



Review Articles

Is Transcranial Direct Current Stimulation (tDCS) Effective for the Treatment of Pain in Fibromyalgia? A Systematic Review and Meta-Analysis

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Abstract: **Background:** Fibromyalgia is a debilitating condition characterized by chronic widespread pain. It is believed to be caused by dysfunction of the central nervous system (CNS) but current treatments are largely ineffective. Transcranial direct current stimulation (tDCS), a neuro-modulation technique that targets the CNS, may offer a new line of treatment. **Objective:** To systematically review the most up-to-date literature and perform a meta-analysis of the effects of tDCS on pain intensity in fibromyalgia. **Methods:** The following databases were searched from inception: Medline (Ovid), PsychInfo, CINAHL, Cochrane Library, and Web of Science. Studies were eligible if they were randomized controlled trials, quasi-randomized trials, and non-randomized. Crossover and parallel-group design studies were included. Risk of bias was assessed for all included studies. Meta-analysis was conducted on studies investigating pain intensity after tDCS in participants with fibromyalgia and analyzed using standardized mean difference and 95% confidence intervals. **Results:** Fourteen clinical studies were included. Ten were controlled trials and 4 were within-subjects crossover studies. Meta-analysis of data from 8 controlled trials provides tentative evidence of pain reduction when active tDCS is delivered compared to sham. However, substantial statistical heterogeneity and high risk of bias of primary studies prevent more conclusive recommendations being made. **Conclusions:** tDCS is a safe intervention with the potential to lower pain intensity in fibromyalgia. However, there is a need for more empirical research of the neural target sites and optimum stimulation parameters to achieve the greatest effects before conducting further clinical studies.

Perspective: *This systematic review and meta-analysis synthesizes current evidence for the clinical effectiveness of tDCS in the treatment of fibromyalgia pain. There is only tentative evidence of pain reduction when active tDCS is compared to sham. High heterogeneity and risk of bias across studies suggest a need for further empirical research.*

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Fibromyalgia is a debilitating chronic pain condition affecting approximately 5.4% of the UK population.¹⁹ Its primary symptoms include chronic widespread muscle pain, fatigue, sleep disturbances, tenderness (allodynia), and hyperalgesia to pressure over tender points.^{53,54} Its pathogenesis is uncertain but may be due to dysfunction of the central nervous system (CNS),³¹ possibly related to abnormal processing of pain

expectation amongst other CNS abnormalities.⁸ Current treatments include antidepressant and antiepileptic medication, exercise, cognitive behavioral therapy, and patient education. No treatments are curative and there is a need for more effective treatments that specifically target the CNS and some of the potentially reversible processes that may be driving chronic pain.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that can modulate cortical excitability and is safe and easy to administer. Anodal tDCS depolarizes the soma or cortical pyramidal neurons⁴⁶ and this is typically, but not always, associated with an increase in excitability as measured by transcranial magnetic stimulation (TMS).^{21,22} tDCS may also interfere with functional connectivity, synchronization, and oscillatory activities in cortical and subcortical networks of the CNS, as demonstrated previously in primary motor cortex (M1).^{44,45} If fibromyalgia is a dysfunction of the CNS, then tDCS could be useful in relieving pain. A summary of the available literature³⁶ provided evidence-based guidelines (determined by a panel of experts) on the therapeutic use of tDCS for fibromyalgia pain from 11 studies (published up until September 2016) containing a mix of randomized controlled trials (RCTs) and crossover studies. Level B recommendation (probable efficacy) was proposed for anodal tDCS of left M1 (with the cathode over right orbitofrontal cortex) in fibromyalgia. Zhu et al,⁵⁵ who meta-analyzed 6 RCTs (published up until October 2015), also suggest that anodal tDCS to M1 is effective for the relief of fibromyalgia pain but potential biases and small sample sizes mean there is insufficient evidence to draw any firm conclusions.

The purpose of this article is to systematically review the evidence from the most up-to-date literature (published up until October 2018) and conduct a meta-analysis including all study types to determine the clinical impact of anodal tDCS for the treatment of fibromyalgia pain to inform clinical practice and the design of future studies.

Methods

Data Source and Search Methods

Guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis statement were consulted to develop this systematic review.³⁹ The computerized databases Medline (Ovid), PsychInfo, CINAHL, Cochrane Library, and Web of Science were used to search for relevant studies. Searches were performed between September 27, 2018 and October 24, 2018 (from the date of inception of each database) using a combination of controlled vocabulary (ie, medical subject headings) and free-text terms. Search strategies were modified to meet the specific requirements of each database (see Supplementary Materials for Medline search strategy). Hand searches of the reference lists of included studies and previously published systematic reviews were also conducted.

Criteria for Considering Studies and Study Selection

Studies investigating human participants over 18 years with fibromyalgia pain lasting for at least 3 months were included. We focused on those studies using tDCS where pain intensity was reported as an outcome measure. A published full text of the study was required. Studies where pain intensity was not an outcome, case studies, or studies where there was no experimental control were excluded. Reviews, theses, and abstracts were excluded. All types of study designs were included. Two reviewers (D.M.L. and P.G.W.) screened titles and abstracts obtained from the searches to identify relevant studies, and then screened full reports of studies against the eligibility criteria. A third reviewer (L.A.) acted as arbiter.

Risk of Bias Assessment

Two reviewers independently assessed risk of bias in the studies (D.M.L. and P.G.W.). The Cochrane Collaboration's assessment tool was used and consisted of assessment of selection bias, attrition bias, blinding, and sample size.²⁸ Additionally, for studies with a crossover design, measures taken to control for crossover effects were analyzed. For RCTs, checking the presence of an intention to treat analysis assessed the way in which investigators dealt with dropouts. If consensus could not be reached, a third reviewer (L.A.) acted as arbiter.

Data Synthesis and Analysis

Information extracted from studies included study design, sample size, treatment characteristics, control group characteristics, and pain outcome measure and results.

Meta-analysis was conducted on studies investigating change in pain intensity in participants with fibromyalgia after tDCS. Data from pain intensity measured with NRS or VAS anchored at 0 to 10 (or 100) were pooled and analyzed using Revman 5.1 software. Data from RCTs and crossover studies were analyzed as standardized mean difference (SMD) and 95% confidence intervals (CI) calculated using the generic inverse-variance and random effects model. We entered crossover trials into a meta-analysis where risk of bias associated with carry-over effects was considered to be low. We combined the results of crossover studies with parallel studies using the generic inverse-variance method as suggested by Cochrane.²⁸ The standard error of the SMD was calculated imputing a correlation coefficient. Correlation coefficients were calculated from the raw data when available, and when not available the correlation coefficient from a study with similar design and comparisons was used. A sensitivity analysis was conducted when imputing a correlation coefficient (Supplementary Materials Fig S1).²⁸ Studies with multiple comparison groups were included by combining the control groups to create a single pairwise comparison.²⁸ When analyses resulted in a significant effect ($P \leq .05$)

the SMD was back-transformed to mean difference using the mean standard deviation of the post-treatment sham group score of the studies included in the analysis. The mean difference was then used to calculate percentage change of active stimulation compared with the mean poststimulation score from the sham groups of the included studies.

