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Individual differences of maladaptive brain changes in migraine and their relationship with differential effectiveness of treatments

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Individual differences of maladaptive brain changes in migraine and their relationship with differential effectiveness of treatments

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ABSTRACT

Migraine is a difficult disorder to identify with regard to its pathophysiological mechanisms, and its treatment has been primarily difficult owing to interindividual differences. Substantial rates of nonresponsiveness to medications are common, making migraine treatment complicated. In this review, we systematically analyzed recent studies concerning neuroimaging findings regarding the neurophysiology of migraine. We linked the current imaging research with anecdotal evidence from interindividual factors such as duration and pain intensity of migraine, age, gender, hormonal interplay, and genetics. These factors suggested the use of nonpharmacological therapies such as transcranial magnetic stimulation, transcranial direct current stimulation, and placebo therapy for the treatment of migraine. Finally, we discussed how interindividual differences are related to such nondrug treatments.

1 Introduction

Migraine is a widespread, immobilizing disease that is characterized by recurring moderate-to-severe headaches and constitutes a significant healthcare or social setback because it considerably influences people’s quality of life [1]. Migraine occurs in approximately 12% of the general population [2] and has a higher prevalence in females [3]; in the United States alone, its estimated healthcare costs equal to approximately $1 billion [4]. Migraine is triggered by visual, olfactory, and auditory stimuli [5]. Such sensory hypersensitivities are present during and between migraine attacks, are definitely unique to migraine, and are not found in other headache or pain disorders. The suffering and debilitation caused by migraine are extensive, affecting every aspect of a migraineur’s life, and migraine is the fifth leading cause of emergency room visits in the United States.
States alone [6]. Nowadays, researchers have suggested that the development and maintenance of migraine may be owing to neurovascular abnormalities, and are related to the dysfunction of the central nervous system [7].

Although numerous pharmacological choices are available to treat migraine, none of them is ideal for most individuals. For example, acetaminophen [8] and nonsteroidal anti-inflammatory drugs (NSAIDs) [9] are the first line of efficacious treatment for migraine. NSAID-triptan combinations [10, 11], dihydroergotamine [12], nonopioid combination analgesics [13], and few antiemetics [14] provide additional evidence-based choices. Although opioid-containing combination analgesics can help a specific group of patients, they should not be utilized frequently because of risk of overuse and addiction issues [15]. The opioid crisis is of increasing importance both clinically and politically because two of three drug overdose deaths involve opioid use [16]. Opioids were initially prescribed for postsurgical and cancer-related pain conditions [17]. At the end of the 20th century, opioid prescriptions for treating all forms of pain became the standard care [17]. This significant increase in opioid prescriptions led to opioid use disorder, which now affects approximately 2 million individuals in the United States, and opioid-related deaths [18]. Although opioids are prescribed for managing various forms of pain, evidence of their long-term efficacy and safety is limited [17].

To alleviate the opioid crisis, practitioners are encouraged to consider nondrug options [19] for the treatment of migraine, especially in patients who encounter side effects or drug interactions, are treatment resistant, or have medical conditions wherein taking medications is contraindicated [20]. Nonpharmacological treatments include different types of nondrug modalities such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and placebo therapies, just to name a few, although more research is needed to confirm the results of these new treatment opportunities. TMS is a noninvasive and safe technique that has been utilized for over 30 years in many aspects of neuroscience and medicine to treat depression, movement disorders, and epilepsy, as well as for rehabilitation [21, 22]. This method works by applying a coil to the scalp that produces a fluctuating magnetic field, inducing an ionic current in the cortex. This approach alters the firing pattern and excitability of cortical neurons depending on the frequency [23]. TMS can be used both diagnostically and therapeutically to prevent and treat migraine [24]. In addition, tDCS can be an effective, noninvasive, and painless therapeutic modality for preventing and treating migraine [25, 26]. It is a neuromodulation technique, which is similar to repetitive TMS (rTMS) and causes reversible alterations in neuron excitability in cortical areas [27]. rTMS disrupts or enhances the firing of neurons, whereas tDCS modulates these firing rates by altering resting membrane potential [28]. Other techniques that are available include transcranial alternating current stimulation, transcranial near-infrared stimulation, functional electrical stimulation, transcutaneous electrical nerve stimulation, pulsed radio-frequency, peripheral nerve stimulation, and electroacupuncture [29]. Meanwhile, numerous placebo treatments for migraine offer safe and alternative outcomes [30, 31]. However, similar to the use of medication treatments, everyone will not respond the same way to nonpharmacological modalities.

