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Non-invasive brain stimulation at dorsolateral prefrontal cortex of migraine patients: a systematic review and meta-analysis

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Introduction
Migraine is highly prevalent and disabling; many patients remain refractory despite therapeutic advances, including CGRP antagonists. Non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), emerge as promising strategies by modulating cortical excitability and nociceptive circuits. The dorsolateral prefrontal cortex (DLPFC) stands out as a therapeutic target due to its role in descending pain modulation.

Objective
This systematic review and meta-analysis aims to evaluate the efficacy and safety of NIBS applied to the DLPFC in migraine patients.

Methods
Conducted according to PRISMA guidelines using the PICOTT strategy, a systematic search was performed in PubMed, Embase, Cochrane Library, Web of Science, PsycINFO and Scopus. Two independent reviewers screened studies, resolving disagreements by a third reviewer consensus. Randomized controlled trials (parallel/crossover) without time restrictions in adults with migraine (with/without aura, chronic/episodic) undergoing NIBS on the DLPFC compared to sham were included. Analyzed outcomes were pain duration, frequency, pain intensity, MIDAS and acute medication use. Combined interventions or other primary headaches were excluded. Statistical analyses were performed using R software.

Results
The initial search identified 1,923 studies. After applying eligibility criteria, 7 RCTs (4 rTMS and 3 tDCS) were included (N=187). Analysis focused on the DLPFC, restricted to outcomes with 3 or more studies, revealed that neuromodulation significantly reduced pain duration compared to control, presenting a pooled standardized mean difference (SMD=-0.98; 95% CI [-1.92; -0.04], p=0.0411; I^2=88%). In contrast, DLPFC stimulation did not demonstrate statistical superiority to sham for pooled global migraine frequency (SMD = -0.58; 95% CI [-1.45; 0.29], p=0.193; I^2=87.5%) and pooled pain intensity (SMD=-0.24; 95% CI [-0.60; 0.13], p=0.2012; I^2=34.6%). Similarly, impact on functional disability evaluated by MIDAS (SMD=-0.75; 95% CI [-2.28; 0.78], p=0.3375; I^2=78.3%) and acute rescue medication use (SMD=-0.10; 95% CI [-0.50; 0.29], p=0.6021; I^2=25%) presented no significant differences. No serious adverse events occurred; mild, transient side effects were strictly local, manifesting as itching, tingling, and erythema for tDCS, and scalp discomfort or mild headache for rTMS.

Conclusion
Current evidence suggests that NIBS targeted to the DLPFC exhibits potential selective efficacy in shortening migraine pain duration. However, given the high statistical heterogeneity, a relatively small pooled sample size, and the lack of significant impact on frequency or intensity, these findings must be interpreted with caution. The DLPFC remains a promising, safe adjuvant target, but large-scale, standardized clinical trials are needed to definitively confirm its clinical therapeutic value.

Keywords:
Migraine disorders
Non-invasive brain stimulation
Dorsolateral prefrontal cortex
Repetitive transcranial magnetic stimulation
Transcranial direct current stimulation

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