Review article

Primary headache disorders: From pathophysiology to neurostimulation therapies

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ABSTRACT

Primary headache disorders including migraine, cluster headache, and tension-type headache are among the most common disabling diseases worldwide. The unclear pathogenesis of primary headache disorders has led to high rates of misdiagnosis and limited available treatment options. In this review, we have summarized the pathophysiological factors for a better understanding of primary headache disorders. Advances in functional neuroimaging, genetics, neurophysiology have indicated that cortical hyperexcitability, regional brain dysfunction, central sensitization and neuroplasticity changes play vital roles in the development of primary headache disorders. Moreover, we have also discussed a series of neurostimulation approaches with their stimulation mechanism, safety and efficacy for prevention and treatment of primary headache disorders. Noninvasive or implantable neurostimulation techniques show great promise for treating refractory primary headache disorders.

1. Introduction

According to the third edition of the International Classification of Headache Disorders published in 2018, headaches can be divided into primary headaches, secondary headaches, neuropathies or facial pains, and other headaches [1]. Primary headache disorders are headaches that are caused by independent pathomechanisms and not by other underlying diseases of the body, whereas secondary headaches mostly develop as secondary symptoms due to some organic diseases or infections. Owing to their unclear cause and the severe and prolonged pain, primary headache disorders always develop into refractory headaches.

Primary headache disorders, which mainly include migraine, cluster headache (CH) and tension-type headache (TTH) are the leading causes of disability worldwide. In the Global Burden of Disease Survey 2019, headache disorders were in the top five causes of disability-adjusted life-years (DALYs) [2]. Data showed that the global prevalence of migraine was around 14.0% (males 8.6%, females 17.0%), and of TTH 26.0% (males 23.4%, females 27.1%) [3]. And these headaches especially migraine are always comorbid with depression, epilepsy, stroke and myocardial infarction, which cause disabilities, impairments of work and daily activities, and bring...
about a heavy and hitherto unrecognized socioeconomic burden. Also, clinical misdiagnosis is common for headache patients. TTH is overdiagnosed in the emergency department, and patients with migraine were more likely (13.8%) to have been diagnosed with TTH [4], which delay the treatments. A population-based door-to-door survey has shown only around 14% patients are correctly diagnosed, 33% are misdiagnosed, and 53% remain undiagnosed in China [5], which may be attributed to the unclear pathophysiology of primary headaches and the inadequate clinical diagnostic technology.

Advances in functional neuroimaging, neurophysiology and genetics have facilitated research on the pathophysiology and management of primary headache disorders. In this review, we have summarized some understanding of pathophysiology proposed to improve previous explanations, including vascular theory, trigeminovascular theory and neural theory. Moreover, neurostimulation techniques of primary headache disorders show better efficacy and tolerance compared with pharmacological treatments. But the potential utility and standard treatments of each type of neurostimulation have yet to be completely defined. One of the major obstacles is that the stimulation mechanisms of each neurostimulation technique is presented with limited research and evidence. In this review, we based on the knowledge of pathophysiological mechanism to summarize the development and look to the future of neurostimulation therapies for taking better care of headache patients.

2. Migraine

Migraine is a disabling disorder with headache attacks always lasting 4–72 h, of which the typical characteristics are unilateral location, pulsating quality, aggravation by routine physical activity, hypersensitivity to light and sound, nausea, and vomiting [6,7]. About one-third of migraine patients have undergone aura with fully reversible visual, language, sensory, or other central nervous system symptoms, such as scintillations, vertigo and tinnitus. The pain can occur at any part of the head, especially the posterior cervical and trapezius regions [8]. Moreover, chronic migraine usually persists for 15 or more days/month; consecutively for more than 3 months [9].

2.1. Cortical spreading depression

Cortical spreading depression (CSD) is a wave of excitation, followed by neuronal and glial depolarization with massive efflux of K\(^+\) and excessive glutamate neurotransmission, that propagates slowly (2–6 mm/min) across the brain surface [10]. In early 1941, Lashley found that the temporal propagations of CSD are similar to those of the spread of the migraine aura across the visual cortex [11], which suggested that CSD might be the cause of the visual aura associated with migraine. CSD has been extensively studied in animal models [12,13], and a variety of experimental methods can be used to evoke CSD, including local mechanical stimulation or brain injury, electrical stimulation, KCl and so on [13]. It shows that the spread of CSD maybe not dependent on neuronal action potentials because of dis inhibition of the sodium channel blocker tetrodotoxin [14], which suggests CSD seems to propagate via non-synaptic mechanisms with affecting adjacent neuronal dendrites or glia cells [15]. Actually, the definitive electrophysiological proof of CSD during migraine aura in humans is still lacking and factors that trigger the spontaneous occurrence of CSD in migraine are unclear. Genome wide association studies have identified that some genetic variations in familial hemiplegic migraine (FHM) cause excessive localized increases in K\(^+\) or glutamate to render the neurons of cerebral cortex prone to hyperexcitability [16,17].