Clinical importance of the pooled effect size was considered using the criteria proposed in the IMMPACT consensus statement.¹⁶ Decrease in pain of 15% or less was judged as no important change, decrease in pain of more than 15% was judged as a minimally important change, of 30% or more was judged as a moderately important change and of 50% or more was judged as a substantially important change.

A subgroup analysis comparing data of active tDCS to M1 against sham tDCS was predetermined. No other subgroup analysis was predetermined. We used only the data analyzed in the trial for analysis in cases of missing data due to withdrawals or dropouts. Heterogeneity between comparable trials was assessed using a standard chi-squared test and I^2 statistics. When chi-squared resulted in a P value $< .1$, statistically significant heterogeneity was considered present. When $I^2 > 60\%$, substantial heterogeneity was considered present.²⁸ We planned to conduct a sensitivity analysis by excluding studies with 2 or more high risk of bias in case of substantial heterogeneity. We planned to analyze the potential for publication bias by examining funnel plots in the case of sufficient pooled data.

If it was not possible to include studies in the meta-analysis, studies were individually analyzed and effect sizes calculated for comparisons within each study using SMD. When comparisons were significant ($P \leq .05$) effect sizes were interpreted according to Cohen's d effect size.¹⁰ When further details about studies were needed, the corresponding author of each study was contacted.

Results

The search found 134 records, of which 56 were duplicates and 78 were screened by title and abstract. Twenty studies were potentially relevant and full reports obtained and screened. Six studies were excluded with reasons. Fourteen studies met the eligibility criteria and were included for review (Fig 1).

Characteristics of Included Studies

Fourteen studies (452 participants; 347 female) were included for review (Table 1). Ten were RCTs and 4 were within-subjects crossover studies. Mean age of participants ranged from 31 to 58 years. Pain duration (where reported) ranged from 6 months to 17 years.

Treatment Characteristics

Anodal tDCS was administered at an intensity of 2 mA for 11 studies,^{6,15,17,23,24,33,37,38,47,51,52} 1.5 mA for 2 studies,^{43,50} and 1 mA for one study.³⁰ The target sites were 1) left primary motor cortex (M1; corresponding to C3 on the 10–20 system for electrode placement in

electroencephalography) with the cathode placed over right supraorbital (SO) cortex^{17,23,24,30,37,38,47,51}; 2) right Dorsolateral Prefrontal Cortex (DLPFC; corresponding to F4) with the cathode placed over left DLPFC (corresponding to F3)⁶ or anode over left DLPFC and cathode over right DLPFC⁵⁰ or right SO³³; and 3) right occipital nerve stimulation with the cathode placed over the left (corresponding to right and left side of the C2 dermatome)^{6,15} or left occipital nerve stimulation with the cathode placed over the right.⁵⁰ In only one study was the reference electrode placed in an extra-cephalic site on the contralateral arm.³³ In all studies active tDCS stimulation was applied for 20 minutes. However, the number of sessions varied from 1^{37,52} to 10^{30,47} with the most frequently reported number of consecutive sessions being 5.^{17,23,24,33,38,51}

For the sham condition, all but one study reported using the same electrode montage as the active condition with the same current density, which lasted for durations of between 10 and 43 seconds. Eleven studies applied the sham stimulation at the start of the session only,^{6,15,17,24,37,38,43,47,50-52} 2 applied it at both the start and end of the session,^{23,33} and 1 did not apply any stimulation.³⁰

Risk of Bias

The 10 RCTs had generally low risk of bias associated with random sequence generation, incomplete outcome data, blinding of the participant and blinding of the assessor (see Table 2). Unclear risk of bias was more associated with allocation concealment; high risk of bias was associated with an absence of sample size calculation. Risk of bias of crossover studies indicated flaws associated with absence of sample size calculations and blinding of the participant and assessor and allocation concealment. Sample sizes were between 9 and 58 participants.

Effects of Intervention

Data from pain intensity could be pooled from 9 trials ($n = 264$). We were unable to include data from^{15,37,43,50,51} because pain intensity data were not reported or available upon request.

Data from 8 trials comparing active tDCS against sham tDCS could be analyzed and resulted in a significant effect in favor of active tDCS using a random-effects model ($Z = 2.72$, $P = .007$; $SDM = -.50$, 95% CI $-.87, -.14$; Fig 2A). This effect size is equivalent to a percentage change of 17% (95% CI 5%, 29%), which is above the threshold for a clinically important difference (CID), although the lower bound of the confidence interval is below the threshold. I^2 statistics indicated substantial heterogeneity ($I^2 = 65\%$).

A subgroup analysis was conducted including data from the RCTs only. Data from 6 RCTs could be analyzed and resulted in a significant effect in favor of active tDCS using a random-effects model ($Z = 3.01$, $P = .003$; $SDM = -.66$, 95% CI $-1.09, -.23$; Fig 2B). This effect size is equivalent to a percentage change of 22% (95% CI

