Review Article Brain Conflux

Neuromodulation and Electrophysiological Monitoring in Headache Management: Current Advances and Future Perspectives

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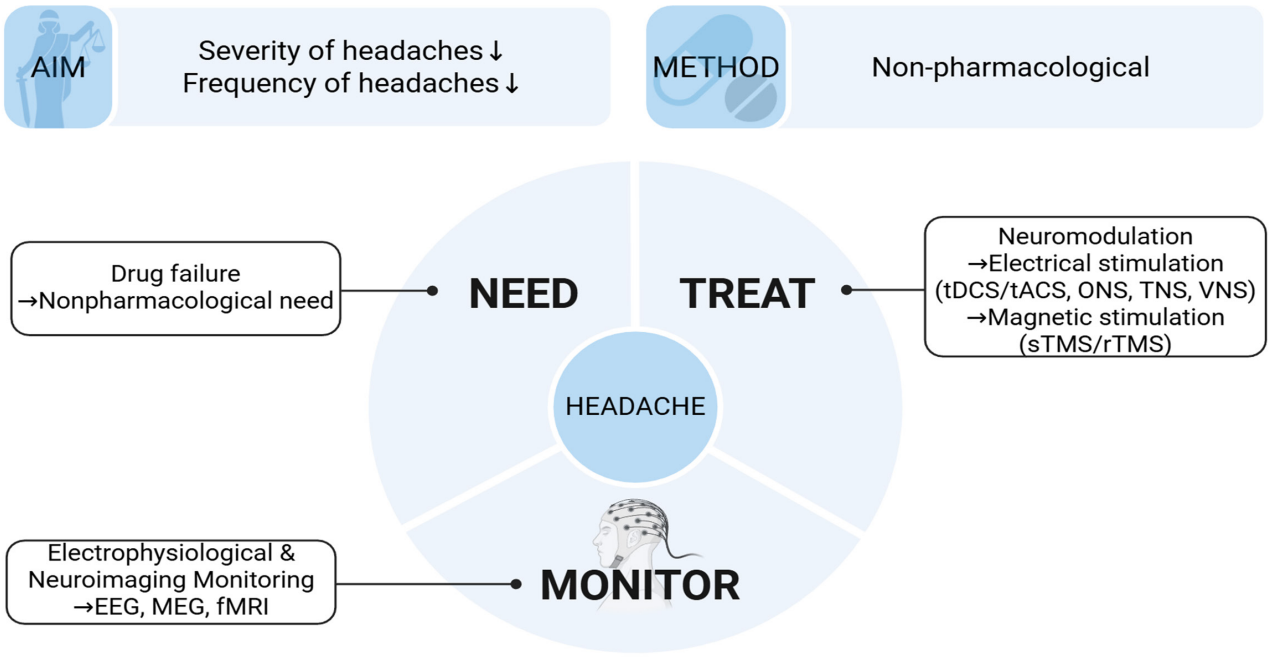
Graphical Abstract



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Review Article

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Neuromodulation and Electrophysiological Monitoring in Headache Management: Current Advances and Future Perspectives

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Abstract

Headache disorders such as migraine are major causes of disability worldwide. Pharmacological treatments are often insufficient, particularly in resistant or refractory cases. Neuromodulation techniques, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and peripheral approaches such as occipital nerve stimulation (ONS), trigeminal nerve stimulation (TNS), sphenopalatine ganglion (SPG) stimulation, and non-invasive vagus nerve stimulation (nVNS), offer promising alternatives. Electrophysiological methods including electroencephalography (EEG), magnetoencephalography (MEG), evoked potentials, and TMS combined with EEG (TMS-EEG) provide mechanistic insights and potential biomarkers for treatment monitoring and personalization. Here, we summarize emerging findings on neuromodulation and electrophysiological biomarkers in headache disorders, highlight their mechanistic underpinnings, and propose future directions for optimizing individualized treatment strategies. Key challenges remain, including small sample sizes, heterogeneous stimulation protocols, and limited long-term data. Future research should prioritize multicenter randomized controlled trial (RCT), closed-loop neuromodulation, and multimodal integration to advance precision headache medicine.