Migraine can be divided into different subtypes such as migraine with aura, migraine without aura, migraine without head pain, hemiplegic migraine, retinal migraine, chronic migraine, vestibular migraine, and various headaches [32]. The classification of migraine into different subtypes is important because the pathophysiology,
mechanism, brain alterations, and treatment approaches are quite different in these cases [32]. Furthermore, current research suggests that the brains of migraineurs suffering from these subtypes are significantly different in terms of structure and function [33–36] owing to gender [37], age [38, 39], genetic [40] and psychological makeup [41], and causal variables, which make therapeutic assignment complicated and difficult. Apart from finding appropriate migraine medicaments, interindividual differences associated with the causal variables mentioned above make treating migraine complicated. For example, most migraineurs are females, whose specific migraine treatments involve hormonal interplay [39, 42], and even children are affected, thereby making medical care more challenging [38, 43]. Targeted therapy has numerous potential advantages, including decreased exposure of patients to medications that may be harmful or ineffective, and reduced financial burden spent on those remedies [44]. It is worth considering whether there exist subtypes of migraine that might benefit from targeted therapies based on the above causal factors [45].

Neuroimaging studies have revealed multiple structural and functional abnormalities in multiple cortical and subcortical brain regions in association with migraine [46–52]. Advanced magnetic resonance imaging (MRI) methods are helping to improve our knowledge about brain alterations in migraineurs. They can objectively measure neuroimaging findings (quantitative biomarkers) diagnostically and delineate therapeutic care pathways [53]. Functional MRI (fMRI) is a useful and noninvasive modality used to detect neural changes associated with increased blood flow when an area of the brain is being used either at rest or during a task [54]. It can linearly track within-person differences in migraine, providing novel insights into the brain activity linked to pain stimuli or other behaviors [36, 55–58]. Structural MRI uses strong magnetic fields, gradients, and radio waves to generate images of the brain, especially between gray matter (GM) and white matter (WM) volume that identifies brain structural alterations for many conditions of the central nervous system, including demyelinating diseases, dementia, cerebrovascular disease, infectious diseases, Alzheimer’s disease, epilepsy [59], and chronic pain [60]. Diffusion tensor imaging (DTI) is another MRI technique that measures restricted water diffusion in tissues to produce neural tract images, and numerous brain abnormalities can be detected by examining specific anisotropy and diffusivity measures. Its fiber orientation and strength estimation are very accurate, and it has widespread potential implications in the fields of cognitive neuroscience and neurobiology [61]. It also provides useful structural information for detecting changes in WM tracts in patients with chronic pain [62, 63]. These methods can be used together in pain studies because each has its unique strengths and practicalities. In this review, we summarize neuroimaging modalities and analyses associated with migraine and assess selective causal factors of interindividual differences among migraineurs, which would aid in categorizing them into alternative nondrug treatments.

2 Neuroimaging and migraine

Migraine is predominantly a brain function disorder. Many researchers have focused on analyses of functional connectivity to investigate specific brain region organization/functional networks in the pathophysiology of migraine, including neural activation patterns in response to painful or noxious stimuli [64–70], even in children [71]. However, it is not necessary that neurologically normal migraine patients be subjected to undergo neuroimaging methods [68]. Instead, neuroimaging methods are recommended
for migraineurs who have increased migraine frequency, severity, or altered clinical characteristics, migraine with confusion, hemiplegic migraine, and other serious conditions [68]. There are also obvious structural changes in GM that lead to migraine, especially in the cingulate, frontal lobes, and limbic areas [72, 73]. Positron emission tomography and single-photon emission computed tomography were utilized to examine the serotonergic system in migraineurs’ brains [74] and the underlying mechanisms of sensory hypersensitivity [75]. Since migraine attacks are extremely unpleasant, neuroimaging during an acute attack is rarely done. Thus, migraine imaging experiments are mainly conducted during the interictal phase [72].