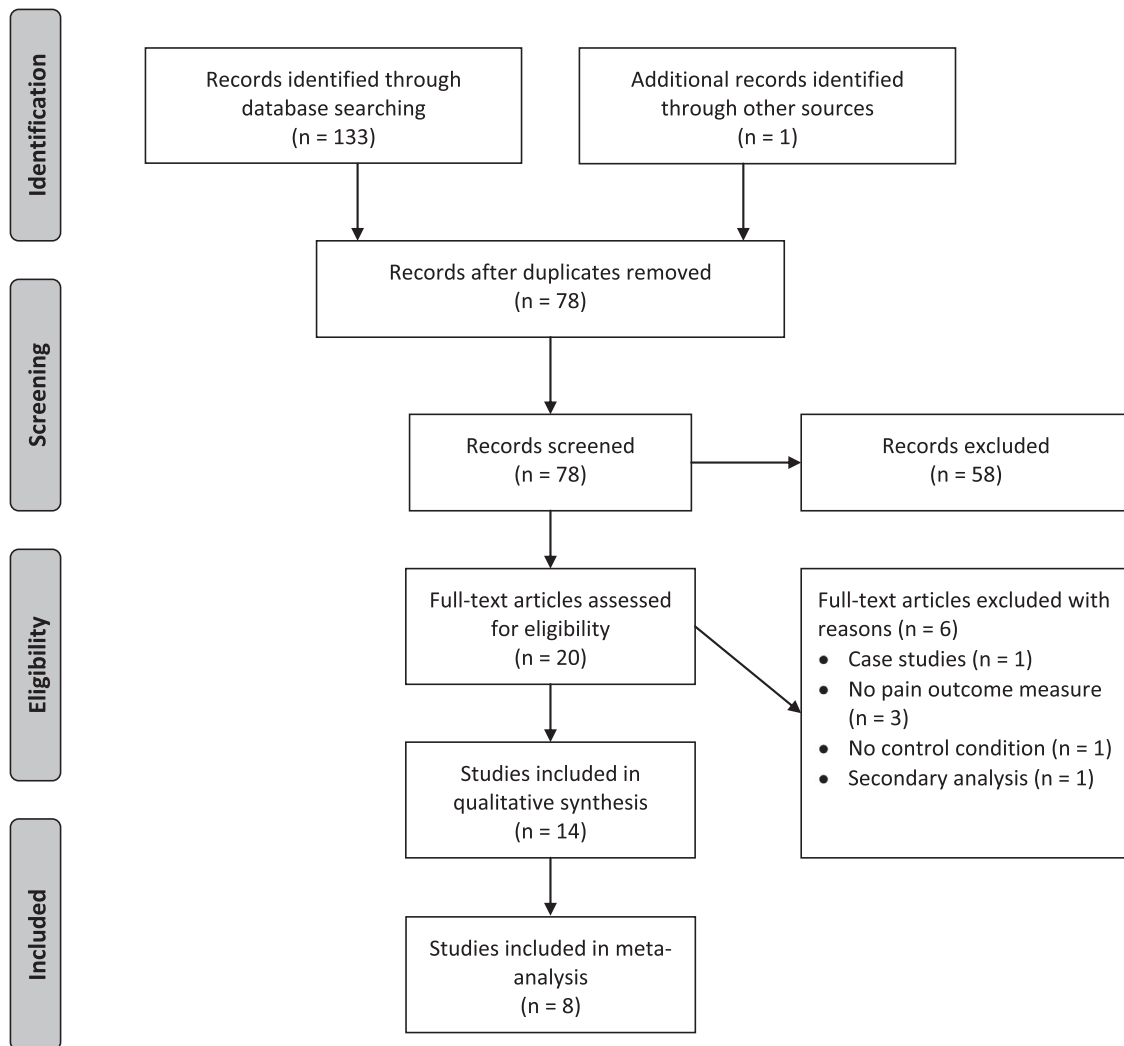


Figure 1. Preferred reporting items for systematic review and meta-analysis flow diagram. From: Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 4:1, 2015.

8%, 36%), which is above the threshold for a CID, but the lower bound of the confidence interval is below the threshold. I^2 statistics indicated substantial heterogeneity ($I^2 = 65\%$).

Subgroup analysis was conducted in studies comparing active tDCS to M1 against sham tDCS. A total of 7 studies were included and a significant effect in favor of active tDCS to M1 was found ($Z = 2.20$; $P = .030$; $SMD = -.50$, 95% CI $-.94, -.05$; Fig 2C), but with substantial heterogeneity ($I^2 = 69\%$). This effect size is equivalent to a percentage change of 17% (95% CI 2%, 31%), which is above the threshold for a CID but the lower bound of the confidence interval is substantially below the threshold.

Sensitivity analyses excluding data from trials that were classified as having 2 or more high risk of bias did not reduce statistical heterogeneity (see [Supplementary Materials Fig S1](#)). Visual inspection of the data indicated that the study conducted by Khedr et al³³ could be the source of variability in the data as it was 2 standard mean differences from the standardized mean. A sensitivity analysis excluding data from Khedr, Omran, Ismail, El-Hammady, Goma, Kotb et al³³ reduced statistical

heterogeneity. The analysis comparing active tDCS against sham tDCS included 7 trials and resulted in a significant effect in favor of active tDCS using a random-effects model ($Z = 2.63$, $P = .009$; $SDM = -.35$, 95% CI $-.61, -.09$; Fig 3A). This effect size is equivalent to a percentage change of 12% (95% CI 3%, 20%), which is below the threshold for a CID. I^2 statistics indicated moderate heterogeneity ($I^2 = 30\%$).

The subgroup analysis including data from RCTs (but excluding data from³³) resulted in a significant effect favoring active tDCS ($Z = 3.46$, $P = .0005$, $SMD = -.46$; 95% CI $-.72, -.20$; Fig 3B). This effect size is equivalent to a percentage change of 15% (95% CI 7%, 24%), which is below the threshold for a CID. I^2 statistics indicated low heterogeneity ($I^2 = 12\%$). The subgroup analysis comparing active tDCS to M1 against sham tDCS resulted in no significant overall effect ($Z = 1.81$; $P = .07$; Fig 3C), but low heterogeneity ($I^2 = 17\%$).

A funnel plot was created to analyze publication bias (see [Supplementary Materials Fig S2](#)) but there were an insufficient number of trials to allow a meaningful conclusion.

Table 1. Characteristics of Studies Included in the Review

STUDY AND DESIGN	CLINICAL CONDITION (TOTAL N)	STIMULATION DETAILS	CONTROL GROUP	PAIN OUTCOME MEASURE AND RESULTS
Bin Yoo et al ⁶ RCT	Fibromyalgia (n = 58)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • DLPFC stimulation: 2 mA direct current, surface sponge electrodes (7 × 5 cm²), ramp up time = 10 s • ONS stimulation: 1.5 mA direct current, surface sponge electrodes (7 × 5 cm²), ramp up time = 5 s <p>Brain regions</p> <ul style="list-style-type: none"> • DLPFC stimulation: anode over right DLPFC, cathode over left corresponding to F4 and F3 channels, respectively. • ONS stimulation: anode over right occipital region and cathode over left (right and left side of C2 dermatome). <p># and duration of sessions</p> <ul style="list-style-type: none"> • ONS group had 20 min over 8 consecutive sessions for 4 wk (tDCS twice weekly) • ONS+DLPFC had 40 min over 8 consecutive sessions for 4 wk (tDCS twice weekly) <p>ONS group: n = 21, age: 47.81 ± 8.23 y, 20F, pain duration: NR ONS+DLPFC group: n = 21, age = 45.76 ± 10.80 y, 20F, pain duration NR</p>	<p>Sham</p> <ul style="list-style-type: none"> • Same electrode montage as active tDCS but stimulator current delivery lasted for 10 s only <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 8 consecutive sessions for 4 wk (tDCS twice weekly) <p>n = 16, age: 47.19 ± 8.14 y 15F, pain duration: NR</p>	<p>Pain intensity</p> <ul style="list-style-type: none"> • NRS <p>No effect of stimulation on NRS (<i>P</i> = .49) and no significant interaction between stimulation trial and type of stimulation (<i>P</i> = .096).</p>
De Ridder and Vanneste ¹⁵ Within-subjects crossover	Fibromyalgia (n = 19, age: 46.11 ± 7.85 y, 15F, pain duration: NR)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • 2 mA direct current, surface sponge electrodes (35 cm²), ramp up and down time = 5 s <p>Brain regions</p> <ul style="list-style-type: none"> • Anode placed over right C2 dermatome; Cathode over left C2 dermatome <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min of 3 sessions across 1 wk (1 session of 20 min every 2 d) 	<p>Sham</p> <ul style="list-style-type: none"> • Same electrode montage as active tDCS but stimulation ramped up to 1.5 mA and turned off after 10 s. <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min of 3 sessions across 1 wk (1 session of 20 min every 2 d) 	<p>Pain intensity</p> <ul style="list-style-type: none"> • NRS <p>Significant suppression effect of 18.60% for active vs sham tDCS (<i>P</i> = .007).</p>
Fagerlund et al ¹⁷ RCT	Fibromyalgia (n = 50; 2 dropout)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • 2 mA direct current, surface sponge electrodes (35 cm²), ramp up and down time = NR <p>Brain regions</p> <ul style="list-style-type: none"> • Anode placed over left C3 to stimulate M1; Cathode over right SO <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 5 consecutive days 	<p>Sham</p> <ul style="list-style-type: none"> • Electrode montage and current: NR but stimulation ramped up over 8 s, followed by 30 s of stimulation and 5 s ramp down time. <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 5 consecutive days <p>n = 24, age: 48.17 ± 10.56 y, 21F, pain duration: 18.50 ± 10.56 y</p>	<p>Pain intensity</p> <ul style="list-style-type: none"> • NRS <p>Pain unpleasantness</p> <ul style="list-style-type: none"> • NRS <p>Significant pain reduction between active vs sham tDCS group [<i>F</i>(1,47) = 56.82, <i>P</i> = .012]. 13.6% mean pain reduction in active group vs 1.70% pain reduction in sham group. tDCS had no effect on pain unpleasantness</p>