Keywords: headache; neuromodulation; electrophysiological monitoring; neuroimaging

Introduction

Headache disorders, particularly migraine and cluster headache, represent a leading cause of neurological disability worldwide, exerting profound impacts on patients' quality of life, workforce productivity, and healthcare systems [1]. Although pharmacological treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), triptans, and calcitonin gene-related peptide (CGRP) antagonists remain the mainstay of therapy, their effectiveness is often limited, and many patients struggle with inadequate response, side effects, or medication overuse [2].

A particularly challenging subgroup is composed of patients with resistant or refractory migraine, defined by inadequate response to at least three preventive drug classes (resistant) or to all available classes (refractory) [3]. These patients, often burdened by ≥8 monthly days of disabling headaches, are thought to suffer from complex pathophysiological mechanisms involving maladaptive synaptic plasticity, central sensitization, and altered hypothalamic–limbic connectivity [3]. For them, conventional pharmacological strategies are frequently unsatisfactory, creating an urgent need for effective non-pharmacological approaches.

Neuromodulation has emerged as a promising strategy in this context (Figure 1). By applying electrical or magnetic stimulation, neuromodulation techniques aim to regulate abnormal excitability and dysfunctional network activity in both central and peripheral nervous systems. Several non-invasive devices have already received Food and Drug Administration (FDA) approval for headache management, including single-pulse transcranial magnetic stimulation (sTMS), non-invasive vagus nerve stimulation (nVNS), and transcutaneous supraorbital stimulation (tSNS) [4]. Furthermore, electrophysiology not only provides mechanistic validation but also holds promise for developing biomarkers to monitor treatment response and guide individualized neuromodulation strategies [5-7]. The specific mechanisms of action and primary central or peripheral targets for these neuromodulation techniques are summarized in Table 1.

Transcranial magnetic stimulation

TMS is a non-invasive neuromodulation technique that induces cortical currents via magnetic fields [8]. TMS and repetitive

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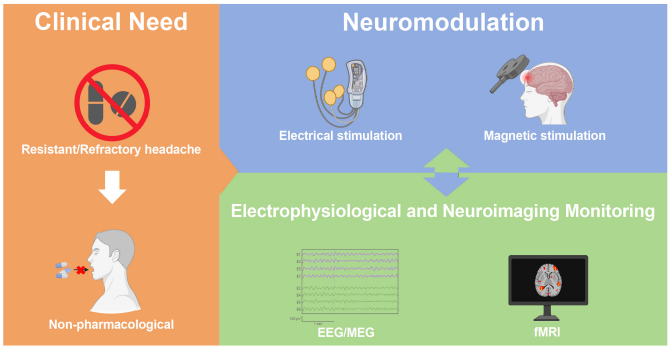
Figure 1. Conceptual framework of neuromodulation and electrophysiological monitoring in headache management.
Clinical need arises from resistant and refractory headache, where conventional pharmacological strategies often fail. Neuromodulation approaches, including electrical stimulation (e.g., transcranial direct current stimulation, vagus nerve stimulation, occipital nerve stimulation) and magnetic stimulation (e.g., single-pulse or repetitive transcranial magnetic stimulation), provide non-pharmacological treatment alternatives. Electrophysiological monitoring techniques, such as electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI), offer mechanistic insights and potential biomarkers to guide personalized interventions and facilitate closed-loop neuromodulation strategies.



firmed that sTMS provides significant acute relief in migraine attacks and prolongs pain-free intervals in a subset of patients [12].

rTMS has been more extensively studied as a preventive therapy. High-frequency stimulation (5–10 Hz) enhances cortical excitability, while low-frequency stimulation (1 Hz) reduces hyperexcitability. rTMS targeting the primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) has shown benefits in reducing headache frequency and severity in chronic migraine [13-14]. Additionally, rTMS has been explored in cluster headache, particularly in refractory cases, with promising though preliminary results [15].

TMS-electroencephalography (EEG) studies have revealed disrupted excitatory–inhibitory balance in migraineurs. Resting motor thresholds (RMT) and phosphene thresholds (PT) are often fluctuating, with migraine with aura patients typically showing increased cortical excitability [16-18]. Importantly, rTMS has been shown to normalize habituation deficits in visual and somatosensory evoked potentials, suggesting that it acts by modulating impaired synaptic plasticity [19].

