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Review

Therapeutic Applications of rTMS in Migraine Prophylaxis

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Abstract

Migraine is one of the main causes of neurological disability, especially in young adults. Recent developments in preventive migraine therapies have improved outcomes for many patients, while highlighting the need for additional therapeutic options for those who remain refractory to pharmacological prophylaxis. Repetitive Transcranial Magnetic Stimulation (rTMS) has emerged as a promising neuromodulatory tool. We searched published literature for articles describing the efficacy of different rTMS protocols in the treatment of migraine. The literature search was conducted using PubMed and Scopus for articles published up to March 26, 2026. Twenty-four articles were categorized based on cortical targets (primary motor cortex [M1], dorsolateral prefrontal cortex (DLPFC), Vertex, Visual Cortex or Multifocal). High-frequency rTMS (HF-rTMS) targeting either the M1 or the left DLPFC demonstrated potential efficacy for specific goals such as reducing monthly migraine days, pain intensity, and medication intake. According to studies using neurophysiological data (obtained via transcranial magnetic stimulation-electroencephalography (TMS-EEG)), clinical improvement correlates with enhanced frontotemporal network connectivity and restored cortical plasticity. Guided rTMS stimulation through functional connectivity between the DLPFC and the pregenual cingulate cortex (PGC) may increase the precision of pain processing network modulation. Low-frequency rTMS (LF-rTMS) protocols also show potential benefits, including reductions in headache frequency, intensity, disability and medication use, although the supporting evidence is limited and derived primarily from small and uncontrolled studies. Multifocal rTMS paradigms showed promising efficacy in episodic migraine. Considerable heterogeneity in study design, stimulation protocols, and outcome measures limited the ability to draw reliable conclusions. Frequency and localization may be important determinants of clinical success. Future research should focus on network-based, personalized stimulation protocols to potentially increase long-term therapeutic benefit.

Keywords: migraine disorders; transcranial magnetic stimulation; motor cortex; neuromodulation; prefrontal cortex

1. Introduction

Migraine is considered to be one of the main causes of neurological disability worldwide [1]. Although there are several available preventive medications, a proportion of patients that do not respond appropriately and/or discontinue treatment due to side effects still remains [2,3]. Meanwhile, the prevalence of migraine is estimated to be over 1 billion people worldwide and it has been recognized as the second most disabling disorder globally, measured in years lived with disability, and the first among women aged 15–49 years, according to the Global Burden of Disease Study 2023 [4,5,6]. Despite the increasing number of pharmacological interventions in the past two decades, ranging from triptans to calcitonin gene-related peptide (CGRP) antagonists, a significant subset of patients remains refractory to the regular prophylactic therapy or experiences adverse effects, resulting in a high prevalence of medication overuse headache (MOH) [7].

The pathophysiology of migraine entails an abnormal cortical excitability [8]. The cerebral cortex of migraine patients is often hypersensitive and characterized by dysfunction of sensory stimuli, which probably engages the trigeminovascular system and irregular thalamocortical oscillations [9]. This pathobiological mechanism has prompted research towards neuromodulation as an alternative, non-pharmacological therapy.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive method that uses oscillating magnetic fields to stimulate specific cortical regions, with high-standard approved applications in neurological and psychiatric disorders [10]. The effects produced by altering synaptic plasticity through rTMS can be either excitatory or inhibitory, depending on high or low frequency, correspondingly, with duration beyond the time of application [11]. Several anatomical targets have been discovered in the past two decades, with main representatives being the primary motor cortex (M1), a brain region known for chronic pain processing, the dorsolateral prefrontal cortex (DLPFC), which is crucial for cognitive and emotional network modulation of acute and chronic pain and the vertex region, a key center for the intensity and localization of pain.

Despite the promising evidence of the first pilot studies, the results from later studies are conflicting [12,13]. The establishment of a standardized treatment protocol remains a challenge, mainly due to the use of different stimulation frequencies (1 Hz vs. 10–20 Hz), the specific cortical target regions and the placebo effect, observed in device-based trials. Furthermore, the development of multifocal paradigms and the emergence of new transcranial magnetic stimulation-electroencephalography (TMS-EEG) data impose a re-evaluation of the evidence [14].

Although single pulse transcranial magnetic stimulation (sTMS) has long been approved as prophylactic treatment for migraine by the Food and Drug Administration (FDA) [15,16], there is only indication that rTMS application could be possibly used for migraine prevention. Non-invasive neuromodulation is a promising alternative prophylactic treatment for migraine, mainly intended for patients with contraindications and/or non-responders to traditional pharmacotherapy [10,17]. Despite this formal recognition, research is evolving towards optimizing individualized intervention strategies.

The purpose of this review is to synthesize the clinical outcomes of studies and case series conducted through March 2026. In human patients with migraine (P), rTMS interventions (I) were compared to non–rTMS-based interventions (sham; transcranial direct current stimulation (tDCS); pharmacological treatment; different rTMS protocols) or pre- and post-rTMS are reported (C). Improvements in clinical (e.g., migraine frequency and intensity) and non-clinical outcomes (e.g., electroencephalography (EEG) markers or biomarkers) were assessed (O). Different types of studies were retrieved (S). We assumed that rTMS intervention would lead to greater clinical improvements in adults with migraine by evaluating the efficacy of different cortical targets and stimulation parameters; we aim to provide a clearer consensus on the role of rTMS in the prophylactic management of chronic and episodic migraine.

2. Literature Review

2.1 Literature Search

The present narrative review was designed to synthesize and critically integrate findings that address the role of rTMS in the prophylactic treatment plan of patients migraine. Based on this concept, we adopted a structured but non-systematic review framework, in order to provide a comprehensive synthesis of the available literature, through March 2026. Since the design of our review is narrative, no formal guidelines, risk of bias or quality assessment were applied. Instead, a qualitative synthesis was used to integrate study findings, prioritizing observational and randomized controlled trials. The current review was not registered in any database. This study did not require an ethical board approval or written informed consent by the participants.

A structured search was conducted to obtain articles investigating the effect of rTMS on individuals being diagnosed with migraine until the 26th of March 2026 in the following databases: PubMed (National Library of Medicine) and Scopus (Elsevier). The search strategy included the following inquiry: (“migraine” OR “migraine with aura” OR “chronic migraine”) AND (“repetitive transcranial magnetic stimulation” OR “transcranial magnetic stimulation” OR “TMS” OR “rTMS”). A manual examination of the reference list of each eligible study was also performed. The review was independently performed by two authors (D.T. and C.M.). Disagreements were resolved after being discussed with a third tie-breaking evaluator (V.S.).