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Table 1. Continued

STUDY AND DESIGN	CLINICAL CONDITION (TOTAL N)	STIMULATION DETAILS	CONTROL GROUP	PAIN OUTCOME MEASURE AND RESULTS
Foerster et al ²³ Within-subjects crossover	Fibromyalgia (n = 12, age: 47.6 ± 10.6 y, 12F, pain duration: NR)	n = 24, age: 49.04 ± 8.63 y, 24F, pain duration: 17.73 ± 7.54 y Stimulation type • atDCS Parameters • 2 mA direct current, surface sponge electrodes (size: NR), ramp up and down time = NR Brain regions • Anode over left motor cortex; Cathode over right SO # and duration of sessions • 20 min over 5 consecutive days	Sham • Same electrode montage as active tDCS but current applied for 30 s at beginning and end of session, ramp time: NR # and duration of sessions • 20 min over 5 consecutive d	Pain intensity • VAS No significant change in VAS score for the sham-vs active tDCS (P = .16).
Fregni et al ²⁴ RCT	Fibromyalgia (n = 32)	Stimulation type • atDCS Parameters • 2 mA direct current, surface sponge electrodes (35 cm ²), ramp up and down time = NR Brain regions • M1 group: Anode over M1 (C3); Cathode over contralateral SO • DLPFC group: Anode over left DLPFC (F3); Cathode over contralateral SO # and duration of sessions • 20 min over 5 consecutive days M1 group: n = 10, age: 54.8 ± 9.3 y, 10F, pain duration: 10.0 ± 7.8 y)DLPFC group: n = 11, age: 54.2 ± 7.4 y, 11F, pain duration: 8.4 ± 9.3 y)	Sham • Same electrode montage as M1 group but stimulation turned off after 30 s, ramp time: NR # and duration of sessions • 20 min over 5 consecutive days n = 10, age: 50.8 ± 10.2 y, 10F, pain duration: 8.1 ± 7.5 y)	Pain intensity • VAS Significant main effect of group [F (2,29) = 5.98, P = .007]. Change in pain over time in M1 group significantly different from that in sham group (t (317) = 2.22, P = .027). No difference in DLPFC group.
Jales Junior et al ³⁰ RCT	Fibromyalgia (n = 20, age: 46.4 ± 10.615 y, 20F, pain duration: NR)	Stimulation type • atDCS Parameters • 1 mA direct current, surface sponge electrodes (3 × 5 cm), ramp up and down time = NR Brain regions • Anode over left M1; Cathode over right SO # and duration of sessions • 20 min once a week for 10 consecutive weeks n = 10 (age and pain duration: NR)	Sham • Same electrode montage but no stimulation given # and duration of sessions • 20 min once a week for 10 consecutive weeks n = 10 (age and pain duration: NR)	Pain intensity • VAS Pre- vs post-test difference only (P = .031; no comparison with sham)VAS scores:Pre-test sham = 6.7Post-test sham = 5.6Pre-test active = 6.05Post-test active = 3.6

(continued on next page)

Table 1. Continued

STUDY AND DESIGN	CLINICAL CONDITION (TOTAL N)	STIMULATION DETAILS	CONTROL GROUP	PAIN OUTCOME MEASURE AND RESULTS
Khedr et al ³³ RCT	Fibromyalgia (n = 40)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • 2 mA direct current, surface sponge electrodes (24 cm², current density = .08 mA/cm²), ramp up and down time = 15 s) <p>Brain regions</p> <ul style="list-style-type: none"> • Anode over left M1 (C3) in patients with bilateral or right-sided pain or C4 if left-sided pain • Reference electrode over contralateral arm <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 5 consecutive d/wk for 2 wk <p>n = 18, age: 31.1 ± 10.99 y, 17F, pain duration: 6.1 ± 2.65 mo)</p>	<p>Sham</p> <ul style="list-style-type: none"> • Same electrode montage as active tDCS but stimulation lasted only 30 s at beginning and end of session <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 5 consecutive d/wk for 2 wk <p>n = 18, age: 33.89 ± 11.18 y, 17F, pain duration: 6.05 ± 2.53 mo)</p>	<p>Pain intensity</p> <ul style="list-style-type: none"> • VAS <p>Significant time x group interaction for VAS (P = .001) post 5 and 10 sessions only (P = .001 for both).</p>
Mendonca et al ³⁷ RCT	Fibromyalgia (n = 30)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • 2 mA direct current, surface sponge electrodes (40 × 40 mm), ramp up and down time = 8 s <p>Brain regions</p> <ul style="list-style-type: none"> • Anode over left M1 (C3); Cathode over right SO <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min, 1 session <p>Anodal stimulation of M1 group: n = 6, age: 44.5 ± 10.5 y, 5F, pain duration: NR)</p> <p>Anodal stimulation of SO group: n = 6, age: 42.6 ± 9.2 y, 6F, pain duration: NR)</p> <p>There was also 2 cathodal stimulation groups (n = 12; not reported here)</p>	<p>Sham</p> <ul style="list-style-type: none"> • Electrode montage: NR, duration = 30 s <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min, 1 session <p>n = 6, age: 43.5 ± 10.4 y, 6F, pain duration: NR)</p>	<p>Pain intensity</p> <ul style="list-style-type: none"> • NRS <p>Anodal SO decreased pain (P = .015). No effect for anodal M1 reported.</p>