At the network level, TMS likely exerts therapeutic effects through reshaping abnormal thalamo-cortical excitability [20]. This aligns with EEG/magnetoencephalography (MEG) findings of increased low-frequency (δ, θ) and reduced α oscillations in migraine, supporting the hypothesis that neuromodulation restores pathological oscillatory dynamics.

Electrical neuromodulation

Transcranial direct current stimulation (tDCS) applies weak direct currents (typically 1–2 mA) between scalp electrodes to modulate neuronal resting membrane potentials, thereby altering cortical excitability. Anodal stimulation induces depolarization and increases excitability, whereas cathodal stimulation induces hyperpolarization and decreases excitability. In migraine, tDCS has been applied to the DLPFC, M1, and occipital visual cortex [21]. Clinical trials have reported that anodal tDCS over the DLPFC alleviates pain sensitization [22], while cathodal tDCS over the occipital cortex may reduce visual aura and lower photic sensitivity thresholds [23]. Several randomized controlled trial (RCT) have shown reductions in attack frequency and medication use, supporting the preventive role of tDCS in chronic migraine [24]. Transcranial alternating current stimulation (tACS) delivers sinusoidal currents at specific frequencies, entraining endogenous brain oscillations and modulating frequency-specific activity. Although still in early stages of investigation, tACS shows preliminary efficacy in headache research. Preliminary findings suggest that tACS over the visual cortex has the potential to terminate migraine attacks [25].

Deep brain stimulation (DBS) represents an important, though highly specialized, neuromodulation option for patients with medication-refractory cluster headache. A growing body of case reports and small case series has demonstrated that stimulation of deep pain-modulating structures—most notably the posterior hypothalamus and, more recently, the ventral tegmental area—can achieve meaningful and sustained reductions in attack frequency and pain severity in a majority of treated patients. These findings highlight the pivotal role of hypothalamic–brainstem circuits in cluster headache pathophysiology. Although sample sizes remain limited and the

Table 1. Neuromodulation techniques in headache management.

Neuromodulation method	Mechanism of action	Primary targets
sTMS/rTMS	Modulates cortical excitability; suppresses CSD; reshapes thalamo-cortical network activity	Visual cortex, M1, DLPFC
tDCS	Alters resting membrane potentials; anodal increases excitability, cathodal decreases excitability	DLPFC, M1, occipital cortex
tACS	Entrainment of brain oscillations; phase alignment with endogenous rhythms	Visual cortex, thalamo-cortical circuits
ONS	Modulates nociceptive transmission in trigeminovascular system	Greater occipital nerve
TNS/t-SNS	Alters trigeminal nociceptive pathways; modulates brainstem excitability	Supraorbital and supratrochlear branches of trigeminal nerve
SPG stimulation	Modulates parasympathetic outflow and craniofacial autonomic reflexes	Sphenopalatine ganglion
VNS/nVNS	Influences parasympathetic pathways and brainstem networks; modulates pain and autonomic regulation	Vagus nerve

procedure carries inherent neurosurgical risks, DBS offers a potential therapeutic avenue for the small subset of individuals who fail to benefit from all available pharmacological and peripheral neuromodulation strategies. Ongoing refinements in targeting, imaging guidance, and device programming are expected to further optimize safety and long-term efficacy [26]. Electrophysiological monitoring (EEG, MEG, evoked potentials) provides insights into the mechanisms of tDCS/tACS. Studies indicate that tDCS can normalize habituation deficits in visual and somatosensory evoked potentials, pointing to its role in restoring aberrant synaptic plasticity [27]. Meanwhile, tACS achieves phase alignment with endogenous oscillations, modulating thalamo-cortical dynamics and laying the groundwork for closed-loop neuromodulation paradigms [28].

Despite promising evidence, current applications of tDCS/tACS are limited by heterogeneity in electrode placement, stimulation parameters, and outcome measures, resulting in inconsistent reproducibility. Small sample sizes and short follow-up periods further restrict guideline-level recommendations. Future research should focus on large-scale, multicenter RCT and on integrating electrophysiological biomarkers to optimize individualized stimulation protocols.

