analysis of EEG neurofeedback effect on post-treatment pain intensity (0-100 scale) in studies that used conventional EEG neurofeedback approach. Negative values of mean difference indicate that effect favours the intervention compared to control/other treatment.

Figure 5. Forest plot of sensitivity analysis for the effect of EEG neurofeedback on post-treatment pain intensity (0-100 scale), excluding studies with high risk of bias. Negative values of mean difference indicate that effect favours the intervention compared to control/other treatment.

Tables

Table 1. Risk of bias assessment of 10 included RCT studies.


Table 3. Details of neurofeedback protocols in the included randomised controlled trial (RCT) and non-randomised studies. EMG: electromyography, TENS: transcutaneous electrical nerve stimulation, SMR: sensorimotor rhythm, sgACC: subgenual anterior cingulate cortex, dACC: dorsal anterior cingulate cortex.
References


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Table 1. Risk of bias assessment of 10 included RCT studies.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Selection bias</th>
<th>Performance bias</th>
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<th>Sample size (F/M)</th>
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<th>Minimum completed sessions</th>
<th>% pain reduction (post-treatment) (follow-up)</th>
<th>Significant improvements</th>
<th>Reported negative side effects</th>
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<td>Al-Taleb (2019)</td>
<td>CNP after SCI</td>
<td>15</td>
<td>50.6 ± 14.1</td>
<td>15</td>
<td>32.4% (pre- to post-session)</td>
<td>Pain intensity</td>
<td>Hypersensitivity in the feet</td>
<td>Data have been compared from pre- to post-session.</td>
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<td>Caro (2011)</td>
<td>Fibromyalgia</td>
<td>15 (14/1)</td>
<td>66.7 ± 12.3</td>
<td>15</td>
<td>39.1% (post-treatment)</td>
<td>Pain intensity</td>
<td>Fatigue</td>
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<td>Elbogen (2021)</td>
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<td>41 (6/35)</td>
<td>38.6 ± 10.0</td>
<td>36</td>
<td>15.9% (post-treatment)</td>
<td>Pain intensity</td>
<td>Depression</td>
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<td>50.0 ± 4.0</td>
<td>20</td>
<td>35.1% (pre- to post-session)</td>
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<td>Strong spasm, manifested as uncontrolled movements of the legs</td>
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<td>Chronic pain after TBI</td>
<td>38 (7/31)</td>
<td>33.4 ± 8.0</td>
<td>27</td>
<td>6.2% (post-treatment) 4.2% (3-month)</td>
<td>Depression (3-month)</td>
<td>Sleep (3-month)</td>
<td>Fatigue</td>
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<td>Chronic pain</td>
<td>10 (6/4)</td>
<td>48.5 (20-67)</td>
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<td>N/A</td>
<td>N/A (case series)</td>
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<tr>
<td>Jacobs and Jensen (2015)</td>
<td>Chronic pain</td>
<td>4 (2/2)</td>
<td>34.0 ± 17.9</td>
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<td>N/A (case series)</td>
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<tr>
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<td>CPRS-I</td>
<td>18 (16/2)</td>
<td>40.8 (17-56)</td>
<td>1</td>
<td>41.9% (pre- to post-session)</td>
<td>Pain intensity</td>
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| Jensen (2013a)       | Chronic pain after SCI | 30 (8/22)       | 49.2 (22-77)              | 1                         | 4.3% (pre- to post-session)                  | Not significant          | Not reported                  |                                                                      | Data have been compared from pre-
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<th>Study (Year)</th>
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<th>Sample</th>
<th>Baseline (Mean ± SD)</th>
<th>Outcome</th>
<th>Change (post-treatment)</th>
<th>Change (Follow-up)</th>
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<td>Jensen (2013b)</td>
<td>Chronic pain after SCI</td>
<td>10 (3/7)</td>
<td>46.1 ± 12.6</td>
<td>9.9%</td>
<td>5.0% (3-month)</td>
<td>12</td>
<td>Decrease in Theta</td>
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<td>Kayiran (2007)</td>
<td>Fibromyalgia</td>
<td>3 (3/0)</td>
<td>32.0 ± 0.8</td>
<td>54.8%</td>
<td>N/A (case series)</td>
<td>3</td>
<td>Increase in Alpha</td>
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<td>Mayaud (2019)</td>
<td>Chronic LBP</td>
<td>16 (16/0)</td>
<td>37.0 (15-52)</td>
<td>28.7%</td>
<td>34.4% (6-month, n=11)</td>
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<td>Anxiety (12-month)</td>
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<td>9 (1/8)</td>
<td>37.3 ± 12.6</td>
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<td>Pain intensity</td>