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Table 1. Continued

STUDY AND DESIGN	CLINICAL CONDITION (TOTAL N)	STIMULATION DETAILS	CONTROL GROUP	PAIN OUTCOME MEASURE AND RESULTS
Mendonca et al ³⁸ RCT	Fibromyalgia (n = 45)	Stimulation type • atDCS Parameters • 2 mA direct current, surface sponge electrodes (35 cm ²), ramp up and down time = 30 s Brain regions • Anode over left M1 (C3); Cathode over right SO # and duration of sessions • 20 min over 5 consecutive days (Mon to Fri) tDCS group: n = 15, age: 49.9 ± 10.6 y, 15F, pain duration: 125.6 ± 100.2 mo) tDCS/Aerobic Exercise (AE) group: n = 15, age: 44.5 ± 14 y, 14F, pain duration: 140.6 ± 72.2 mo)	Sham • Same electrode montage as active tDCS but stimulation turned off after first 30 s # and duration of sessions • 20 min over 5 consecutive days (Mon to Fri) n = 15, age: 46 ± 11.8 y, 15F, pain duration: 149.3 ± 111.1 mo)	Pain intensity • NRS No significant difference between active vs sham tDCS ($P > .05$). Significant differences for tDCS/AE group vs AE alone ($P = .007$) and vs tDCS alone ($P = .0056$).
Plazier et al ⁴³ Within-subjects crossover	Fibromyalgia (n = 9, age: 42 ± 4.23 y, 9F, pain duration: NR)	Stimulation type • atDCS Parameters • 1.5 mA direct current, surface sponge electrodes (35 cm ²), ramp up and down time = NR Brain regions • One electrode over left C2 dermatome and one over right (anode and cathode not specified). # and duration of sessions • 20 min over 3 sessions in 1 week every 2 d	Sham • Same electrode montage as active tDCS but stimulation turned off after 10 s # and duration of sessions • 20 min over 3 sessions in 1 wk every 2 d	Pain intensity • NRS Significant difference between sham (M = 6.33) vs real (M = 4.94) occipital tDCS ($P = .04$) demonstrating a suppression effect of 21.96%.
Riberto et al ⁴⁷ RCT	Fibromyalgia (n = 23)	Stimulation type • atDCS Parameters • 2 mA direct current, surface sponge electrodes (35 cm ²), ramp up and down time = 5 s Brain regions • Anode over left M1 (C3); Cathode over contralateral SO # and duration of sessions • 20 min once a week for 10 wk n = 11, age: 58.3 ± 12.1 y, 11F, pain duration: 9.9 ± 11.8 mo)	Sham • Same electrode montage as active tDCS but stimulation turned off after 30 s # and duration of sessions • 20 min once a week for 10 wk n = 12, age: 52.4 ± 11.5 y, 12F, pain duration: 6.4 ± 10.5 mo)	Pain intensity • VAS No difference between active vs sham tDCS pre vs post-test ($P = .67$).

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Table 1. Continued

STUDY AND DESIGN	CLINICAL CONDITION (TOTAL N)	STIMULATION DETAILS	CONTROL GROUP	PAIN OUTCOME MEASURE AND RESULTS
To et al ⁵⁰ RCT	Fibromyalgia (n = 42)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • 1.5 mA direct current, surface sponge electrodes (35 cm²), ramp up and down time = 5 s <p>Brain regions</p> <ul style="list-style-type: none"> • C2 tDCS group: Anode over left C2 dermatome; Cathode over right C2 dermatome • DLPFC tDCS group: Anode over left DLPFC; Cathode over right DLPFC (F3 and F4, respectively) <p># and duration of sessions</p> <ul style="list-style-type: none"> • C2 tDCS group: 20 min twice a week for 4 wk • DLPFC tDCS group: 20 min twice a week for 4 wk <p>C2 tDCS group: n = 15, age: 47.13 ± 10.01 y, 12F, pain duration: NR</p> <p>tDCS group: n = 11, age: 47.81 ± 10.17 y, 10F, pain duration: NR</p>	<p>Sham</p> <ul style="list-style-type: none"> • Electrode montage: 8 participants received C2 tDCS and 8 received DLPFC tDCS. Current ramped up over 5 s to 1.5 mA and then ramped down again (total 10 s) <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min twice a week for 4 wk <p>n = 16, age: 46.19 ± 49.0 y, 14F, pain duration: NR</p>	<p>Pain intensity</p> <ul style="list-style-type: none"> • NRS <p>Significant differences between DLPFC vs sham stimulation (t(25) = 3.19, P = .004, d = 1.28) and C2 vs sham stimulation (t(29) = 3.19, P = .003, d = 1.18) but not between DLPFC and C2 stimulation (P = .78).</p>
Valle et al ⁵¹ RCT	Fibromyalgia (n = 41, age: 54.8 ± 9.6 y, 41F, pain duration: NR)	<p>Stimulation type</p> <ul style="list-style-type: none"> • atDCS <p>Parameters</p> <ul style="list-style-type: none"> • 2 mA direct current, surface sponge electrodes (35cm²), ramp up and down time = 30secs <p>Brain regions</p> <ul style="list-style-type: none"> • M1 tDCS group: Anode over left M1 (C3); Cathode over contralateral SO • DLPFC tDCS group: Anode over left DLPFC (F3); Cathode over contralateral SO <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 10 daily sessions (Mon to Fri over 2 wk) <p>M1 tDCS group: n = 14 (age and duration of pain: NR)</p> <p>DLPFC tDCS group: n = 13 (age and duration of pain: NR)</p>	<p>Sham</p> <ul style="list-style-type: none"> • Electrode montage same as M1 tDCS but stimulation turned off after 30 s <p># and duration of sessions</p> <ul style="list-style-type: none"> • 20 min over 10 daily sessions (Mon-Fri over 2 wk) <p>n = 14 (age and duration of pain: NR)</p>	<p>Pain intensity</p> <ul style="list-style-type: none"> • VAS <p>M1 and DLPFC tDCS significantly reduced pain compared to baseline but not compared to sham.</p>

(continued on next page)

Table 1. Continued

STUDY AND DESIGN	CLINICAL CONDITION (TOTAL N)	STIMULATION DETAILS	CONTROL GROUP	PAIN OUTCOME MEASURE AND RESULTS
Villamar et al ⁵² Within-subjects repeated measures	Fibromyalgia (n = 18, age: 50.3 ± 8.5 y, 15F, pain duration: 10.7 ± 6.8 y)	Stimulation type • HD-atDCS Parameters • 2 mA direct current, surface sponge electrodes (35 cm ²), ramp up and down time = 30 s Brain regions • Anode over left M1 (C3) (4 ring electrodes over Cz, F3, T7, and P3); Cathode/reference: NR # and duration of sessions • 20 min once There was also a cathodal stimulation ses- sion (not reported here)	Sham • Same electrode montage as active tDCS but stimulation turned off after 30 s # and duration of sessions • 20 min once	Pain intensity • NRS Significant group difference between tDCS and sham seen 30 min after end of stimulation (P = .031).

atDCS, anodal transcranial Direct Current Stimulation; RCT, Randomized Controlled Trial; ONS, Occipital Nerve Stimulation; VAS, Visual Analogue Scale; NR, Not Reported; DLPFC, Dorsolateral Prefrontal Cortex; M1, primary motor cortex; SO, supraorbital cortex; HD-atDCS, High Definition-anodal transcranial Direct Current Stimulation.