Peripheral stimulation

Occipital nerve stimulation (ONS) is one of the most extensively studied neuromodulation approaches. Initially designed for occipital neuralgia, ONS has since been investigated in chronic migraine and cluster headache. Multiple RCT demonstrated that ONS significantly reduces headache days and improves disability scores such as Migraine Disability Assessment (MIDAS) in chronic migraine [29-32].

External trigeminal/supraorbital nerve stimulation (t-SNS), exemplified by the Cefaly® device, has gained FDA approval for migraine prophylaxis. The trigeminal nerve carries sensory components for much of the head and innervates muscles in the lower jaw. It then divides into the ophthalmic (V1), maxillary (V2), and mandibular (V3) branches. The PREMICE multicenter RCT showed that t-SNS reduces migraine frequency with minimal adverse effects, mostly limited to transient paresthesia [33]. Compared with oral preventives, t-SNS offers a superior safety profile, making it suitable for patients intolerant or unwilling to use daily medications. The first RCT to show the effectiveness of non-invasive supraorbital and supratrochlear peripheral nerve stimulation (PNS) for migraines was completed by Schoenen et al. in 2013. In this study, 67 patients with at least two migraine attacks per month were randomized to either sham or stimulation with daily sessions of tSNS with Cefaly device. After 3 months of treatment, the stimulation group experienced a significant reduction in the average number of migraine days, with 38% achieving a >50% response. This study overall demonstrated a 26% therapeutic gain, which is within the range of those reported for other commonly used migraine treatments [34].

The sphenopalatine ganglion (SPG) plays a pivotal role in craniofacial autonomic pathways and cluster headache pathophysiology. Implantable SPG microstimulators, activated by patients during attacks, have demonstrated efficacy in aborting acute cluster headache episodes and in reducing attack frequency in long-term follow-up [35].

Both invasive and nVNS have been studied. Non-invasive VNS (nVNS, e.g., GammaCore®) has been FDA approved for cluster headache and migraine. RCTs confirmed its effectiveness in acute cluster headache treatment and in reducing headache frequency in some chronic migraine patients [36-39]. The PREVA trial demonstrated that adjunctive nVNS significantly reduced chronic cluster headache attacks (−5.9 vs. −2.1 per month) and achieved ≥50% pain reduction in 40% of patients versus 8.3% in controls [40]. In ACT1, nVNS was effective for acute episodic cluster headache but not chronic cases, with Goadsby et al. reporting similar European findings [37-38]. For migraine, the EVENT study found no significant preventive effect at 2 months, but extended open-label use showed reduced headache days [36]. The PRESTO trial confirmed that nVNS significantly improved acute migraine pain freedom between 30–120 minutes, provides clinically meaningful pain relief in selected endpoints comparable to pharmacologic treatments [39]. Overall, nVNS appears more effective in episodic cluster headache and acute migraine, while its preventive role in chronic migraine requires further validation.

ONS, trigeminal nerve stimulation (TNS), SPG, and VNS represent promising neuromodulatory strategies, particularly for resistant and refractory migraine patients (≥3 preventive drug failures). However, challenges remain, including heterogeneity in devices and stimulation parameters, limited sample sizes and follow-up duration, and barriers related to cost and accessibility. Future directions should emphasize large-scale RCTs, integration with electrophysiological biomarkers, and development of personalized stimulation protocols. A comprehensive overview of typical parameters, clinical outcomes, adverse events, and current evidence levels for these neuromodulation modalities is provided in Table 2.

Electrophysiological and neuroimaging monitoring in headache treatment

Headache—especially migraine—is marked by cyclical dysfunction of thalamo-cortical circuits and sensory processing [41]. Converging evidence from EEG/MEG/functional magnetic resonance imaging (fMRI) supports abnormal thalamo-cortical coupling and enhanced low-frequency oscillations even interictally, providing quantifiable targets and response markers for neuromodulation. According to Puledda et al., interictal migraineurs typically display reduced alpha and enhanced slow rhythms (theta/delta), predominantly in posterior regions, which tend to normalize as the attack approaches. Visual and somatosensory evoked potentials consistently demonstrate a deficit of habituation, with responses potentiating rather than decrementing across blocks; this abnormality often reverses during the ictal phase, pointing to dysfunction of synaptic plasticity mechanisms [19]. Gomez-Pilar et al. systematically reviewed 24 studies (EEG/MEG/fMRI) and highlighted medium-to-fast frequency bands, especially the beta band, as promising biomarkers to differentiate chronic migraine (CM) from episodic migraine (EM). EEG and MEG findings showed significantly higher high-beta power in CM, while MEG connectivity analyses revealed reduced beta-band node strength in anterior cingulate, insula, and somatosensory cortices in CM patients, linking beta-band dysfunction to migraine chronification [42].