When comparing migraine patients with healthy controls, there was abnormal connectivity among many brain regions involved in pain processing [52, 76, 77], sensory-discriminative pain processing (somatosensory cortex and posterior insula) [65, 78], affective emotional processing (anterior insula, anterior cingulate cortex, and amygdala), cognitive processing (hippocampus, parahippocampal gyrus, and orbitofrontal cortex), and pain modulation (periaqueductal gray area and nucleus cuneiformis) [76, 79–88]. One of the key theories from these investigations is that there appears to be an imbalance in pain signaling processing, leading to hypersensitivities as well as a lack of normal habituation in migraineurs; this is due to poor inhibition of pain signaling pathways [64, 89]. Chronic pain, as defined by Apkarian et al. in 2009, is “a state of continuous learning, which has a close connection with an unconditionally pain-related stimulus, without the opportunity to disrupt the association with continuous pain” [90]. This can be a chain of neural alterations from autonomic, sensory, and disgust pathways that create remnants of memory that alter the brain structurally, leading to the formation of long-term memory [91]. As migraine is characterized by recurrent moderate-to-severe headaches, functions of the brain may be constantly reorganized during long-term migraine, so that novel knowledge can be linked with functional connectivity patterns between brain regions. Other researchers have agreed that the generation of migraine is beyond a neurovascular model and involves a dysfunctional neurolimbic pain network [92].

Additionally, researchers have discovered alterations in resting-state functional connectivity of the dorsal pons, brainstem, and hypothalamus, as well as dopaminergic networks in migraineurs [72]. Nagesh et al. found that the red nucleus and substantia nigra were activated during migraine, possibly owing to nociceptive and autonomic dysfunction [93]. Several researchers imaged the brainstem to study the mechanisms of chronic migraine and found that the hypothalamus was important in regulating the pathophysiology during acute and chronic migraine [94–96]. Based on the above findings, May suggested that the pathophysiology and genesis of migraine attacks are probably not just the result of a single “brain stem generator” [97]. They pointed out that spontaneous oscillations of complex networks involving the hypothalamus, brainstem, and dopaminergic networks lead to changes in activity in certain subcortical and brainstem areas, thus changing susceptibility thresholds and not only starting but also terminating headache attacks [97].

Another important model proposed by Borsook et al. suggested that the insula plays a role in migraine and other chronic pain conditions because migraine is associated with a range of sensory, emotional, and cognitive symptoms [98]. The insula can thus act as a cortical hub that processes all this migraine input. Research has indicated that migraine changes the activation of
the insula and can even affect insular function with long-term attacks [98].

Alternately, migraine occurrence may be explained by a maladaptive feed-forward allostatic cascade model and how it might lead to alternative courses of treatment [1]. Although migraine is a recurring pain condition, it still utilizes global synchronization in various pain-processing functions, resulting in an abnormal transmission network [7, 99, 100]. Borsook et al. proposed an allostatic load model of migraine that explains how long-term and high-frequency migraine attacks change normal physiological stability and reinforce painful emotions [1]. They noted that although stress can precipitate migraine onset, it may lead to poor habituation [1] because emotions and migraine-related pain perception are closely associated [101]. In other words, when stress becomes more frequent or intense, the allostatic load, which pertains to use and abuse on all physiological systems involved in stress adaptation, becomes irregular and poorly adapted and completely changes the migraineurs’ neural networks. This then results in an unbreakable cycle of the brain’s poor response to repeated stress, causing behavioral and physiological changes that increase the allostatic load even more [1].