2.2. Trigeminovascular system and neuroinflammation

Early studies have identified that vasculature plays a primary role in migraine, whereas several magnetic resonance angiography studies have shown that the dilation of intracranial or extracranial arteries is not necessarily correlated with spontaneous migraine [18,19]. Some studies have reported that acute and preventive migraine therapies that worked by constricting blood vessels or preventing vasodilation were ineffective. In 1979, Moskowitz introduced the trigeminovascular theory that trigeminal innervation of the meninges and its blood vessels and released neuropeptides play the key roles in migraine [20,21]. In rodents, CSD initiates with immediate or delayed activation of trigeminovascular neurons in the trigeminal ganglion and spinal trigeminal nucleus [22], similar to the activation patterns that aura phenomena typically precede headache in patients. This suggests that CSD might evoke head pain by activation of meningeal nociceptors at the origin of the trigeminovascular pathway [21], although in debate.

Neuropeptides released from activated trigeminocervical C-fibers, including substance P (SP), calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP) induce dural neurogenic inflammation to activate or sensitize of dural nociceptors [23]. Among those vasoactive peptides, CGRP shows the maximum efficacy in migraine pathophysiology with its concentration in plasma of jugular vein significantly increases during migraine attacks [24]. Based on this mechanism, CGRP antagonists targeting CGRP peptide or its receptor and triptans suppressing CGRP release from C-fibers are clinically effective [25].

Neuroinflammation as a potential target also catches migraine researchers’ attentions, especially its role in migraine chronicification. Neurogenic inflammation caused by released neuropeptides shows four main features: vasodilation, leukocyte infiltration, mast cell degranulation, and microglia activation with increased production of inflammatory mediators [26]. CGRP and SP can bind their receptors on smooth muscle of dural vessels and cause vasodilation. And both neuropeptides can induce mast cell degranulation through their specific receptors and further sensitize meningeal nociceptors [26,27]. In migraine with aura, imaging evidence suggested microglial and parameningeal inflammatory activity, while macrophage activation was not evident in migraine without aura [28]. Rodents studies have showed that CSD can lead parenchymal inflammatory response in dura about 20 min after a single CSD [29,30]. The parenchymal inflammatory cascade mediated by CSD contains some main proinflammatory elements between neurons, astrocytes and microglia, including pannexin 1 (Panx1) large-pore channels [31,32], inflammasomes [33], interleukin-1β (IL-1β) and high
mobility group box protein 1 (HMGB1) from neurons [33,34], nuclear translocation of the transcription factor nuclear factor-kappa B (NF-kB) in astrocytes [35,36].

2.3. Abnormal activation of brain regions

The findings of functional imaging studies, especially positron emission tomography (PET), have observed increase in regional cerebral blood flow in the rostral brainstem during migraine attacks, however the activation of brainstem still sustained even after sumatriptan treatments had relieved the nausea, phonophobia, and photophobia [37]. A study revealed that the locus coeruleus, raphe nucleus, and periaqueductal grey matter (PAG), are active during and after migraine, which may induce migraine headache. Normally, the brainstem nuclei inhibit trigeminal neurons; however, any nuclear abnormality in brainstem would allow the trigeminal neurons to fire and send pain signals to the sensory cortex [38,39]. It has been suggested that not only the midbrain and pons but also the hypothalamus is activated during migraine attacks [40]. A study on rodents supported the observation that the paraventricular hypothalamic nucleus directly controls the activities of the spinal trigeminal nucleus to modulate pain in migraine [41].

Brief frame of mechanisms of migraine with many factors was shown as Fig. 1. The exact processes involved in migraine occur as parallel and overlapping phenomena rather than a linear cascade of events [42].