2.2 Eligibility Criteria, Study Selection and Data Extraction

Our criteria for inclusion were the following: (a) articles demonstrating the effects of rTMS on individuals diagnosed with migraine and/or migraine subtypes, such as episodic migraine, chronic migraine, vestibular migraine or MOH; (b) original articles, including randomized controlled trials, observational studies, pilot studies and/or case series; (c) the overall number of participants being reported in the study, (d) studies carried out on humans, (e) studies including adult participants and adolescents ≥15 years old, (f) articles written in English, (g) studies including a detailed documentation of the technical aspects applied in the rTMS protocol, (h) studies reporting the clinical outcomes in terms of headache frequency and intensity, migraine-related disability, medication use and responder rates. The criteria for exclusion were the following: (a) studies not mentioning the outcome of rTMS on migraine patients, (b) studies not involving human subjects, (c) studies including participants <15 years old, (d) articles not written in English, (e) articles being reviews, meta-analyses, case reports, book chapters, conference abstracts, editorials, commentaries, or poster presentations, (f) articles irrelevant to the topic, (g) retracted articles. We excluded duplicate results identified through search in PubMed and Scopus with EndNote citation manager software (v20, Clarivate, Philadelphia, PA, USA). After eliminating duplicate records, every title and abstract underwent screening for potential relevance. Further eligibility evaluation was conducted on these articles, retrieving the full text. Eventually, 24 studies [12,13,14,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38] met the inclusion criteria and were integrated into the final synthesis of our review. The studies included were categorized according to the targeted cortical region.

3. Studies Evaluating rTMS in Migraine

The main cortical targets investigated for migraine prophylaxis are illustrated in Fig. 1.

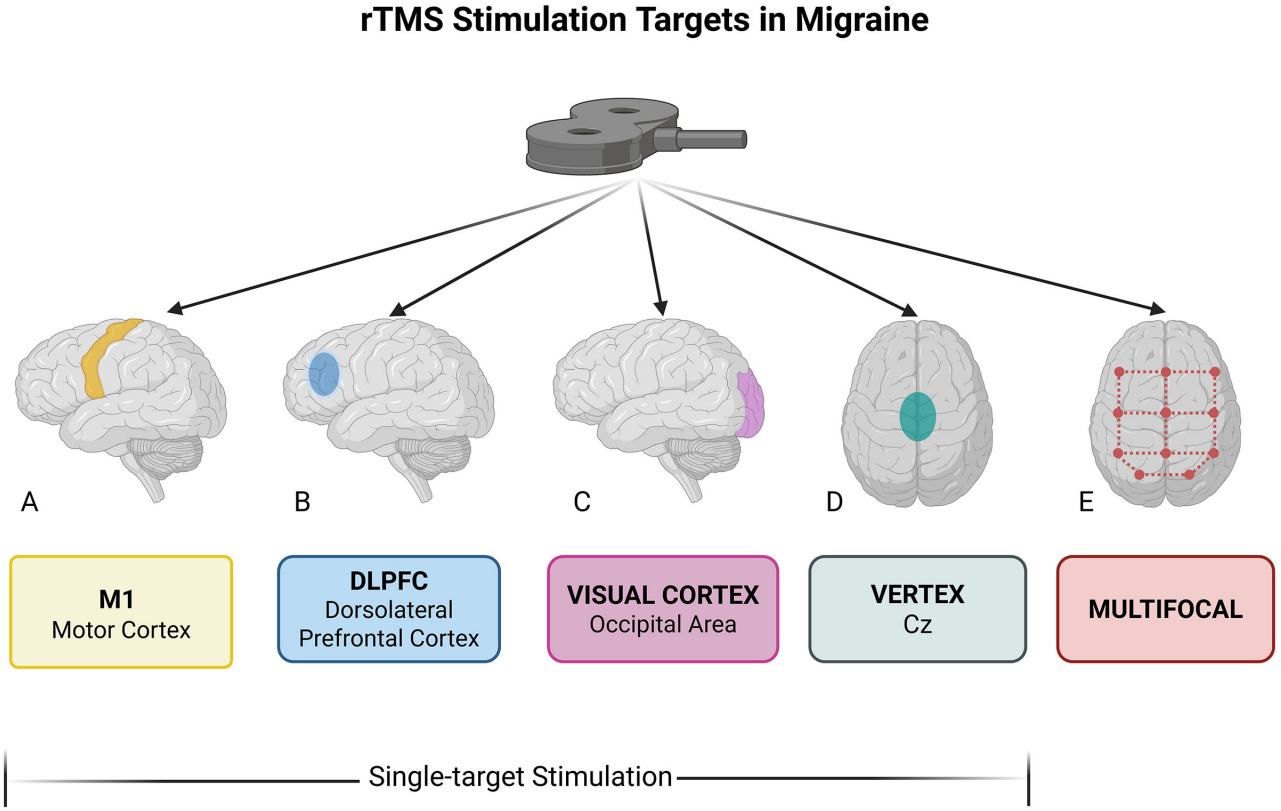

Fig. 1. rTMS stimulation targets that are mainly applied for migraine prophylaxis. M1, primary motor cortex; DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; Cz, central midline electrode. Fig. 1 was prepared using the BioRender platform (under license to VS, Created in BioRender. Siokas, V. (2026), https://BioRender.com/gp1thfm).

3.1 Studies Evaluating rTMS to Primary Motor Cortex (M1)

Several studies evaluated high-frequency rTMS (HF-rTMS) applied to the primary motor cortex. In a clinical study conducted by Misra et al. (2012) [20], 51 migraine patients were included (median age 32 years; predominantly females) who did not respond to at least two prophylactic medications. Patients were submitted to three rTMS sessions of 8 Hz frequency, over the left M1 region (abductor digiti minimi target spot) at 70% of motor threshold. The results exhibited significant reduction in migraine intensity, frequency, rescue medication use and disability ($p < 0.0001$), with maximum improvement during the first week of rTMS application. Particularly, 98% of patients reached an improvement percentage of >50% in headache scores within two weeks of use.

In a successive randomized trial by Misra et al. (2013) [13], 100 migraine patients with ≥4 episodes per month. HF-rTMS (10 Hz) delivered over three sessions resulted in >50% reductions in both headache frequency and visual analogue scale (VAS) scores in both active and sham groups; however, improvements were significantly greater in the active treatment group. Benefits were most pronounced in the first week and declined over time. Secondary outcomes, including headache severity and migraine-related disability also showed improvement after treatment with HF-rTMS, while the reductions noticed in rescue medication use were not statistically significant.

Kumar et al. [19] randomized 20 patients with chronic migraine to active or sham rTMS. Ten sessions of 10 Hz stimulation over left M1 produced significant reduction in the mean VAS, headache frequency, and Migraine Disability Assessment (MIDAS) score in real rTMS group which was maintained after 1 month of follow-up. However, no significant differences were observed in MIDAS scores at three-month follow-up.

Misra et al. [21] further investigated the role of β-endorphin (βE) in 93 patients undergoing 10 Hz rTMS. Significant improvements in headache frequency (91.3%) and severity (67.4%) were observed following active stimulation, although notable improvements were also reported in sham groups. Clinical improvement correlated with increased βE levels.