TMS-EEG uncovers abnormal excitatory/inhibitory recruitment in migraine, particularly with aura. Findings include paradoxical responses to inhibitory rTMS/tDCS protocols, reflecting malfunctioning of short-term depression/long-term depression plasticity mechanisms [43]. Techniques like paired associative

stimulation (PAS) and short-latency afferent inhibition (SAI) confirm disrupted thalamo-cortical GABAergic and cholinergic control, which fluctuates across migraine phases, reinforcing the theory of migraine as a disorder of abnormal synaptic plasticity [44-46].

Differences between CM and EM are consistent across modalities (EEG, MEG, fMRI, PET), supporting electrophysiological monitoring as a candidate tool for biomarker-based subtyping, prognosis, and individualized treatment strategies. For instance, EEG/MEG studies reveal higher relative beta power and altered connectivity strength in CM compared to EM, while fMRI and PET findings point to disrupted pain-processing networks and metabolic abnormalities in the anterior cingulate, insula, and thalamus. This multimodal convergence underscores the robustness of electrophysiological alterations as state markers of migraine progression [42]. From a clinical standpoint, such biomarkers could aid in distinguishing patients at risk of chronification, guiding early escalation to preventive or neuromodulatory therapies. Machine-learning models integrating electrophysiological, neuroimaging, and clinical features have shown promise in predicting which patients are most likely to benefit from specific neuromodulation interventions. Such data-driven approaches may enable individualized treatment selection by identifying neural signatures associated with favorable therapeutic response. In addition, electrophysiological metrics—such as habituation deficits, beta-band oscillatory changes, and thalamo-cortical dysrhythmia—may complement clinical scales (e.g., MIDAS, HIT-6) to refine disease burden assessment and stratify patients for targeted interventions. These tools could also improve the identification of subgroups likely to benefit from specific neuromodulation approaches (e.g., TMS for cortical hyperexcitability, tACS for oscillatory entrainment). Importantly, electrophysiological monitoring may bridge the gap between phenotype and treatment personalization: CM and EM patients differ not only in headache frequency but also in their neurophysiological signatures, which may explain variability in therapeutic response. By integrating electrophysiological biomarkers into clinical trials and real-world monitoring, clinicians could move toward precision headache medicine, tailoring preventive strategies and neuromodulation parameters according to an individual's cortical and network-level profile.

Other neuromodulation approaches such as ultrasound neuromodulation and photobiomodulation have also been explored for headache treatment; however, evidence remains scarce. More robust clinical trials are needed to determine their therapeutic value.

Conclusion

Clinically, a considerable subset of patients—particularly those with resistant or refractory migraine—remain poorly responsive to conventional pharmacological strategies [3], highlighting an urgent need for neuromodulation as an alternative or adjunctive treatment. Closed-loop neuromodulation represents an emerging strategy in which stimulation parameters are continuously adapted based on real-time neural signals, allowing more precise engagement of pathophysiological circuits implicated in migraine. Compared with traditional open-loop paradigms, closed-loop systems have the potential to enhance therapeutic efficacy, reduce unnecessary stimulation, and minimize adverse effects. Integrating multimodal neuroimaging (e.g., fMRI, structural MRI, DTI) with electrophysiological measures (EEG/MEG) can further refine individualized therapy by identifying patient-specific biomarkers, mapping dysfunctional networks, and guiding stimulation timing and location. Such multimodal approaches could ultimately enable personalized, adaptive neuromodulation, improving long-term outcomes in patients with refractory or resistant migraine. At the same time, electrophysiological monitoring (EEG, MEG, evoked potentials, TMS-EEG) has provided unique insights into dynamic network alterations and abnormal synaptic plasticity mechanisms across the migraine cycle [19], while also emerging as a candidate biomarker for clinical subtyping and prognosis (chronic vs. episodic migraine) [41].