3. Cluster headache

Cluster headache (CH) is a typical type of trigeminal autonomic cephalgia, which are relatively uncommon headaches with clinical features of unilateral and severe headache and prominent cranial autonomic symptoms that are ipsilateral to the head pain, such as conjunctival injection and lacrimation [6]. Based on remission periods, CH can be classified into episodic or chronic CH. Episodic CH attacks occur in periods lasting from 7 days to 1 year, whereas chronic CH attacks occur for 1 year or longer, with a remission period of less than 3 months. Usually, the pain of CH is maximal around or behind the eye, and it may spread to other regions such as the ipsilateral temple. During severe attacks, the intensity of pain is excruciating, termed as “suicide headache,” and patients are unable to be touched or even lie down. Therefore, CH patients often show restless, violent, and even self-hurting behaviors [43,44]. Moreover, the headache always shows circadian rhythm and the seasonal variation of cluster periods [45,46].

Based on the severe pain and the autonomic craniofacial phenomena, many studies have proved the activation of the trigeminal system and the craniofacial parasympathetic nerve in CH [43,47]. The striking rhythmic feature suggests the involvement of the hypothalamus, which modulates the biological clock, in these mechanisms; this speculation is supported by findings from neuroendocrinological and neuroimaging studies [48,49].

3.1. Trigeminal–parasympathetic system

During the CH attacks, the neurons of the gasserian ganglion release a large amount of messenger CGRPs as vasodilators and modulate the activity of nociceptive trigeminal neurons [50]. Pain signals are received from the cranial vessels and dura mater afferent
from the trigeminovascular system, and these synapses are in the trigeminocervical complex, including the trigeminal nucleus caudalis (TNC) and dorsal horns of C1 and C2. The projection leads to the thalamus and activates cortical areas, resulting in pain [51]. Many animal experiments have detailed the interactions between the trigeminocervical complex and the posterior hypothalamus. Moreover, the superior salivatory nucleus (SSN) is connected with the hypothalamus in the same manner as is the trigeminal nucleus. The SSN contains the cell bodies of facial parasympathetic nerve fibers, and it is functionally connected with the trigeminal nucleus in the brainstem. The activation of the first division of the trigeminal nerve induces the trigeminal–parasympathetic reflex [52,53]. The parasympathetic nerve fibers are divided into two parts: some nerves passing through the sphenopalatine ganglion (SPG) and some passing through the otic and carotid mini ganglia to mediate a series of autonomic phenomena such as lacrimation and rhinorrhea, conjunctival injection, and extracranial and intracranial vasodilation in CH [54]. Effective treatments such as electrical stimulation of SPG and chemical inhibition of onabotulinum toxin A in the SPG emphasize the relevant role of SPG in the cluster attacks [55,56].

3.2. Activation of hypothalamus

The endogenous circadian rhythm is mediated by the suprachiasmatic nuclei of the ventral hypothalamus, which control melatonin expression and secretion [57]. Neuroendocrinological studies have shown a blunted nocturnal peak in melatonin in patients with CH, which could account for the high frequency of CH occurring at night [58]. However, the related molecular mechanisms remain unclear because clinical trials with melatonin showed conflicting results [59]. A PET study showed a distinct activation in the inferior hypothalamic grey matter ipsilaterally with the pain [60]. Schulte and May suggested that the observed hypothalamic activation maybe not a consequence of the pain signals transmitted by trigeminal neurons but the trigger of CH and migraine [61]. Studies in animal models have reported that the posterior hypothalamus could modulate the neuronal activity of the TNC [62]. It is so remarkably complex pathogenesis of CH that hypothalamus seems to not be the single CH “generator”. Now advanced neuroimaging findings strongly suggest cortical-hypothalamic-brainstem functional interconnections and the involvement of diencephalic-mesencephalic structures could better explain and broaden the pathophysiology of CH [63,64]. Anatomical components in the pathogenesis of cluster headache were shown in Fig. 2.

4. Neurostimulation methods for treatment of primary headache disorders

Patients who fail to respond to a list of pharmacological treatment may benefit from alternative neurostimulation methods. There have been more than 20 years for neurostimulation therapies to be studied for the treatment of primary headache disorders. In the present study, we focus on the neurostimulation options for migraine and cluster headache. Based on the above knowledge that migraine or CH is a disorder of neuronal networks, neurostimulation methods intent to modulate different mechanisms in different neuroanatomical sites [65]. Neuromodulation treatments can be divided into noninvasive treatments and implantable neuro-modulation devices. The basic principle of neurmodulation is to participate in the modulation of neuronal structures directly or indirectly that transmit painful stimuli or signals in the brain. These treatments involve modulation of the brain regions where
Table 1
Some available studies on neurostimulation methods for primary headache disorders (year 2015 – 2022).