A randomized controlled trial by Kalita et al. [22] compared high-rate rTMS with rTMS in combination with amitriptyline treatment in 83 migraine patients. The combination therapy of rTMS with amitriptyline exhibited lower frequency of headache compared with rTMS alone. Specif-

Table 1. Characteristics of studies evaluating rTMS applied to M1.

Author (year)/Country	Population	Intervention (rTMS protocol)	Comparator	Follow-up	Efficacy outcomes measured/scales/tools	Main results
Misra et al. (2012) [20]/India	n = 51, f = 45, age range = 16–61 y, median age = 32 y, refractory migraine	Left M1, 8 Hz, 584 pulses, 3 sessions on alternative day, 70% MT	None	4 weeks	Frequency, severity, disability, diary, VAS	Significant improvement in migraine frequency, severity, number of rescue medications and VAS.
Misra et al. (2013) [13]/India	n (initiated) = 100 (rTMS = 50, sham = 50), f = 88, age range = 17–65 y, median age = 35 y, ≥4 attacks/month n (completed) = 95	Left M1, 10 Hz, 600 pulses, 3 sessions on alternative day, 70% MT	Sham	4 weeks	Frequency, severity, disability, diary, VAS	Improvement regarding, headache frequency, VAS score functional disability in rTMS group compared to sham stimulation group.
Teo et al. (2014) [24]/Singapore	n = 9, (rTMS = 6, sham = 3), age range = 21–65 y, chronic migraine	Right M1, 10 Hz, 1000 pulses, 10 sessions, 80% RMT	Sham	2 months	Frequency, severity, medications used, diary	Premature termination with high dropout rate (50%) due to worsening headaches.
Zardouz et al. (2016) [37]/USA	n = 5, f = 0, age range = 32–60 y, mean age = 47.2 y, episodic and chronic migraine	Left M1, 10 Hz, 2000 pulses, 5 sessions (separated in 1- to 2-week intervals for a period of 2 months), 80% RMT	None	2 months	Frequency, intensity, duration	Decrease in intensity, frequency, and duration of headaches and NRS.
Shehata et al. (2016) [23]/Egypt	n (initiated) = 29 (rTMS = 14, -BTX-A = 15), f = 19, age range = 21–52 y, mean age = 32.65 y n (completed) = 26	Left M1, 10 Hz, 2000 pulses, 80% RMT	BTX-A	12 weeks	Frequency, severity, attack-aborting medications. diary, VAS, HIT-6, HDI	Improvement in both groups, more sustainable though in BTX-A group.
Misra et al. (2017) [21]/India	n = 93, f = 75, age range = 18–65 y, median age = 35 y, ≥4 attacks/month Three groups: (I) 3 sessions to n = 24, (II) 1 session n = 22 and (III) sham n = 47	Left M1, 10 Hz, 600 pulses, 3 sessions, 70% MT	1 session (Left M1, 10 Hz, 600 pulses) or Sham	1 month	frequency, severity, functional disability, number of rescue medications, diary, VAS, βE, MOR and DOR plasma levels	The headache severity improved in 31/46 (67.4%) patients and headache frequency in 42/46 (91.3%) in rTMS group. Improvement correlated with βE level.
Kumar et al. (2021) [19]/India	n = 20 (rTMS = 10, sham = 10), f = 11, age range = 18–47 y, mean age = 33 y, chronic migraine	Left M1, 10 Hz, 600 pulses, 10 sessions, 70% RMT, navigated	Sham	1 month	Frequency, intensity, disability, diary, VAS, STAI, BDI, MIDAS (3 months follow-up available)	Significant improved regarding VAS, headache frequency, and MIDAS in rTMS group which was maintained after 1 month of follow-up.
Kalita et al. (2021) [22]/India	n (initiated) = 83 (rTMS = 41, rTMS+AMT = 42), f = 72, age range = 18–55 y, mean age = 31.13 y, chronic migraine n (completed) = 50	Left M1, 10 Hz, 600 pulses, 3 sessions on an alternate day repeated every month for 3 months, 70% MT	rTMS vs rTMS + AMT	3 months	Frequency, severity, diary, VAS	rTMS+ amitriptyline group patients had more than 50% reduction in headache days and in headache severity at 3 months, compared to rTMS group.

rTMS, repetitive transcranial magnetic stimulation; M1, Primary Motor Cortex; f, female; y, years; MT, motor threshold; RMT, resting motor threshold; VAS, visual analogue scale; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; MIDAS, Migraine Disability Assessment; βE, β endorphin; MOR, μ-opioid receptors; DOR, δ-opioid receptors; BTX-A, botulinum toxin type A; HDI, 25-item Henry Ford Hospital Headache Disability Inventory; HIT-6, Headache Impact Test-6; AMT, amitriptyline; NRS, numerical rating scale.

Table 2. Characteristics of studies evaluating rTMS applied to DLPFC.