The following study did not compare active tDCS with sham tDCS and therefore could not be included in the meta-analysis. Mendonca et al³⁸ randomly allocated 45 participants into 3 groups: 1) tDCS/ aerobic exercise (AE), which received active intervention of AE training and active tDCS; 2) AE, which received active intervention of aerobic exercise and sham tDCS; and 3) tDCS, which received sham aerobic exercise and active tDCS. A between-groups comparison indicated no significant pain reduction comparing tDCS/AE and AE (SMD = -.35, 95% CI -.92, .22; P = .23), no significant pain reduction comparing tDCS/AE and tDCS (SMD = -.53, 95% CI -1.13, .06; P = .08), and no significant pain reduction comparing tDCS and AE (SMD = .24, 95% CI -.32, .80; P = .40). Follow-up data at 2 months showed no significant effect on comparisons between tDCS/AE and AE (SMD = -.21, 95% CI -.83, .42; P = .51), tDCS/AE and tDCS (SMD = -.29, 95% CI -.92, .33; P = .36), and tDCS and AE (SMD = .08, 95% CI -.63, .80; P = .82).

Follow-up data from a further 2 studies were pooled. There was a significant large effect in favor of active tDCS at 1-month follow-up in Khedr et al³³ (SMD = -2.10, 95% CI = -3.01, -1.20, P < .001) and no significant effect of active tDCS at 1-month follow-up in Fagerlund et al¹⁷ (SMD = -.28, 95% CI -.72, .16, P = .22).

Side Effects of Intervention

Five studies reported mild or minor adverse effects following intervention including skin redness, tingling and itching under the site of stimulation,^{15,24,38,51} sleepiness and headache,²⁴ and mood change¹⁷ but these were equally distributed across groups of active and control stimulation. It was stated that patients did not experience adverse reactions from the intervention in 4 studies^{43,47,50,52} and there was no mention of adverse reactions in the remaining reports.

Discussion

This systematic review included 14 studies, of which 10 were RCTs, the largest cohort of clinical studies on the effects of tDCS on fibromyalgia pain sampled to date. A meta-analysis of data from 8 trials provides tentative evidence of pain reduction when active tDCS is delivered compared to a sham intervention. However, substantial statistical heterogeneity and high risk of bias of primary studies prevent more conclusive recommendations being made at this time.

The results of the meta-analysis show that active tDCS versus sham has a small-to-moderate effect on subjective ratings of pain intensity in patients with fibromyalgia with a percentage change of 17%, which is above the threshold for a CID. Just taking into account the results from the 6 RCTs also found in favor of active tDCS with an effect size equivalent to a percentage change of 22%. Although most studies have used M1 as the target site, a subgroup analysis of the 7 studies comparing active tDCS to M1 against sham found only a small-moderate effect in favor of active tDCS

Table 2. Risk of Bias of Studies Included in the Review

STUDY	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	INCOMPLETE OUTCOME DATA	BLINDING (PARTICIPANT)	BLINDING (ASSESSOR)	SAMPLE SIZE CALCULATION	INTENTION TO TREAT ANALYSIS
<i>RANDOMIZED CONTROLLED TRIALS</i>							
Bin Yoo et al ⁶	●	●	●	●	●	●	N/A
Fagerlund et al ¹⁷	●	●	●	●	●	●	N/A
Fregni et al ²⁴	●	●	●	●	●	●	N/A
Jales Junior et al ³⁰	●	●	N/A	●	●	●	N/A
Khedr et al ³³	●	●	●	●	●	●	N/A
Mendonca et al ³⁷	●	●	●	●	●	●	N/A
Mendonca et al ³⁸	●	●	●	●	●	●	N/A
Riberto et al ⁴⁷	●	●	●	●	●	●	●
To et al ⁵⁰	●	●	●	●	●	●	N/A
Valle et al ⁵¹	●	●	●	●	●	●	N/A
<i>WITHIN-SUBJECTS CROSSOVER DESIGNS</i>							
STUDY	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	INCOMPLETE OUTCOME DATA	BLINDING (PARTICIPANT)	BLINDING (ASSESSOR)	SAMPLE SIZE CALCULATION	CROSSOVER
De Ridder and Vanneste ¹⁵	●	●	●	●	●	●	●
Foerster et al ²³	●	●	●	●	●	●	●
Plazier et al ⁴³	●	●	●	●	●	●	●
Villamar et al ⁵²	●	●	●	●	●	●	●

Key: Green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias; N/A, not applicable.