<table>
<thead>
<tr>
<th>Neurostimulation methods</th>
<th>Headache type</th>
<th>Study type (starting year)</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Primary outcome</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rTMS (theta burst stimulation)</strong></td>
<td>Migraine</td>
<td>Preliminary open-label (2015) [99]</td>
<td>9</td>
<td>1</td>
<td>Mean migraine days/month was reduced (8.6 ± 8.7 vs 2.9 ± 2.7)</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>rTMS</strong></td>
<td>Chronic migraine</td>
<td>Pilot randomized (2016) [100]</td>
<td>29</td>
<td>3</td>
<td>71.4% patients reported 75% reduction of both headache frequency and severity, but with less sustained effect after 12 wks</td>
<td>One patient had transient tinnitus on the day of session</td>
</tr>
<tr>
<td><strong>High frequency rTMS</strong></td>
<td>Chronic migraine/medication overuse headache</td>
<td>Single-centre prospective randomized double-blinded (2019) [101]</td>
<td>14</td>
<td>6</td>
<td>Mean number of headache days/month reduced by 45.5% and 40% in hf-rTMS and sham groups</td>
<td>Only 1 complained a mild discomfort in left hemiface during active stimulation</td>
</tr>
<tr>
<td><strong>rTMS</strong></td>
<td>Chronic migraine</td>
<td>An exploratory study (2021) [102]</td>
<td>20</td>
<td>1</td>
<td>The headache frequency/month of real rTMS group (17.4 ± 1.33 vs 10.2 ± 2.21) and sham rTMS group (17.6 ± 1.42 vs 18 ± 1.6)</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>tDCs</strong></td>
<td>Refractory chronic migraine</td>
<td>Pilot, double-blind, placebo-controlled, randomized (2017) [82]</td>
<td>13</td>
<td>1</td>
<td>Stimulation of the DLPFC exhibited greater improvements in headache impact, pain intensity, and quality of life compared with groups M1 and sham stimulation group</td>
<td>Group M1 reported more sleepiness, and itching or tingling on the scalp</td>
</tr>
<tr>
<td><strong>Cathodal tDCS</strong></td>
<td>Episodic or chronic migraine</td>
<td>Randomized, single-blind, and sham-controlled (2020) [81]</td>
<td>45</td>
<td>12</td>
<td>Reduction of migraine pain frequency, duration, and intensity in M1/S1 stimulation group</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>tDCs</strong></td>
<td>Chronic migraine with medication overuse</td>
<td>Double blind, randomized (2020) [103]</td>
<td>135</td>
<td>12</td>
<td>No differences between stimulation and sham group</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>tDCs</strong></td>
<td>Resistant chronic migraine</td>
<td>Randomised, patient-assessor blinded, sham-controlled (2022) [104]</td>
<td>36</td>
<td>36</td>
<td>The percentage of reduction from the end of first month (~21% ± 22 vs. ~2% ± 25) to the end of follow-up (3-month post-treatment) (~32% ± 33 vs. ~6% ± 39)</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>nVNS</strong></td>
<td>Chronic migraine</td>
<td>Prospective, multicenter, double-blind, sham-controlled pilot (2016) [105]</td>
<td>59</td>
<td>8</td>
<td>The mean change from baseline in headache days was ~7.9 after 8 months</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>nVNS</strong></td>
<td>Episodic migraine with/without aura</td>
<td>Multicenter, double-blind, randomized, sham-controlled (2018) [106]</td>
<td>248</td>
<td>–</td>
<td>Pain relief at 30/60/120 min after headache attacks</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>nVNS</strong></td>
<td>Episodic migraine</td>
<td>Multicentre, double-blind, randomised, sham-controlled (2019) [107]</td>
<td>341</td>
<td>9</td>
<td>Negative for number of headache days/month (4 weeks before treatment compared to weeks 9–12)</td>
<td>No significant ads reported</td>
</tr>
<tr>
<td><strong>ONS</strong></td>
<td>Chronic migraine</td>
<td>Randomized, double-blinded (2015) [108]</td>
<td>8</td>
<td>–</td>
<td>Mean VAS score was decreased from 8.20 ± 1.22 to 1.35 ± 0.84</td>
<td>No technical malfunctions or complications</td>
</tr>
<tr>
<td><strong>Burst ONS</strong></td>
<td>Chronic migraine and chronic cluster headache</td>
<td>Retrospective clinical case series (2019) [109]</td>
<td>17</td>
<td>–</td>
<td>Significant mean reduction of 10.2 headache days/month in CM, and reductions in headache frequency (92%) and intensity (42%) in CCH</td>
<td>Two patients required explantation due to infection</td>
</tr>
<tr>
<td><strong>ONS</strong></td>
<td>Intractable chronic cluster headache</td>
<td>Randomised, double-blind, multicentre, phase 3, electrical dose-controlled (2021) [89]</td>
<td>131</td>
<td>6</td>
<td>Half had a 50% or higher reduction in attack frequency and 16 (12%) of 130 had no attacks in the last 4 weeks</td>
<td>59 serious ads occurred in 46 participants, including dislocation or fracture of electrodes/leads, and a right-middle cerebral</td>
</tr>
</tbody>
</table>
transcranial magnetic stimulation; S1, primary sensory cortex; SPGS, sphenopalatine ganglion stimulation, tDCs, transcranial direct current stimulation. Rodents studies have shown that a single magnetic impulse is able to prevent neuronal firing in the visual cortex in a dose-dependent manner and suppressed CSD with increased electrical threshold, potentially depending on GABAergic circuits