Author (year)/Country	Population	Intervention (rTMS protocol)	Comparator	Follow-up	Efficacy outcomes measured/scales/tools	Main results
Brighina et al. (2004) [25]/Italy	n = 11, (rTMS: 6, sham: 5), f = 7, mean age = 47 y, chronic migraine	Left DLPFC, 20 Hz, 12 sessions, 90% MT	Sham	2 months	Frequency, intensity, Headache index, diary	Significantly reduced headache attacks, headache index and number of abortive medications 1 month after the end of the treatment in the rTMS group.
Conforto et al. (2014) [12]/Brazil	n (initiated) = 18 (rTMS = 9, sham = 9), f = 18, age range = 18–80 y, mean age = 38.8 y, chronic migraine n (completed) = 14	Left DLPFC, 10 Hz, 1600 pulses, 23 sessions, 110% RMT	Sham	8 weeks	Pain intensity, Frequency, MIDAS, BDI, State Anxiety Inventory, Trait Anxiety Inventory, diary	Number of headache days decreased significantly more in the sham group than in the rTMS group.
Granato et al. (2019) [29]/Italy	n (initiated) = 16 n (completed) = 14, (rTMS = 7, sham = 7), mean age = 45.8 y, chronic migraine and MOH	DLPFC, 20 Hz, 10 sessions, 100% MT	Sham	3 months	Headache days, hours, intensity, SDI, MIDAS, Hamilton Rating Scale	No significant differences between groups.
Sahu et al. (2019) [26]/India	n = 41 (rTMS = 20, sham = 21), f = 31, age range = 18–60 y, mean age = 30.78 y	Left DLPFC, iTBS, 10 sessions (2 per day adjunctive to other migraine treatment), 80% AMT	Sham	12 weeks	Frequency, duration, severity, headache diary, MIDAS	Significant decrease in frequency, duration, and severity of migraine in the rTMS group, more pronounced during the initial 2 weeks.
Amin et al. (2020) [27]/Egypt	n (initiated) = 33, (rTMS = 14, sham = 19), f = 31, mean age = 34.41 y, episodic migraine n (completed) = 29	Left DLPFC, 5 Hz, 5 sessions, 900 pulses, 100% MT	Sham	1 month	Frequency, intensity, duration, headache diary, number of abortive pills used per month, NPRS, HIT-6	Statistically significant reduction of migraine (≥50%) in almost 70% of a sample of episodic migraineurs with a concomitant decrease in functional disability.
Shah et al. (2022) [31]/India	n = 108, (HF-rTMS = 36, LF-rTMS = 36, sham = 36), f = 91, mean age = 31 y, chronic migraine	Left DLPFC, HF (8 Hz, 584 pulses, 3 sessions on alternative day, 70% MT) LF (1 Hz, 500 pulses in 2 trains, 3 sessions on alternative day, 70% MT)	Sham	4 weeks	Frequency, severity, functional disability, VAS, MIDAS	The number of attacks per month decreased in the HF-rTMS compared to the LF-rTMS and sham groups. The VAS score, duration in the HF-rTMS group was significantly lowered at four weeks compared to baseline.
Naji et al. (2024) [18]/Iran	n = 72, (rTMS = 36, tDCS = 36), f = 53, mean age = 39.4 y	rTMS, Left DLPFC, 10 Hz, 600 pulses, 3 sessions, 70% MT tDCS, Anodal left DLPFC, cathodal right DLPFC, current intensity of 2 mA, density equivalent to 0.08 A/m^2 for 20 minutes 12 sessions	tDCS	1 month	Intensity, impacts of headache in daily life, anxiety, depression, HIT-6, VAS, HADS	Improvement in depression in the rTMS group, without though statistically significant differences between the groups regarding the impact of headaches on daily life, anxiety and pain intensity.
Clemente et al. (2025) [28]/Italy	n = 12, f = 3, age range = 23–74 y, mean age = 51.42 y, chronic migraine refractory to anti-CGRP	Initial sham stimulation phase applied to all the participants, Left DLPFC, iTBS (accelerated, 20 sessions over four consecutive days, with five sessions per day, resulting in a total of 32,400 stimuli), 110% RMT, navigated	-	2 months	headache diary, MHDs, MMDs, NRS, MIDAS, BDI-II, BAI, HDRS, SAS-I, TMT- A, TMT-B, Digit Span Backward, Symbol Digit Modalities Test, Phonemic and Semantic Verbal Fluency Test, Stroop test, EEG analysis	Improvement of monthly headache days, monthly medication days, and headache intensity trend for improvement for anxiety, depression, and cognitive performance, and normalization of neurophysiological markers after real iTBS.

Table 2. Continued.

Author (year)/Country	Population	Intervention (rTMS protocol)	Comparator	Follow-up	Efficacy outcomes measured/scales/tools	Main results
Song et al. (2025) [14]/China	n = 28 migraineurs, (HF-rTMS = 14, sham = 14), f = 17, mean age = 37.45 y	Left DLPFC, 20 Hz, 700 pulses, 14 sessions, 90% RMT	Sham	1 month	migraine severity, frequency, VAS, MMD, EEG	Increased frontotemporal network connectivity, correlating with VAS and MMD scores reduction.
Khairkar et al. (2025) [30]/India	n = 5, f = 2, age range = 29–48 y, mean age = 36.8 y, treatment-refractory migraine	Left DLPFC, 20 Hz, 400 pulses, 5 sessions in the first week followed by weekly sessions for additional 4 weeks, 90% RMT, The cases had been previously treated with 10 Hz rTMS, 600 pulses 5–9 sessions	-	3–6 months	Frequency, severity	Significant reduction in frequency and severity, evident, lasting over a follow-up period of 3–6 months.
Zhen et al. (2026) [36]/China	n = 21, f = 15, age range = 20–61 y, mean age = 36.7 y	Left DLPFC (strongest functional connectivity with PGC), 10 Hz, 1800 pulses, 10 sessions, 100% RMT	None	2 months	Frequency, severity, sleep disturbances, headache diary, PSQI, patient global impression of change, brain functional connectivity	Personalized rTMS had a significant effect on headache frequency and intensity.

HF, high-frequency; LF, low-frequency; DLPFC, dorsolateral prefrontal cortex; RCT, randomized controlled trial; iTBS, intermittent theta-burst stimulation; MHDs, monthly headache days; MMDs, monthly medication days; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; HDRS, Hamilton Depression Rating Scale; SAS-I, Starkstein Apathy Scale; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; EEG, electroencephalography; NPRS, Numeric Pain Rating Scale; SDI, symptomatic drug intake; MOH, medication overuse headache; HC, healthy controls; MMD, monthly migraine days; tDCS, transcranial direct current stimulation; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh sleep quality index; PGC, pregenual cingulate cortex.

ically, the group of patients that used the combination therapy showed a statistically significant difference in the reduction of headache frequency of over 50% compared with the group that used rTMS alone ($p < 0.0001$) and a significant reduction in the VAS scores ($p = 0.01$) at three months of treatment.

A pilot randomized trial conducted by Shehata et al. [23] compared HF-rTMS versus botulinum toxin A (BTX-A) injection, as prophylactic treatment, in 29 patients with chronic migraine. Both treatments produced significant improvements in examined outcomes at early follow-up. However, while BTX-A effects were sustained at 12 weeks, rTMS effects diminished and were no longer statistically significant. Finally, Zardouz et al. [37], reported decrease in the intensity, frequency, and duration of migraines in patients with episodic or chronic migraine receiving HF-rTMS in motor cortex. The characteristics of the studies evaluating rTMS to primary motor cortex are presented in Table 1 (Ref. [13,19,20,21,22,23,24,37]).

3.2 Studies Evaluating rTMS to Dorsolateral Prefrontal Cortex (DLPFC)

Brighina et al. [25] demonstrated that 20 Hz rTMS over the left DLPFC significantly reduced headache index, attack frequency, and abortive medication use compared with sham treatment. In contrast, Conforto et al. [12] found no significant reduction in headache days with active rTMS compared to baseline, while the sham group showed significant improvement, suggesting a strong placebo effect.

Sahu et al. [26] evaluated intermittent theta-burst stimulation (iTBS) over the left DLPFC in 41 patients. Active stimulation significantly reduced migraine frequency, duration, and severity with effects persisting for at least three months. A more recent single-blind controlled study by Clemente et al. [28] investigated an accelerated iTBS protocol targeting the DLPFC in 12 patients with chronic migraine refractory to anti-CGRP monoclonal antibodies. A sham session preceded the procedure that was followed by a two-month follow-up period. After active stimulation, significant reduction of headache days and days under medication per month was observed, as well as of headache intensity. Improvement was also noticed in cognitive performance and emotional state, including anxiety and depression [28].