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<td>Intensification of symptoms, followed by a more marked reduction in intensity</td>
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<table>
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<th>Neurofeedback protocol</th>
<th>Electrode or brain region</th>
<th>Neurofeedback sessions</th>
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<td>Alpha neurofeedback</td>
<td>Temperature and EMG biofeedback</td>
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<td>Primary headache</td>
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<td>No treatment/TENS</td>
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<td>N/A</td>
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<td>Knee osteoarthritis-related pain</td>
<td>EEG neurofeedback</td>
<td>Sham</td>
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<td>pgACC, dACC, SSC</td>
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<td>No treatment</td>
<td>Alpha (not specified) None</td>
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<td>20 sessions 30 minutes</td>
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<td>Fibromyalgia</td>
<td>Electromagnetic stimulation</td>
<td>Sham</td>
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<td>Fibromyalgia</td>
<td>EEG neurofeedback</td>
<td>Attention control</td>
<td>Alpha (8-12 Hz) or SMR (12-15 Hz), Theta (4-7 Hz) and Beta (18-22 Hz)</td>
<td>C3/Cz/C4</td>
<td>20 sessions</td>
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<tr>
<td>Al-Taleb (2019)</td>
<td>CNP after SCI</td>
<td>EEG neurofeedback</td>
<td>No control</td>
<td>Alpha (9-12 Hz), Theta (4-8 Hz) and Beta (20-30 Hz)</td>
<td>Between C2-C4</td>
<td>≤4 pre-treatment hospital sessions and 2-105 home sessions</td>
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<td>Fibromyalgia</td>
<td>EEG neurofeedback</td>
<td>No treatment</td>
<td>SMR (12-15 Hz), Theta (4-8 Hz) and Beta (22-30 Hz)</td>
<td>Cz</td>
<td>40-98 sessions (mean = 58 sessions)</td>
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<td>EEG neurofeedback</td>
<td>No control</td>
<td>Alpha (not specified), N/A</td>
<td>FP1</td>
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<td>No control</td>
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<td>20-40 sessions</td>
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<td>Chronic pain</td>
<td>EEG neurofeedback</td>
<td>No control</td>
<td>SMR (12-15 Hz) or low Beta (15-18 Hz), Theta (4-8 Hz) and high Beta (22-30 Hz)</td>
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<td>EEG neurofeedback</td>
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<td>EEG neurofeedback</td>
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<td>No control</td>
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<td>Kayiran (2007)</td>
<td>Fibromyalgia</td>
<td>EEG neurofeedback</td>
<td>No control</td>
<td>SMR (12-15 Hz)</td>
<td>C4</td>
<td>10</td>
</tr>
<tr>
<td>Mayaud (2019)</td>
<td>Chronic LBP</td>
<td>EEG neurofeedback</td>
<td>No control</td>
<td>Alpha (not specified)</td>
<td>One electrode (of 19 electrodes) at a time</td>
<td>20</td>
</tr>
<tr>
<td>Nelson (2015)</td>
<td>Headache</td>
<td>Electromagnetic stimulation</td>
<td>No control</td>
<td>N/A</td>
<td>Two electrodes were placed in a predetermined order over all areas of the cortex during the course of treatment</td>
<td>20</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Control/Other</td>
<td>Study weight</td>
<td>Mean difference [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>---------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen 1980</td>
<td>10 59 28.3</td>
<td>22 64.8 28.5</td>
<td>5%</td>
<td>-5.8 [-9.9, -1.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farahani 2014</td>
<td>15 41.8 19.8</td>
<td>15 56.7 11.8</td>
<td>12%</td>
<td>-14.8 [-26.5, -3.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kayran 2010</td>
<td>18 16.4 9</td>
<td>18 32.5 11.4</td>
<td>21%</td>
<td>-16.1 [-22.8, -9.4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanne 2006</td>
<td>31 59.2 28.7</td>
<td>28 56.8 25.1</td>
<td>10%</td>
<td>0.4 [-13.3, 14.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew 2020</td>
<td>5 40 20</td>
<td>5 64 25.6</td>
<td>3%</td>
<td>-24.0 [-52.6, 4.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew 1987</td>
<td>5 20.8 12.3</td>
<td>4 36.5 4.9</td>
<td>15%</td>
<td>-17.7 [-27.5, -7.9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prilosec 2018</td>
<td>30 27 20.8</td>
<td>32 45 19.6</td>
<td>14%</td>
<td>-16.0 [-28.1, -3.9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terranea 2020</td>
<td>9 53.3 28.3</td>
<td>8 68.1 28.5</td>
<td>3%</td>
<td>-14.8 [-41.8, 12.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu 2021</td>
<td>60 36 18</td>
<td>20 42.4 16.7</td>
<td>17%</td>
<td>-4.4 [-13.0, 4.2]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
\chi^2 = 18.73, \quad df = 11, \quad p = 0.019; \quad I^2 = 39.0%
\]