Abbreviations: CM, chronic migraine; CCH, chronic cluster headache; DBS, deep brain stimulation; DLPFC, dorsal lateral prefrontal cortex; hf-rTMS, high frequency rTMS; M1, primary motor cortex; nVNS, non-invasive vagus nerve stimulation; ONS, occipital nerve stimulation; rTMS, repetitive transcranial magnetic stimulation; S1, primary sensory cortex; SPGS, sphenopalatine ganglion stimulation, tDCs, transcranial direct current stimulation; VAS, visual analogue scale; VTA, ventral tegmental area.

headache is triggered and produced (deep brain stimulation [DBS]), modulation of antinociceptive pathway (occipital nerve stimulation [ONS]), modulation of cortical excitability (transcranial magnetic stimulation, TMS, and transcranial electrical stimulation [tES]), and direct suppression at the level of peripheral neurons or spinal cord (transcutaneous electrical nerve stimulation [TENS]) [66,67] (see Table 1).

4.1. Magnetic stimulation

In 1985, the first scientific study on the application of magnet fields on headache was published [68]. The majority of 40 patients after magnetic stimulation reported an improvement of headache symptoms. Later, different methods applying pulsed magnetic field have been developed to treat migraine or other types of headaches, including single pulse transcranial magnetic stimulation (sTMS), the repetitive transcranial magnetic stimulation (rTMS) and peripheral nerve magnetic stimulation. The idea behind magnetic stimulation is a time-varying pulse of magnetic current in an external coil inducing perpendicular electrical current that flows tangentially to cortex generating action potentials in cortical neurons. Rodents studies have shown that a single magnetic impulse is able to prevent the CSD [69] and inhibited ventroposteromedial (VPM) thalamic spontaneous neuronal activity [70]. Recent experiments using calcium imaging and GCaMP-expressing mice showed that sTMS did not depolarize cortical neurons but it inhibited spontaneous neuronal firing in the visual cortex in a dose-dependent manner and suppressed CSD with increased electrical threshold, potentially depending on GABAergic circuits [71]. And it showed that sTMS significantly modulated spontaneous and C-fibre evoked
transcraniovascular activity recorded from third order thalamic neurons [70]. Single-pulse TMS has been approved by the FDA for acute and preventive treatment of migraine with aura.

Compared with sTMS, rTMS is believed to change and modulate cortical activity beyond the stimulation period, and the mechanisms may similar with the neuronal plasticity of long-term potentiation (LTP) and long-term depression (LTD). Low-frequency rTMS (<1 Hz) inhibits cortical excitability and increases cortical silent period duration and reduces motor-evoked potential amplitudes, while higher frequencies (>5–20 Hz) induce stimulation [72,73]. Nowadays, magnetic stimulation as a safe and painless non-invasive neurostimulation technique is regularly used for both an acute and preventive treatment for migraine, while it’s rarely applied on cluster headache. Notably, a few studies investigating rTMS for prevention of migraine had conflicting results, concluding that rTMS was not superior to sham stimulation for several measured outcomes. Different specifications in stimulation parameters (intensity, frequency, number and duration of stimulation sessions) and participant inclusion criteria might explain for these mixed results.