Amin et al. [27] reported that 5 Hz rTMS over one week resulted in ≥50% reduction of the number of migraine attacks in almost 70% of treated patients compared to 25% in controls ($p = 0.02$), alongside clinically meaningful improvements in Headache Impact Test-6 (HIT-6) scores. Another randomized study assessing HF-rTMS as an adjunct to detoxification in medication-overuse headache found no significant differences between active and sham groups, despite overall clinical improvement [29].

A TMS-EEG study demonstrated that 20 Hz stimulation over the left DLPFC significantly increased frontal-temporal connectivity, which correlated with reductions in migraine frequency and intensity ($p < 0.001$), with sustained effects at one month [14]. A small case series suggested that escalation to 20 Hz stimulation may provide additional benefit to patients refractory to standard 10 Hz protocols, with sustained improvement over 3–6 months [30].

Naji et al. [18] randomized 72 patients with migraine to either the rTMS (left DLPFC, 10 Hz, 600 pulses, 3 sessions, 70% motor threshold [MT]) or tDCS (anodal left DLPFC, cathodal right DLPFC, current intensity of 2 mA, density equivalent to 0.08 A/m^2 for 20 minutes across 12 sessions) groups. Participants received 3 and 12 sessions of stimulation over the left DLPFC. Although depression improved in the rTMS group, no statistically significant differences were observed between the two groups regarding the impact of headaches on daily life, anxiety and pain intensity [18].

A randomized, single-blind trial (n = 108) comparing high- and low-frequency rTMS demonstrated that high-frequency stimulation significantly reduced headache frequency, intensity and duration at four weeks ($p < 0.001$), whereas low-frequency stimulation showed no therapeutic benefit [31].

In the study of Zhen et al. [36], guided rTMS stimulation through the functional connectivity between the DLPFC and the PGC was a key approach to increase precision of pain processing network modulation. More precisely, personalized rTMS (10 Hz, 1800 pulses, 10 sessions, 100% resting motor threshold [RMT]), guided toward the optimal stimulation target within the left DLPFC (considered the region with the strongest functional connectivity with PGC), had a significant effect on headache frequency and intensity [36]. The characteristics of the studies evaluating rTMS to DLPFC are presented in Table 2 (Ref. [12,14,18,25,26,27,28,29,30,31,36]).

3.3 Comparative Interventions, Other Cortical Targets (Vertex and Visual Cortex), Multifocal Stimulation

3.3.1 Comparative Interventions (DLPFC vs M1)

A four-arm randomized study (n = 137) compared rTMS targeting M1 or left DLPFC with topiramate and sham stimulation. All active treatments significantly improved headache frequency, intensity, medication use and Headache Impact Test-6 (HIT-6) scores at 1 and 2 months. Both rTMS protocols were superior to sham and demonstrated efficacy comparable to topiramate [34].

3.3.2 Vertex and Visual Cortex

A placebo-controlled trial (n = 27) evaluating 1 Hz rTMS over the vertex found no significant differences between active and sham groups across primary or secondary outcomes, despite within-group improvements [33]. In a prospective study of 40 migraine patients, Hammad et al. [38] demonstrated that low-frequency-rTMS (LF-rTMS) was associated with significant reductions in headache fre-

Table 3. Characteristics of studies evaluating rTMS applied to visual cortex, vertex, and multifocal.

Author (year)/Country	Population	Intervention (rTMS protocol)	Comparator	Follow-up	Efficacy outcomes measured/scales/tools	Main results
Teepker et al. (2010) [33]/Germany	n = 27 (verum group = 14, placebo group = 13), f = 22, age range = 20–63 y, mean age = 35.48 y	Vertex, 1 Hz, two trains of 500 monophasic pulses, 5 sessions, MT.	Sham	8 weeks	Frequency, intensity, number of pills	No effect vs sham.
Hammad et al. (2021) [38]/Egypt	n = 60 [rTMS = 40 migraineurs (with aura = 10, without aura = 30), HCs = 20], f = 47, age range = 15–55 y, mean age = 30.27 y	Vertex, 1 Hz, two trains of 500 pulses, 5 sessions, RMT.	no sham/HC group for neurokinin A levels	4 weeks	frequency (days/month), attack duration, intensity, abortive medication use, MIDAS score, serum neurokinin A level	Reductions in frequency, attack duration, pain intensity, abortive medication use, MIDAS scores, and serum neurokinin A level.
Todorov et al. (2020) [34]/Bulgaria	n (initiated) = 137, (M1 = 38, left DLPFC = 37, sham = 28, topiramate = 34), f = 108, mean age = 38.97 y, chronic migraine n (completed) = 119	M1, left DLPFC, 15 Hz, 1200 pulses, 5 sessions, 70% MT.	Topiramate + sham	2 months	frequency, intensity, symptomatic medication use, VAS, HIT-6	Improvement compared to sham. No significant differences between the two rTMS groups and the topiramate group.
Leahu et al. (2021) [32]/Moldova and Germany	n (initiated) = 65 n (completed) = 60, (rTMS = 33, sham = 27), f = 52, age range = 20–62 y, mean age = 39.75 y, episodic migraine	Multifocal "swipe"/"spot burst" 6 sessions Firstly, 13 pulse-trains of 140 pulses/train, 67 Hz and 60% of RMT with a 2 s intertrain interval, swipe stimulation by pulling the coil across the three anterior-posterior (fronto-occipital) and two latero-lateral (temporal) tracks. Subsequently, spot burst stimulation, 33 pulse-trains of 15 pulses/train, 67 Hz and 85% of RMT with an 8 s intertrain interval. During spot burst stimulation, each of the 11 marked spot areas was stimulated three times in a row.	Sham	12 weeks	Frequency, VAS, HIT-6, HDI, diary	Statistically significant effect of rTMS at migraine frequency.
Zhu et al. (2026) [35]/China	n (total) = 83 n (after propensity score matching) = 68, (rTMS+pharmacotherapy group = 34, pharmacotherapy alone group = 34), f = 68, mean age = 37.53 y, vestibular migraine	Visual cortex, 1 Hz, 1000 pulses, 10 sessions, 90% RMT.	pharmacotherapy	3 months	Duration, VAS, HIT-6, DHI-T	Significant reduction in HIT-6, no effect in pain intensity (VAS) or dizziness handicap inventory total score (DHI-T).

Table 4. Overview of included studies.