95% precision interval [-22.4, -2.7]
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control/Other</th>
<th>Pain intensity post-treatment (0-100 scale)</th>
<th>Study weight</th>
<th>Mean difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 1990</td>
<td>10 59 28.3</td>
<td>22 64.5 20.5</td>
<td></td>
<td>9%</td>
<td>-5.8 [-26.5, 15.4]</td>
</tr>
<tr>
<td>Farahani 2014</td>
<td>15 41.8 19.0</td>
<td>15 56.7 11.0</td>
<td></td>
<td>13%</td>
<td>-14.8 [-26.5, -3.2]</td>
</tr>
<tr>
<td>Kandian 2010</td>
<td>18 16.4 9</td>
<td>18 32.6 11.4</td>
<td></td>
<td>27%</td>
<td>-16.1 [-22.8, -9.4]</td>
</tr>
<tr>
<td>Mathaw 2007</td>
<td>9 20.5 12.3</td>
<td>4 26.5 4.9</td>
<td></td>
<td>17%</td>
<td>-17.1 [-27.5, -7.3]</td>
</tr>
<tr>
<td>Prindic 2015</td>
<td>26 27 30.0</td>
<td>32 45 19.8</td>
<td></td>
<td>16%</td>
<td>-15.0 [-28.1, -1.9]</td>
</tr>
<tr>
<td>Temara 2020</td>
<td>9 52.3 28.5</td>
<td>8 60.1 25.5</td>
<td></td>
<td>3%</td>
<td>-14.3 [-41.8, 12.2]</td>
</tr>
<tr>
<td>Wu 2029</td>
<td>40 39 18</td>
<td>20 42.4 16.7</td>
<td></td>
<td>20%</td>
<td>-4.4 [-13.0, 4.2]</td>
</tr>
</tbody>
</table>

$\chi^2 = 16.97, \ p < 0.001$; df = 6, $p = 0.03$; $I^2 = 27.5\%$
95% prediction interval [21.7, 6.4]

-13.7 [16.5, -8.8]
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control/Other</th>
<th>Pain intensity post-intervention (0-100 scale)</th>
<th>Study weight</th>
<th>Mean difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fashami 2014</td>
<td>15 41.8 19.8</td>
<td>15 56.7 11.8</td>
<td></td>
<td>22%</td>
<td>-14.8 [-20.5, -3.2]</td>
</tr>
<tr>
<td>Kitzl 2006</td>
<td>31 59.2 28.7</td>
<td>28 50.5 25.1</td>
<td></td>
<td>18%</td>
<td>0.4 [-13.3, 14.2]</td>
</tr>
<tr>
<td>Mattew 2020</td>
<td>5 40 20</td>
<td>5 64 25.8</td>
<td></td>
<td>6%</td>
<td>-2.0 [-62.6, 4.6]</td>
</tr>
<tr>
<td>Pimpare 2018</td>
<td>32 27 20.8</td>
<td>32 45 19.8</td>
<td></td>
<td>28%</td>
<td>-18.0 [-28.1, -1.9]</td>
</tr>
<tr>
<td>Wu 2021</td>
<td>60 38 18</td>
<td>20 42.4 16.7</td>
<td></td>
<td>28%</td>
<td>-4.4 [-13.0, 4.2]</td>
</tr>
</tbody>
</table>

$J^2 = 16.65, Q = 7.26, df = 4, p = 0.10; I^2 = 45.9\%$  
95% precision interval: [-10.4, -3.7]  
-10.4 [-18.2, -2.6]