Another focus point may be the most efficacy cortical areas of stimulation for treatment of migraine, though the DLPFC and motor cortex have been more frequently employed in studies [74].

4.2. Electrical stimulation

Besides magnetic stimulation, the most major part of neurostimulation therapies is electrical stimulation. The analgesic effects of electrical nerve stimulation usually attribute to activation of descending antinociceptive projections controlling from the PAG and the rostroventromedial medulla (RVM) with a decrease in gamma-aminobutyric acid (GABA) levels [75]. We focus mainly on invasive and non-invasive electrical stimulation therapies in migraine and cluster headache, including transcranial direct current stimulation (tDCS), invasive occipital nerve stimulation (iONS), sphenopalatine ganglion stimulation (SPGS) and deep brain stimulation (DBS).

4.2.1. Transcranial direct current stimulation (tDCS)

tDCS applies battery-powered electrodes deliver a low-intensity direct current through the scalp with saline sponge or conductive gel. It suggests that tDCS modulates the synaptic GABAergic activity or NMDA receptor strength to alter neuronal polarization in the cerebral cortex, and tDCS can be either anodal (positive) stimulation to depolarize or cathodal (negative) stimulation to hyperpolarize [76]. An animal study in cats showed that anodal/cathodal tDCS stimulating visual cortex can respectively increase and decrease the amplitude of visually evoked field potentials for 60–70 min. And using the enzyme-linked immunosorbent assay method showed that tDCS can respectively suppress the expression of GABA- and glutamate-synthesizing enzymes [77].

Many clinical studies have applied tDCS on the stimulation of the visual cortex, which is a key area with altered hyperexcitability in migraine [78]. Also some tDCS studies chose DLPFC to stimulate based on its involvement in top-down pain modulating circuits [79]. It has been found that stimulation of DLPFC can modulate the activity of several cortical and subcortical areas, such as the caudate nucleus and the anterior cingulate cortex [80]. Besides, anodal M1 stimulation also has showed a reduction in headache frequency, intensity migraine, and acute medication consumption [81]. In a pilot randomized controlled trial, the therapeutic effect of M1 stimulation was weaker than tDCS on DLPFC in refractory chronic migraine [82]. There is no consensus on the superiority of one region over another and questions about how these pain networks act together still need to answer [83].

4.2.2. Invasive occipital nerve stimulation (iONS)

After failed to respond to available non-invasive neurostimulation, patients could think about trying invasive neurostimulation therapies. iONS is the most widely used electrical neurostimulation technique for chronic refractory headache disorders [84]. An stimulator device usually is surgically placed in the gluteal or prepectoral region, connecting the stimulating wire and electrode implanted subcutaneously in the occipital region to stimulate the greater and lesser occipital nerves [85]. Animal studies have shown that an anatomico-physiological convergence of cervical, somatic, and dural afferents on the second-order nociceptors in the trigemino-cervical complex, which might explain the background of ONS and greater occipital nerve blocks [86]. And continuous occipital nerve stimulation seemed to normalize the functional and metabolic changes in several brain regions that are responsible for pain processing [87]. Actually, understanding of ONS mechanisms in chronic headaches is limited, and researchers suggested that ONS might show a nonspecific neuro-modulatory effect on central pain control systems. Even, some speculate that the ONS stimulation has an effect on the peripheral pain transmission but not on the central modulating areas [88]. A recently published multicenter, phase 3, electrical dose-controlled trial indicated that both 100% ONS intensity and 30% ONS intensity significantly reduced attack frequency in medically intractable chronic cluster headache and were safe and well tolerated [89].

4.2.3. Sphenopalatine ganglion stimulation (SPGS)

Sphenopalatine ganglion is a large extracranial parasympathetic ganglion with autonomic, sensory, and motor afferents. We have described that the SPG plays an important role in the trigeminal–parasympathetic pain reflex of cluster headache. Exactly, the frequency of SPG stimulation exerts different effects on the modulation of pain pathways in cluster headache. Low frequency (5 Hz) SPG stimulation may activate the SPG, causing increased parasympathetic outflow and vasodilation and neurogenic inflammation, thereby resulting in cluster attacks in CH patients, while patients reported pain relief and cessation of autonomic symptoms within 10 min after high frequency (80–120 Hz) SPG stimulation [90,91]. High frequency SPG stimulation may activate parasympathetic neurons or post ganglionic parasympathetic nerve fibers well above the intrinsic firing rates, which may physiologically block parasympathetic outflow and result in an acute effect on head pain and autonomic symptoms [90,92].