There are also limitations in fMRI research, including inadequate number of patients (limited statistical power and significance), poor timing intervals, and variability in methods and data analysis. Few replication studies have been conducted to confirm these results, and more research is needed to increase the confidence interval to establish the applicability of these findings. Overall, additional fMRI investigation is needed using whole-brain meta-analyses and heterogeneity in analysis methods [64]. More investigations should focus on neural regions and networks associated with migraine and their interactions with causal factors, especially during the ictal phase to further identify the specific mechanisms of migraine. Additional longitudinal studies must be conducted to better characterize the effects of attack frequency and to assess longitudinal changes in brain structure and function related to migraine.

3 Factors of individual differences

3.1 Duration and pain intensity

As migraine duration increased, the main theory was that the longer the headache attack lasted, the more remarkable the abnormalities of pain-related information processing in migraine, which may also mirror the properties of the clinical conditions impacting brain functional network organization. Liu et al. assessed the longitudinal GM and WM changes between repeated observations 1 year apart in a group of migraine patients and found that they had decreased GM in the dorsolateral part of the prefrontal cortex, orbitofrontal cortex, and primary/secondary somatosensory cortices at 1-year follow-up [102]. A cross-sectional study showed that subjects with a longer duration of migraine had differences in GM/WM density compared with those with a relatively shorter time, and the authors inferred that migraine may be associated with progressive functional and structural changes in the brain [103]. Understanding how the human brain is reorganized during chronic migraine and its relationship between GM/WM abnormalities can significantly improve treatment approaches.

3.2 Age

The brain has various response mechanisms in dealing with different stressors, which are age dependent [104]. Stressful stimuli that are encountered in early childhood may affect neural stress circuits, causing changes in neuroendocrine
phenotypes that become maladapted and result in susceptibility to disease, including migraine, and poor responses to treatment [105]. Migraines cause significant problems in children, which become more prominent after puberty [106]. Certain remedies can even affect cognitive and executive function in children [107] and may even modify allostatic load [1]. Chronic consequences of migraine on the developing brain are not completely understood, although early exposure to stressful stimuli can change the “trajectory of brain development”, especially in the frontal regions and the amygdala [105].

3.3 Gender and hormones

Migraine has a much higher incidence and prevalence in women than men, according to epidemiologic evidence for sex-related differences [108, 109]. It is affected by a lifetime of alterations in sex hormones ranging from puberty to pregnancy to menopause. Migraines are believed to be caused by decreased estrogen before menstruation known as the “estrogen withdrawal hypothesis” [110]. However, the effect of gender has often been avoided in the clinical management of migraine [111]. Surprisingly, most neuroimaging studies of migraineurs have been predominantly female subjects, while the male counterparts are understudied. There are structural alterations in the insula and precuneus in women who suffer from migraine [52] as compared to men whose changes appear in the parahippocampal gyrus [111]. Resting-state networks of functional connectivity have been reported to be abnormal in women during migraine [79]. Female migraine patients have increased connectivity between the default mode network, central executive network, and insula [85] due to possible sex-specific differences in connectivity strength. Understanding these gender differences may identify gender-specific pathways for furthering new and effective medical development as well as improving research results when controlling the menstrual cycle variables. We feel that genetic research may help in depicting how sex hormones affect migraine pathophysiology.