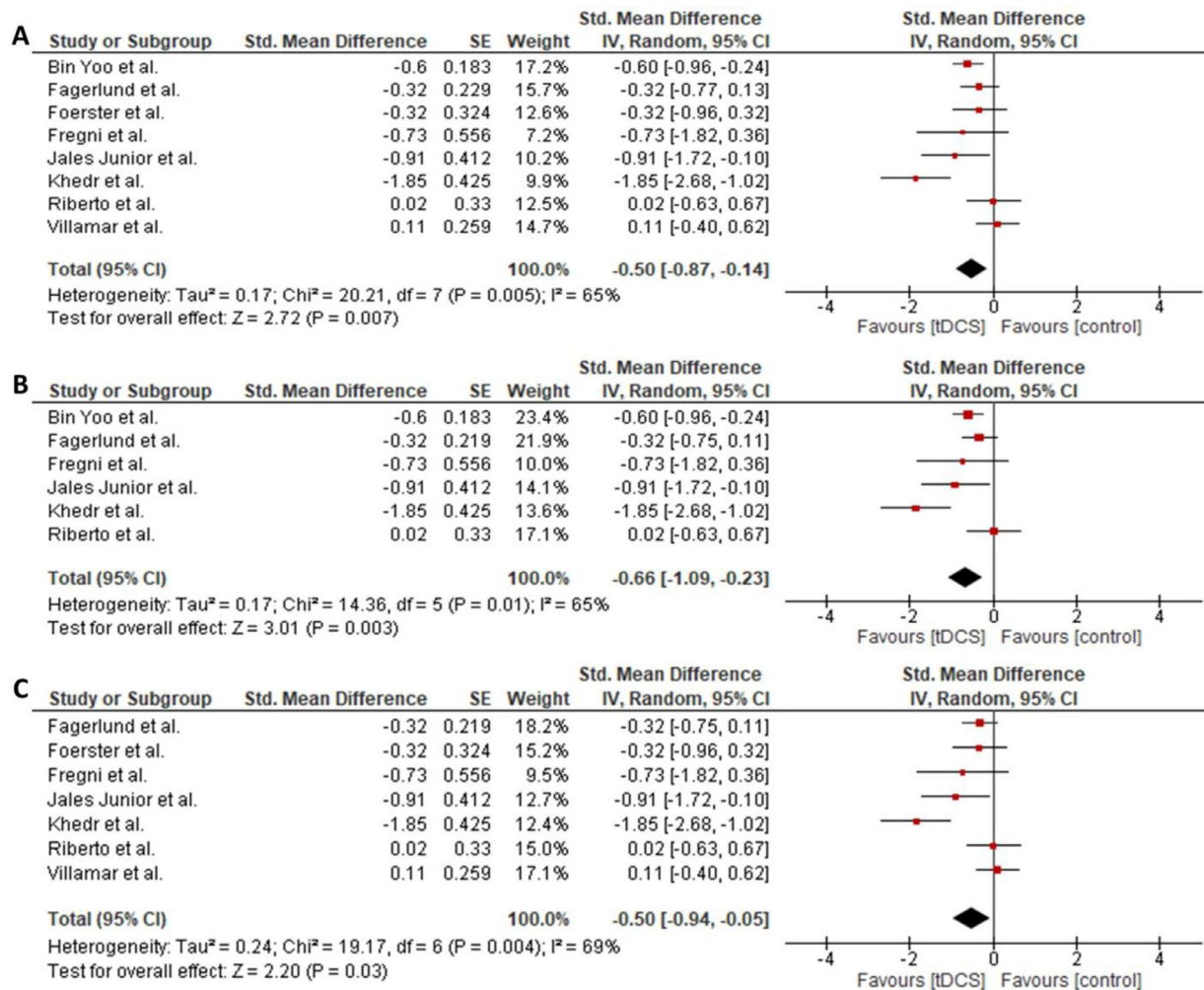


Figure 2. Meta-analysis plots of the effect of anodal tDCS on pain intensity ratings in fibromyalgia. Each line and square represents an individual effect size. Black diamonds indicate standardized effect size. **(A)** Active tDCS versus sham tDCS. **(B)** Subgroup analysis of RCT data only. **(C)** Subgroup analysis of active tDCS to M1 versus sham tDCS.

(equivalent to a percentage change of 17%). However, there is substantial variability in the data in all analyses.

Visual inspection of the data (Fig. 2 and 3) indicate that the study conducted by Khedr et al³³ could be the source of such variability as they report the greatest effects of tDCS (2 SMD from the standardized mean). A sensitivity analysis excluding data from Khedr et al³³ reduced statistical heterogeneity; however, this also reduced the effect of active tDCS down to a percentage change of 12%, which is below the threshold for a CID. Therefore, it seems that the positive effect of tDCS seen in the meta-analysis is driven largely by the results of this one study. What factor(s) are driving the much greater effect of tDCS in this study? Most studies included in the review used 2 mA of anodal stimulation applied for 20 minutes to M1 across several sessions (typically 5 consecutive sessions over 2 weeks, ie, 10 sessions in total). The study by Khedr et al³³ also used these parameters in a sample of 40 patients. The greater number of participants may have increased the power of their statistical findings. However, the unique difference in this study was the position of the reference electrode. This was placed on the contralateral arm in an extra-cephalic site rather than the supraorbital

(cephalic) site favored by most other studies. Using the same reference montage this group have also shown postsurgical opioid consumption is reduced after total knee arthroplasty using tDCS.³² According to the authors, using an extra-cephalic electrode as the reference avoids having 2 electrodes with opposite polarities over the brain,^{1,20} which may subsequently reduce the effects of active tDCS to the target site. Although this is an interesting proposal it is also possible that an extra-cephalic montage stimulates deep and mid-brain structures implicated in pain processing more than other montages.^{4,13} These differences in montage could have consequences for the effectiveness of tDCS as an intervention for fibromyalgia pain. For example, most previous studies using tDCS for fibromyalgia pain have targeted M1 based on findings from repetitive transcranial magnetic stimulation (rTMS), which show evidence for pain relief.⁴⁰ However, this may not be the optimal cortical target as tDCS and rTMS targeting the same motor regions may not produce pain relief through the same mechanism of action.²⁶ To fully understand the effects of different montages computational modeling of the current flow pattern across the brain should be conducted to improve our understanding of the flow