A randomized, double-blind, parallel group study in 2019 as the only sham controlled study in SPGS showed an efficacy of sphenopalatine ganglion stimulation in the acute treatment of chronic cluster headache [93]. However, SPG stimulation is still a
relatively newer, expensive and invasive neurostimulation approach, therefore more high-quality multicenter randomized sham-controlled (RCTs) trials are needed to verify and improve the field of SPGS.

4.2.4. Deep brain stimulation (DBS)

DBS technique was developed following the finding of involvement of the posterior hypothalamus in cluster headache. It was hypothesized that high-frequency electrode stimulation reduced the activation of hypothalamus during the CH attacks. Further neuroimaging studies have shown that hypothalamic stimulation exerts its effect by modulating a complex pattern of activation in some areas (such as somatosensory cortex and precentral, ACC and the ipsilateral trigeminal nucleus and ganglion) and deactivation in other pain-processing areas distant from the hypothalamus [94]. Other possible mechanisms of DBS contain the modulation of the trigeminal parasympathetic reflex in cluster headache [95] and the stimulation of fibers interconnecting the hypothalamus and brainstem [96]. The relatively long latency (the cluster headache did not alleviate before months of management) suggests a more complex and central neuroplastic changes. Moreover, the anatomical targets for DBS stimulation of the ventral tegmental area (VTA) and other structures in the midbrain tegmentum also present significantly effective outcomes [95,97].

Despite the advancement and promising outcomes in DBS treatment, the potential serious adverse events including infections, intraventricular hemorrhage, seizures and severe micturition syncope still might occur. Overall, DBS can only be considered to operate on the most severe refractory headache patients. Nowadays, noninvasive deep brain stimulation via temporally interfering electric fields is rapidly deployable into animal neurophysiology experiments and human clinical trials. This noninvasive strategy is based on the property of neurons that neural electrical activity takes no response to high frequency (>1 kHz) oscillating electric fields and the physical principles that two high frequency electric fields, that differ by a small amount, can form a low-frequency envelope modulated electric field when they meet and might be possible to modulate deeper subcortical neurons [98]. With further improvement of higher precision and more flexibility in the future, the prospects for noninvasive deep brain stimulation are potentially exciting.

5. Conclusion and future directions

Migraine and cluster headache both have the tortuous clinical features and the complex multifactorial pathophysiological mechanisms. There are numerous evidences showing that the trigeminovascular system and neurogenic inflammation play important roles in the development process of migraine. However, the factors modulating susceptibility to attacks and the precise mechanisms triggering the initiation of attacks are still unclear. It is thought that CSD can activate the trigeminovascular system, but clinical studies remain to be conducted. Functional neuroimaging helps to find the abnormally activated brain regions and suggests a possible role of the hypothalamus in generating migraine and cluster attacks, though a more complex and central process including neuroplastic changes are needed to study.

Neuromodulation is an exciting and promising field in primary headache management, but the efficacy evaluation seems to be equivocal due to the limited number of randomized sham-controlled trials and substantial placebo-response rates. Noninvasive tDCS and TMS are relatively harmless and focus on modulating cortical excitability and connectivity. The theory of inhibition of a hyperexcitable visual cortex guides cathodal V1 stimulation in tDCs, meanwhile anodal M1 stimulation shows the concept of M1 excitation for reduction of pain perception. Now the noninvasive techniques have only been applied to acute and preventive treatment of migraine. Their current main challenge is still pursuing the optimal stimulation protocols and brain regions, both depending on the baseline pathophysiological hypothesis. ONS with around 70% efficacy in chronic refractory headache disorders could be the first therapeutic strategy compared with DBS. But the known nonspecific neuro-modulatory mechanism is unconvincing and deserves more fundamental researches. SPGS and DBS also show significant effects on CH patients by stimulating the target brain regions directly, but data suggested more complex pain-modulating networks and mechanisms out of the site of the stimulator tip. In consideration of the risk of serious side effects reported with implanted equipment, noninvasive deep brain stimulation is developed rapidly.

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Data availability statement

No data was used for the research described in the article.

Declaration of interest’s statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