3.4 Genetics

Generational and twin research distinctly showed that migraine is a genetic disorder. There are many common migraine gene variants, which contribute to the subject’s disease susceptibility. Initially, studies identifying gene variants using linkage and association approaches by testing genetic markers had limited success due to lack of robustness (for review see [112]). One such linkage study identified a migraine susceptibility locus on chromosome 4q21–q24 [113]. Additionally, researchers have found other loci (4q28, 17p13, 18q12) showing linkage with specific migraine symptoms and traits (pulsing pain, light and sound sensitivities, exercise overexertion, age at onset, etc.) [114]. Their work revealed no gender difference for 4q24, but there was one for loci 17p13 and 18q12. Another migraine susceptibility locus was discovered on chromosome 10q22 [114]. Interestingly, the 10q22 locus could be a “predominantly female-dominated inheritance pattern” in linked Finnish families. There is more research focusing on sex chromosomes. For instance, migraine susceptibility loci were located on the X chromosome at Xq24–q28 [115], Xp21 [114] and Xp22 [116]. There are also many genetic association studies that identified DNA polymorphisms encoded in proteins from migraine-relevant pathways in the serotonin and dopamine systems [112]. One such study identified DNA variations in the serotonin 5-HT transporter gene that were associated with migraine in women [117]. Another study indicated there were gender differences between C677T and
migraine phenotypes [118]. Women with the TT genotype were significantly associated with unilateral migraine pain, and those with the CT genotype displayed nausea and osmophobia symptoms [118]. Catechol-O-methyltransferase (COMT) Val158Met polymorphism is another migraine-related trait that did not necessarily exhibit pain vulnerability to migraine [119], but interindividual differences in COMT activity influenced clinical responses to migraine medications [120]. COMT also affects hippocampal formation [121], which is involved in the pathophysiological process of migraine formation. It can be inferred that migraine and COMT Val158Met may interact with the hippocampus to create maladaptive stress in chronic pain conditions. Another study showed that there were interactions between COMT and structural volumetric morphology of migraineurs’ brains [40]. Although these genetic findings are interesting, few of them have been replicated and even fewer have been performed on each gender. Therefore, at this time, it is difficult to rely on these initial results and further investigation is needed.

4 Nonpharmacological treatments: TMS, tDCS, and placebo

Finding an effective and beneficial migraine cure is challenging by controlling predisposing factors such as drug overuse. Central neuromodulation methods include TMS [23–25, 122] and tDCS [123]. Repetitive TMS seems to be the most promising with a moderate amount of evidence contributing to decreased migraine frequency, duration, intensity, and impairment (for a comprehensive review on using TMS see [124]). One such study used high-frequency rTMS on the dorsolateral prefrontal cortex to treat chronic migraine attacks frequency [125], and low-frequency rTMS was no more effective in preventing migraine attacks [126]. TMS can also be used to stimulate the visual cortex to modulate phosphene thresholds in migraineurs [127]. Single-pulse TMS has only been utilized in episodic migraine, but without conclusive results [25].

Compared to TMS, tDCS has fewer side effects, is convenient and cheaper [128]. Anodal tDCS is the most commonly used mode stimulating the M1 area, and the cathode is placed on the opposite supraorbital area (1–2 mA current intensity for 15–20 minutes) [29]. Research has demonstrated that anodal stimulation of the dorsolateral prefrontal cortex, primary motor cortex, and visual cortex may help decrease pain in migraineurs [129–132]. Otherwise, sparse research using tDCS in migraine did not show that it had a significant effect on migraine frequency compared with placebo [123], according to findings by Auvichayapat et al. [133]. A couple of tDCS studies reported negative results in preventing migraine because the target brain area was not yet determined. One study used tDCS to stimulate the visual cortex, but there was no decrease in migraine attacks or difference between the two groups [123]. The other was a pilot study that also demonstrated no significant difference in the number of migraine attacks and the intensity and duration between sham stimulation and tDCS [26]. Overall, research using tDCS in migraine prevention and treatment are contradictory due to poor selection of optimal stimulation settings and brain areas.

Placebo analgesia is an effective therapeutic method for migraine by controlling pain perception [134]. The outcomes of placebo can create a treatment effect through certain expectations or cues [135, 136] that engage neural and cognitive processing [137]. Studies have shown that endogenous opiate and dopamine circuits are affected in placebo pain research [138, 139] and that individual differences in these systems may
be directly related to hypoalgesia [140]. Sham acupuncture and surgery demonstrated a greater decrease in migraine attacks than oral placebos [30]. One sham acupuncture pain study showed that psychological factors could decrease migraine frequency and that baseline GM medial prefrontal cortex volume could be used to predict future placebo responses in migraine patients [60]. Central brain stimulation and placebo methods have not been researched adequately to make treatment recommendations for chronic migraine and the results are highly variable. Some research has indicated that insular activation is caused by placebo although more imaging studies are required to show the insula’s role in placebo in migraineurs [98, 134, 141]. Their efficacy in treating migraine has yet to be investigated in large-scale, double-blinded, random controlled experiments.