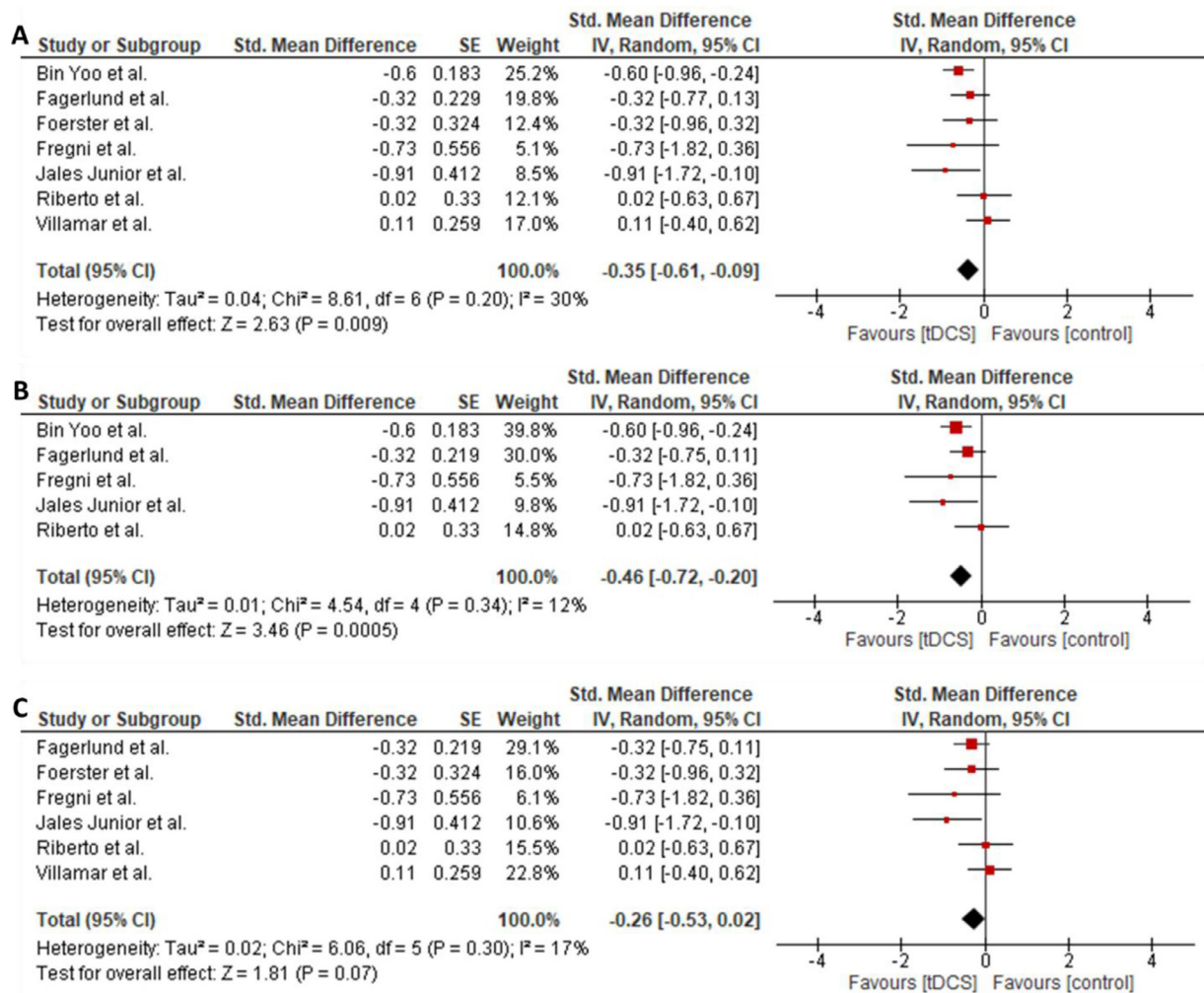


Figure 3. Forest plot of sensitivity analyses of the effect of anodal tDCS on pain intensity ratings in fibromyalgia, excluding data from.¹⁹ Each line and square represents an individual effect size. Black diamonds indicate standardized effect size. **(A)** Active tDCS versus sham tDCS. **(B)** Subgroup analysis of RCT data only. **(C)** Subgroup analysis of active tDCS to M1 versus sham tDCS.

produced by tDCS and identify the optimal tDCS electrode configuration (and stimulation parameters) to achieve maximal stimulation at the desired brain region (s).^{5,41}

The exact mechanism of fibromyalgia pain is currently unknown.²⁵ However, recent evidence suggests it may be linked to abnormalities in the top-down processing of pain anticipation networks, such as insula and DLPFC rather than M1.⁹ It is vital, therefore, that sites other than M1 are explored and to identify these, more basic research into central pain mechanisms in chronic pain is needed. A recent systematic review found that chronic pain was largely associated with increased theta and alpha endogenous brain oscillatory rhythms at rest.⁴² Resting-state theta power in the prefrontal and anterior cingulate cortex (regions involved in cognitive-attentional aspects of pain) was significantly increased in participants with fibromyalgia compared to pain-free controls.¹⁸ Moreover, frontal theta power was significantly positively correlated with pain and tenderness on the day of measurement and tiredness scores. More appropriate methods to modify such oscillatory networks would be transcranial alternating current

stimulation (tACS) or transcranial random noise stimulation (trNS). tACS causes entrainment with ongoing (endogenous) brain rhythms, such as the alpha rhythm. Application of tACS at alpha frequency (10 Hz) to somatosensory cortex significantly lowered subjective pain scores for experimental pain stimuli compared with sham stimulation, but only when the intensity of an upcoming stimulus was uncertain.³ More recently, tACS has been applied to the somatosensory cortex of 20 patients with chronic low back pain to determine its efficacy in reducing pain in a randomized, crossover, double blind sham-controlled pilot study.² Stimulation with alpha tACS (vs sham) significantly increased alpha oscillations in the somatosensory cortex and this correlated with a reduction in pain symptoms. trNS is another transcranial electrical stimulation method which, instead of applying a particular frequency, applies a random noise spectrum using frequencies ranging from 100 to 640 Hz. Curatolo et al¹² applied trNS to motor cortex in 20 female patients with fibromyalgia in a RCT. trNS sessions occurred on 5 days a week for 2 weeks and patients were evaluated on a number of measures. Compared to sham, active trNS

significantly reduced pain, depression, anxiety and Fibromyalgia Impact Questionnaire scores. Such widespread effects may be due to the wide range of stimulation frequencies engaging both pain and cognitive neural networks. Indeed,¹¹ found changes in resting state functional connectivity after repetitive tDCS of motor cortex in fibromyalgia patients, which correlated with reductions in clinical pain and may suggest that tDCS produces analgesic effects by altering thalamic connectivity. Other studies have also suggested that excitatory (glutamate) and inhibitory (GABA) brain metabolites may play a role in the effectiveness of motor cortex tDCS in treating fibromyalgia.²³ However, without simultaneous tDCS-electroencephalography studies being conducted it is unknown exactly what the mechanism of action of tDCS to motor cortex is on pain and cognitive networks. Moreover, it remains unclear which brain regions are actually modulated by the M1-tDCS montage (or any tDCS montage). The current flow induced by a conventional tDCS montage is not particularly focal and can influence a widespread neural network.¹⁴

Finally, a number of novel developments in the field of neurostimulation should also be considered in the application of tDCS to treat fibromyalgia pain. Large variability in findings for neurostimulation might be explained by a brain-state dependency of the effects of neurostimulation. A number of studies have demonstrated that the modulation of corticospinal excitability is brain-state dependent, that is, dependent on the timing of stimulation with respect to the underlying brain state.^{34,35} Thus, a more individual, state-dependent approach might improve neurostimulation outcomes in fibromyalgia (eg,^{29,49}). Another promising development is the application of combined simultaneous stimulation to reduce pain. It has been shown that simultaneous anodal tDCS of the primary motor cortex (M1) combined with peripheral electrical stimulation results in an enhanced, long-lasting, and clinically important reduction of chronic low back pain^{27,48} and neurogenic pain.⁷

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Limitations of the Current Review

Although this systematic review and meta-analysis is based on the largest cohort of clinical studies on the effects of tDCS on fibromyalgia pain sampled to date, the number of participants in the 8 trials selected for the meta-analysis is small ($n = 253$) compared with the numbers included in meta-analyses of the effects of other neuromodulation techniques such as rTMS (eg, 42 trials with $n = 1101$ participants⁴⁰). A further limitation is that we only considered the effects of tDCS on VAS pain intensity scores; however, this is the most frequently cited primary outcome measure for clinical studies and therefore allows us to make the greatest comparison across the available literature. The biggest strength of the current review compared to previous reviews is the fact that we calculate CID in pain scores (percentage change) and can therefore know the clinical impact of the intervention.

Conclusions

Neuromodulation techniques could be a potential new effective treatment for chronic pain conditions thought to be caused by dysfunction of the CNS, such as fibromyalgia. The results of this systematic review and meta-analysis suggest that active tDCS applied at an intensity of 2 mA to left M1 for 20 min/d for 10 sessions appears to be able to lower pain intensity in fibromyalgia. However, there is a need to conduct further experimental studies to know exactly the brain mechanisms of action of the effect and thereby determine the most effective neural targets and optimum stimulation parameters and treatment protocols before conducting further clinical trials.

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2020.01.003>.

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