Author et al. (year)	Migraine subtype	Sample size	Comparator	Cortical target	Stimulation frequency	Findings
Brighina et al. (2004) [25]	Chronic migraine daily or >15 d/mo	11	Sham	Left DLPFC	High	Effective
Teepker et al. (2010) [33]	Migraine attacks >4 d/mo, with or without aura	27	Sham	Vertex	Low	Not effective
Misra et al. (2012) [20]	Migraine attacks >7 d/mo, 1 with aura	51	None	Left M1	High	Effective
Misra et al. (2013) [13]	Episodic or chronic migraine, attacks >4 d/mo, with or without aura	100	Sham	Left M1	High	Effective
Conforto et al. (2014) [12]	Chronic migraine	18	Sham	Left DLPFC	High	Not effective
Teo et al. (2014) [24]	Chronic migraine, attacks >15 d (of which 8 migrainous)/mo, no MOH	9	Sham	Right M1	High	Not effective
Zardouz et al. (2016) [37]	Chronic or episodic migraine with or without aura	5	None	Left M1	High	Effective
Shehata et al. (2016) [23]	Chronic migraine	29	BTX-A	Left M1	High	Less effective
Misra et al. (2017) [21]	Migraine, attacks >4 d/mo, with or without aura	93	Sham	Left M1	High	Effective
Granato et al. (2019) [29]	Chronic migraine and MOH	14	Sham	DLPFC	High	Not effective
Todorov et al. (2020) [34]	Chronic migraine	137	Sham, Topiramate	M1, Left DLPFC	High	Effective- no difference between targets
Sahu et al. (2019) [26]	Migraine with or without aura, >2 d/mo	41	Sham	Left DLPFC	iTBS	Effective
Kumar et al. (2021) [19]	Chronic migraine without aura	20	Sham	Left M1	High	Effective
Amin et al. (2020) [27]	Episodic migraine with or without aura, 4–14 attacks/mo	33	Sham	Left DLPFC	High	Effective
Kalita et al. (2021) [22]	Chronic migraine, attacks >15 d (of which 8 migrainous)/mo	83	rTMS+ Amitriptyline	Left M1	High	rTMS+ Amitriptyline more effective
Hammad et al. (2021) [38]	Migraine with or without aura	40 with migraine and 20 healthy controls	healthy controls for neurokinin A levels	Vertex	Low	Effective
Leahu et al. (2021) [32]	Episodic migraine with or without aura, 2–14 attacks/mo	60	Sham	Multifocal	High	Effective
Shah et al. (2022) [31]	Chronic migraine, attacks >4 d/mo, with or without aura	108	HF- LF- Sham	Left DLPFC	High/Low	Effective HF-rTMS
Naji et al. (2024) [18]	Migraine with indications of preventive treatment for chronic migraine	72	tDCS	Left DLPFC	High	Effective for depression
Clemente et al. (2025) [28]	Chronic refractory migraine, >8 d/mo	12	None	Left DLPFC	iTBS	Effective
Song et al. (2025) [14]	Migraine with or without aura	28	Sham	Left DLPFC	High	Effective
Khairkar et al. (2025) [30]	Treatment-refractory migraine, with or without aura, >4 d/mo	5	None	Left DLPFC	High	Effective
Zhu et al. (2026) [35]	Vestibular migraine	68	Pharmacotherapy	Visual Cortex	Low	Partially effective
Zhen et al. (2026) [36]	Migraine attacks ≥4 d/mo, with or without aura	21	None	Left DLPFC	High	Effective

mo, month; d, days.

quency, intensity, duration, MIDAS scores and abortive medication use after 4 weeks of rTMS. The treatment was well tolerated and accompanied by a decrease in serum neurokinin A levels compared to healthy controls (HC) [38].

In a retrospective study (n = 68), low-frequency (1 Hz) rTMS on visual cortex combined with pharmacotherapy resulted in significantly greater improvement in HIT-6 at three months compared with pharmacotherapy alone, in patients with vestibular migraine [35].

3.3.3 Multifocal High-Frequency Stimulation

A double-blind randomized controlled trial (n = 60) assessed a multifocal HF-rTMS protocol. The active group demonstrated a significantly higher responder rate (>50% reduction in migraine days) compared to sham (42% vs. 26%, $p < 0.05$), along with reductions in attack frequency. No serious adverse events were reported [32].

The characteristics of studies evaluating comparative interventions, other cortical targets (Vertex and Visual Cortex), or multifocal stimulation are presented in Table 3 (Ref. [32,33,34,35,38]).

A summary overview of included studies by migraine subtype, comparator, cortical target, key stimulation characteristics and principal findings is summarized in Table 4 (Ref. [12,13,14,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38]).

4. Discussion

The current review highlights the evolving landscape of rTMS as a prophylactic intervention for migraine. Evaluation of therapeutic protocols, varying in stimulation frequency, cortical target regions and patient cohorts was conducted, attempting to assemble the conflicting data regarding rTMS effectiveness and identify the factors most likely to improve clinical outcomes.

A fundamental element leading to therapeutic improvement, highlighted in almost all the included studies, was the stimulation frequency. Particularly, studies using the application of HF-rTMS on M1 [13,19,20,21] and multifocal trials [32] have shown that stimulation frequencies between 8 Hz and 67 Hz result in a reduction in the intensity and frequency of headache, compared with sham.

In terms of physiology, HF-rTMS is assumed to be excitatory, inducing long-term potentiation (LTP)-like plasticity. Since migraine is typically described by cortical hyperexcitability and adaptation dysfunction, the utility of rTMS in migraine may seem bizarre. However, the effectiveness of HF-rTMS most probably derives from its capacity to rearrange disrupted networks and/or trigger descending inhibitory neural pathways of pain [39]. In contrast, Teepker et al. [33] used 1 Hz low-frequency-rTMS (LF-rTMS) to stimulate the vertex and demonstrated no significant efficacy compared with placebo. Subsequently, Hammad et al. [38] also evaluated LF-rTMS in 40 migraine patients and demonstrated significant reductions in headache frequency, intensity, duration, abortive medication use and MIDAS scores after 4 weeks of treatment, and a significant decrease in serum neurokinin A levels, suggesting a potential effect on neural inflammatory pathways. However, interpretation of these findings is limited, due to the absence of a sham-control group.

Modulation of interconnected cortical and subcortical pain networks plays a key role in the therapeutic effects of rTMS in migraine. Targeting M1 or DLPFC with HF-rTMS activates descending pain- control systems, through descending pain inhibitory and thalamocortical pathways [24,36,40]. Stimulation of the M1 may alter cortical excitability and modulate thalamocortical circuits involved in pain transmission [41]. Subsequently, these effects may influence sensory processing pathways, including the thalamus and other cortical regions involved in pain perception [24]. The mechanism that DLPFC may exert its effect is, also, by influencing the emotional regulation of pain through its functional connectivity with the PGC and glutamatergic/dopaminergic neurotransmission modulation, acting on frontal-limbic networks [40,42]. rTMS stimulation of vertex is thought to reduce cortical hyperexcitability [33]. The LF-rTMS stimulation of the visual cortex may reduce occipital hyperexcitability, modulate visual network connectivity and enhance GABAergic inhibition [35]. Multifocal stimulation mechanisms exert both peripheral and central neuromodulatory effects. These mechanisms include modulation of the trigeminovascular system and suppression of cortical spreading depression, with subsequent reduction of nociceptive input to the trigeminocervical complex and modulation of trigeminocervical pain processing, though trigeminothalamic pathway [32]. The main hypothetical pathophysiologic mechanisms of rTMS in migraine are summarized in Fig. 2.