Challenges and Future Directions

Despite promising advances, the clinical application of neuromodulation and electrophysiological monitoring in headache medicine still faces significant challenges. First, limited trial design and small sample sizes remain a major barrier. Most

Table 2. Summary of neuromodulation modalities for migraine.

Modality	Typical Parameters	Treatment Duration	Primary Outcomes	Adverse Events	Evidence Level
TMS (s/rTMS)	1–10 Hz or single-pulse; intensity 80–120% RMT	Acute: single session; Preventive: 10–20 sessions over 2–4 weeks	Reduction in headache days, acute pain relief	Scalp discomfort, transient dizziness	Moderate
tDCS/tACS	tDCS: 1–2 mA; tACS: 10–40 Hz	20–30 min/day, 5–10 days or repeated cycles	Reduced headache frequency; modulation of cortical excitability	Mild tingling, erythema	Low–moderate
ONS	Implantable pulse generator; 60–90 Hz	Long-term chronic stimulation	Reduction in headache days in chronic migraine	Lead migration, infection, local pain	Moderate
TNS	60–120 Hz, 250 μs pulse width	Daily 20–60 min sessions	Reduced monthly migraine days; acute relief	Local paresthesia, skin irritation	High for prevention
SPG Stimulation	Implantable microstimulator	Acute, on-demand stimulation	Pain relief during attacks, reduced autonomic symptoms	Facial numbness, device discomfort	Moderate
VNS/nVNS	1–5 kHz burst stimulation	Acute: 2–3 cycles per attack; Preventive: multiple cycles/day	Reduced attack frequency and pain intensity	Hoarseness, neck tingling	Moderate

studies are single-center with short follow-up, contributing to heterogeneity in reported outcomes. For instance, RCTs of ONS in chronic migraine have yielded conflicting results, with some showing significant reductions in headache days, while others failed to demonstrate superiority over sham [47]. Similarly, in the EVENT trial of nVNS for migraine prevention, no short-term benefit was observed, with improvements only emerging in a longer open-label phase [35]. Second, heterogeneity in stimulation parameters and techniques hinders reproducibility. Studies vary considerably in target site, stimulation intensity, frequency, and treatment duration, especially for tDCS/tACS, where electrode placement and dosing paradigms differ widely. Device-specific variability and operator expertise further complicate cross-study comparisons. Third, unclear linkage between mechanisms and clinical efficacy poses another challenge. Although EEG/MEG and TMS-EEG studies consistently demonstrate abnormal synaptic plasticity and thalamo-cortical dysrhythmia in migraine, it remains uncertain whether these markers directly mediate therapeutic response, limiting their reliability as predictive biomarkers. However, neuromodulation remains a rapidly evolving field with significant potential to transform headache management.

Abbreviations

TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; tACS, ranscranial alternating current stimulation; ONS, occipital nerve stimulation; TNS, trigeminal nerve stimulation; SPG, sphenopalatine ganglion; nVNS, non-invasive vagus nerve stimulation; EEG, electroencephalography; MEG, magnetoencephalography; RCT, randomized controlled trial; NSAIDs, non-steroidal anti-inflammatory drugs; CGRP, calcitonin gene-related peptide; FDA, Food and Drug Administration; sTMS, single-pulse transcranial magnetic stimulation; nVNS, non-invasive vagus nerve stimulation; tSNS, transcutaneous supraorbital stimulation; rTMS, repetitive TMS; CSD, cortical spreading depression; DLPFC, dorsolateral prefrontal cortex; RMT, resting motor thresholds; PT, phosphene thresholds; DBS, deep brain stimulation; MIDAS, Migraine Disability Assessment ; PNS, peripheral nerve stimulation; fMRI, functional magnetic resonance imaging; CM, chronic migraine; EM, episodic migraine; PAS, paired associative stimulation; SAI, short-latency afferent inhibition.

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Author Contributions

DQ and WW conceptualized the review and supervised the project. QD, XL, WTL conducted the literature review and drafted the manuscript.

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Ethics Approval and Consent to Participate

Not applicable.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

Not Applicable.

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[1] Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. (2024). Lancet, 403(10440), 2133-2161. https://doi.org/10.1016/s0140-6736(24)00757-8

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