The second key element regarding rTMS use was the cortical target region [10]. The majority of the included studies in our review examined predominantly two primary sites: the left DLPFC and the M1. Evidence from a studiy using TMS-EEG has indicated that HF-rTMS, applied to the left DLPFC, improved migraine symptoms by increasing network connectivity between frontal and temporal regions of the cerebral cortex [14]. This cortical target plays a central role in the cognitive assessment and the emotional regulation of pain. However, Granato et al. [29] have shown that HF-rTMS stimulation of the left DLPFC together with detoxification advice did not differ significantly from detoxification advice alone, in patients with chronic migraine and MOH. Consequently, this finding suggests that pharmacological interference may alter or even eliminate DLPFC stimulation efficacy. In contrast, Misra et al. [20] and subsequent trials comparing the M1 with the left DLPFC [34] have demonstrated that the motor cortex may act as an equivalent target. M1 stimulation is considered to modulate the trigeminovascular system by triggering in-

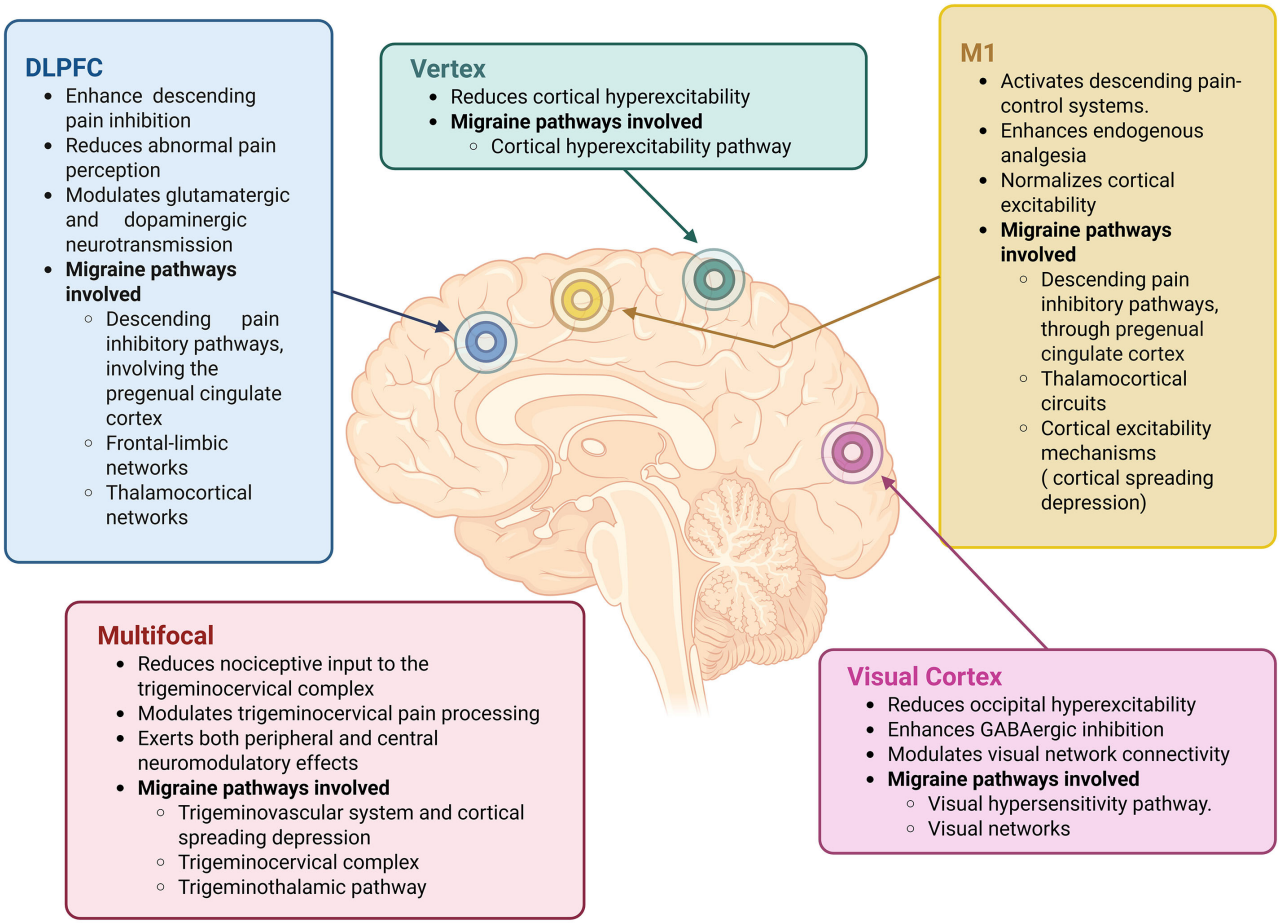

Fig. 2. The main hypothetical pathophysiological mechanisms of rTMS in migraine. Fig. 2 was prepared using the BioRender platform (under license to VS, Created in BioRender. Siokas, V. (2026), https://BioRender.com/uty8uwc).

direct pathways involving the thalamus and the brainstem. Interestingly, Todorov et al. [34] compared rTMS stimulation to M1 and left DLPFC, sham and topiramate treatment in patients with chronic migraine and observed no significant difference between the two rTMS target regions, as well as between the groups of patients treated with rTMS and the group treated with topiramate. Thus, rTMS can be classified as an effective alternative for patients who do not respond or tolerate oral medications.

The multifocal rTMS protocol consisting of high-frequency swipes and spot burst stimulation of 67 Hz outlines a new era of personalized and more methodical neuromodulation [32]. The responder rate of 42% observed in patients treated with multifocal rTMS for episodic migraine versus 26% in the sham group, measured in number of migraine days by Leahu et al. [32], is very encouraging. Therefore, multifocal protocols provide a more inclusive perspective of the pain network than single-point stimulation, by targeting a broader area on the cerebral cortex and thus, covering the spatial variability of the cortical dysfunction in migraine.

A repetitive pattern observed in rTMS literature is the placebo effect, which is commonly observed in device-based studies [29,43]. The rTMS sessions that involve repeated clinic visits, interaction with specialized equipment, and the audible click of the coil seem to increase therapeutic expectations. These contextual therapeutic factors, such as the repeated treatment sessions, may reinforce patients' adherence, engagement and expectations, potentially improving symptom perception and reducing drug intake. In this context, Granato et al. [29] demonstrated that both active and sham HF-rTMS groups exhibited clinical improvement in chronic migraine and MOH, indicating the potential influence of placebo effect on treatment. However, several studies exhibited better clinical outcomes with active stimulation than with sham conditions. Misra et al. [13] noticed that active high-frequency M1 stimulation led to greater reduction in headache frequency and intensity, while Leahu et al. [32] presented higher responder rates with multifocal active stimulation compared with sham. Therefore, despite the fact that contextual factors may augment the overall therapeutic benefit, the main scientific purpose should be the evaluation and optimization of active rTMS stimulation efficacy, through sham-controlled studies and standardized blinding procedures. There is accumulating evidence regarding the clinical applications of TMS-EEG [44]. The

integration of TMS-EEG in this review possibly provides a way to see into the migraineur's brain. The observation that migraine patients exhibit reduced left DLPFC connectivity at baseline and that clinical recovery correlates with the restoration of these networks is quite important. These findings support that migraine should increasingly be understood as a disorder of dysfunctional brain networks. They may explain why the clinical effects of rTMS often persist beyond the stimulation period. The therapeutic benefit of rTMS may derive from alterations in network connectivity and cortical plasticity, still the evidence remains preliminary and additional research is needed to validate this hypothesis.

Furthermore, the current shift from static rTMS protocols to personalized treatment was a significant achievement. RTMS targeting based on individualized functional connectivity instead of standardized anatomical target regions can significantly increase responder rates. Particularly, guiding rTMS stimulation through the functional connectivity between the DLPFC and the PGC seems to be a key approach to increase precision of pain processing network modulation [36].

Previous meta-analyses and systematic reviews have revealed that the DLPFC and the M1 are the most commonly used rTMS cortical target regions for migraine. However, their relative effectiveness may be influenced by patient characteristics and migraine subtype [45]. In vestibular migraine, for instance, a specific subtype of migraine with very limited effective prophylactic treatment options, rTMS has exhibited promising results [35]. Also, a recent systematic review by Zgarbura et al. [40], published after our predefined literature search cut-off, including exclusively randomized controlled trials evaluating the effects of rTMS versus sham stimulation in individuals with migraine, concluded that rTMS is a promising and well-tolerated neuromodulatory intervention for migraine management, in agreement with our findings. However, our review includes a broader synthesis of 24 studies containing multifocal stimulation paradigms, TMS-EEG findings, connectivity-guided approaches, and personalized neuromodulation strategies. Apart from summarizing the clinical outcomes of the included studies, our review also emphasizes the neurophysiological mechanisms underlying rTMS effectiveness and the evolving landscape of network-based stimulation models.

Future research in TMS should focus on closed-loop paradigms, which incorporate real-time EEG monitoring, in order to adapt stimulation parameters to dynamic individual brain states [46]. This approach is further supported by recent evidence reported by Clemente et al. [28], demonstrating that DLPFC-targeted iTBS in patients with chronic migraine refractory to anti-CGRP monoclonal antibodies resulted not only in clinical improvement, but also in normalization of electrophysiological markers and cognitive performance. These findings highlight the potential utility of neurophysiological endpoints as both therapeutic targets and also as real-time feedback signals in adaptive neuromodulation strategies.

Additionally, direct comparisons between rTMS and newer biologic therapies, such as anti-CGRP monoclonal antibodies, are needed to better define the role of neuromodulation within the current treatment algorithm. Importantly, the demonstrated efficacy of rTMS in patients who have failed CGRP-targeted therapies suggests that neuromodulation may represent a viable alternative or adjunctive strategy in migraine populations that are difficult to treat [28].

Despite the promising data, there are several limitations across the current body of research that should be acknowledged. Firstly, a significant challenge across many of the 24 studies, and particularly those by Misra et al. (2013) [13] and Granato et al. (2019) [29], is the presence of a robust placebo response. Achieving perfect blinding in rTMS randomized controlled trials remains a methodological challenge, since the specific cutaneous sensations produced by active stimulation cannot be exactly replicated by sham protocols. This phenomenon was also examined by the recent systematic review by Zgarbura et al. [40], with findings consistent with our review, regarding the potential efficacy of rTMS in migraine management. Nevertheless, despite its stricter methodological design of the aforementioned systematic review, similar limitations persisted, primarily methodological heterogeneity and small sample sizes. Secondly, studies investigating long-term results of rTMS are limited. The majority of the studies included in our review evaluated clinical outcomes only 4 to 12 weeks after rTMS application. A declining tendency in improvement noticed in some patients indicates that the "washout" period of changes in cortical plasticity has not yet been fully investigated. Therefore, a standardized protocol regarding the frequency and maintenance of rTMS use has not yet been released. Furthermore, another limitation is the patient cohort heterogenity of the included studies, considering chronic versus episodic migraine, and the variability in methodological parameters, including intensity, pulse count and inter-train intervals. Moreover, the small sample sizes from several pilot studies and the scarcity of adequately powered sham-controlled trials are considered to be significant constraints, restricting the ability to generalize the results and/or perform high-powered subgroup analyses and meta-analyses. Lastly, a formal risk of bias assessment using standardized tools, such as RoB 2 or ROBINS-I, was not performed in the present review. Consequently, variations in methodological quality, placebo responses, blinding procedures and sample sizes across studies should be taken into consideration, when interpreting the reported findings. Finally, the possibility that some eligible studies failed to be identified through our literature search cannot totally be excluded.

5. Conclusions

The present review suggests a potential benefit of HF-rTMS for migraine prophylaxis, with evidence supporting its safety, efficacy, and tolerability. The M1 and left DLPFC cortical regions are recognized as the most effective and commonly used anatomical targets, demonstrating improvement in terms of headache frequency, pain intensity and migraine-related disability. According to clinical studies, HF-rTMS may represent a promising, non-invasive option for migraine patients who are refractory or do not tolerate the conventional pharmacological prophylactic treatment. LF-rTMS protocols have also demonstrated potential therapeutic benefits, although additional sham-controlled studies are necessary to establish their efficacy. The widespread application of rTMS and its integration into routine clinical use requires further research with large sample-sizes, multi-center design and long-term evaluation periods. Furthermore, the incorporation of certain neuropsychological biomarkers, such as TMS-EEG or functional connectivity guided rTMS stimulation, may lead to a more personalized approach in neuromodulation, while possibly eliminating the placebo effect and maximizing the therapeutic benefit; however, additional research is also needed to establish their clinical utility.

Availability of Data and Materials

Not applicable.

Author Contributions

VS, conceptualization, supervision, writing—original draft preparation, writing—review and editing; CM, made the figures and tables, methodology, writing—original draft preparation, writing—review and editing; IL, made the figures and tables, methodology, writing—review and editing; MS, made the figures and tables, methodology, writing—original draft preparation, writing—review and editing; DT, methodology, writing—original draft preparation, writing—review and editing; SD, made the figures and tables, writing—review and editing; AT, made the figures and tables, methodology, writing—review and editing; PS, made the figures and tables, validation, writing—review and editing; ED, conceptualization, supervision, writing—original draft preparation, writing—review and editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

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