There are many limitations of TMS, tDCS, and placebo therapeutics, especially with regard to bias, insufficient blinding, and small, nonhomogeneous sample size. The most common problem is dealing with the side effects of treatment. TMS can result in headache, migraine, sinusitis, and even has a rare incidence of seizures. The main concern with TMS is overheating of the brain with constant exposure, high intensity, and frequency [23]. The potential side effects of tDCS are not yet known [123]. As for placebo, the observed effects might be due to nonspecific causes, and the extent of these effects will be different, depending on the techniques used [30].

## 5 Individual differences and their relationship with migraine treatments

Recently, one depression study used fMRI to classify depression patients into four neurophysiological subtypes or “biotypes” [142] based on the neurophysiological differences in the connectivity patterns in their brains [143]. These biotypes were differentiated not only clinically but mostly on various clinical symptom descriptions, which would then predict whether TMS would be an effective treatment [142]. Other predictive biomarkers may be utilized to classify subjects depending on these biotypes, and valuable diagnosis can be achieved using guided therapy.

Since most migraineurs are not a homogeneous group, significant individual differences exist for particular cures. In this review, we searched PubMed for works with the keywords “treatment prediction and migraine” and found 48 related articles dating back to 2006. We select and summarize 14 pertinent studies which are specifically related to interindividual differences and treatment responses (Table 1).

According to a systematic review, migraineurs had a 0–56% response rate to placebo modalities [30]. Further evidence has shown that responses to placebo treatment were initiated by the central nervous system as well as through cognitive and mood pathways [137]. Thus, the variability in the treatment success of placebos may be linked with the variations of migraineurs’ brain structure and function. Recently, Liu et al. hypothesized that interindividual variability in the migraine brain could predict placebo hypoalgesia before commencing clinical therapy [41, 60, 147]. They reported that GM volume of the medical prefrontal cortex (mPFC) and its functional connectivity at baseline could predict placebo responses in an 8-week sham acupuncture treatment for migraine, and that patients who had abnormal GM volume of the amygdala were susceptible to persistent headaches and diminished response to placebo treatment [60]. Additionally, using DTI, they further reported that the interindividual variations of the WM tract microstructure of the mPFC-amygdala may be a predisposition for subsequent responses to placebo remedies in migraineurs [147]. Further investigations into the individual
differences of placebo analgesia and effects of other nonpharmacological intervention in chronic pain are warranted to potentially improve treatment strategies and also to be able to develop more efficient clinical trials.

Another significant study showed that personalizing medical care could be used to design a suitable migraine prevention program via psychophysical testing to characterize pronociceptive patients that would respond better to serotonin-norepinephrine reuptake inhibitors [146]. It was concluded that patients with increased pronociceptivity prior to treatment experienced more analgesic effects. Other studies relating to this had insignificant results because of poor experimental design [151, 154].

### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort (n)</th>
<th>Treatment</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barad et al.</td>
<td>402</td>
<td>Response to botulinum toxin A in a migraine cohort with multiple comorbidities</td>
<td>Developed a migraine prophylaxis therapy (PREEMPT) protocol to examine longitudinal treatment responses and assess predictors of treatment effectiveness</td>
</tr>
<tr>
<td>Bravo et al.</td>
<td>173</td>
<td>Botox treatment for migraine</td>
<td>Utilized data mining techniques to predict Botox treatment effectiveness based on different causal factors</td>
</tr>
<tr>
<td>Kisler et al.</td>
<td>55</td>
<td>Migraine treatment with duloxetine</td>
<td>Migraine patients with increased pronociceptivity before treatment experienced more analgesic effects</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>124</td>
<td>8-week sham acupuncture treatment for migraine</td>
<td>Interindividual variability of the white matter tract microstructure of the medial prefrontal cortex-amygdala may be a predisposition for subsequent responses to placebo treatment in migraineurs</td>
</tr>
<tr>
<td>Gago-Veiga et al.</td>
<td>34</td>
<td>Measured premonitory symptoms of migraine to assess the patients’ capability to predict these attacks and allow better response to therapy.</td>
<td>Few patients were reliable predictors based on interindividual differences, but the identification of premonitory symptoms was significantly accurate to make treatment more effective</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>71</td>
<td>8-week sham acupuncture treatment for migraine</td>
<td>Interindividual variability in the migraine brain could predict placebo hypoalgesia before commencing clinical treatment.</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>196</td>
<td>8-week sham acupuncture treatment for migraine</td>
<td>Patients who had abnormal GM volume of the amygdala had susceptibility to persistent migraine and diminished response to placebo treatment.</td>
</tr>
<tr>
<td>Lipton et al.</td>
<td>8233</td>
<td>Acute migraine medication</td>
<td>Predicted inadequate responses to acute migraine treatment using predictors related to sociodemographics, migraine features, comorbidities, and treatment profiles</td>
</tr>
<tr>
<td>Pagán et al.</td>
<td>2</td>
<td>Standard migraine treatments</td>
<td>Used hemodynamic measurements to predict and effectively treat migraine attacks.</td>
</tr>
<tr>
<td>Büchel et al.</td>
<td>Review</td>
<td>Placebo treatments for migraine</td>
<td>Responses to placebo treatment were initiated by the central nervous system as well as through cognitive and mood pathways.</td>
</tr>
<tr>
<td>Meissner et al.</td>
<td>Review</td>
<td>Placebo treatments for migraine</td>
<td>Sham acupuncture and surgery achieved a greater reduction in migraine frequency than oral drug placebos</td>
</tr>
<tr>
<td>Young et al.</td>
<td>22</td>
<td>Migraine treatment with duloxetine</td>
<td>No significant result</td>
</tr>
<tr>
<td>Ishii et al.</td>
<td>60</td>
<td>Migraine treatment with triptans</td>
<td>Analyzed gene polymorphisms, personality characteristics, and migraine traits to develop a scoring system for predicting treatment outcome. Migraineurs with lower scores had a lower risk for not responding to triptan treatment</td>
</tr>
<tr>
<td>Maas et al.</td>
<td>1288</td>
<td>Migraine treatment with triptans and placebo</td>
<td>No significant result</td>
</tr>
</tbody>
</table>
A study relating to nonresponders who received migraine treatment with triptans analyzed gene polymorphisms, personality characteristics, and migraine traits to develop a scoring system for predicting treatment outcome [152] as compared to previous studies by Maas et al. [153, 155]. Migraineurs with lower scores had a decreased risk for not responding to triptan medication [152]. This scoring system still needs a larger sample size to be considered valid. Furthermore, having the knowledge that certain migraine patients will respond better to preventive treatment can be useful in both clinical and research settings. Hence, future research on bigger cohorts may determine the ideal pain sensitivity levels for migraineurs.

One study developed a migraine prophylaxis therapy (PREEMPT) protocol to examine longitudinal treatment responses and assess predictors of effectiveness in patients with multiple overlapping pain disorders [144]. They assessed responses to botulinum toxin A. After 3 months of therapy, decreased migraine attacks appeared in 62% of the subjects. Similarly, another research group utilized data mining techniques to predict Botox effectiveness in migraineurs based on different causal factors [145]. They were able to utilize certain classifiers and clustering methods to predict decreased migraine attack frequency and treatment side effects with a relatively high accuracy. Gago-Veiga et al. were even able to measure premonitory symptoms (PSs) of migraine, which occur before migraine onset, and use them to assess the patients’ capability to predict these attacks and allow better response to therapy in 2018 [148]. However, very few patients were reliable predictors based on interindividual variability since there was no definite baseline characteristic, but the identification of PSs was significantly accurate to make treatment more effective [148].

Another important study predicted inadequate responses to acute migraine medications using predictors related to sociodemographics, migraine features, comorbidities, and treatment profiles of individual patients [149]. This retrospective study provided a limited understanding of the therapeutic outcome predictors related to specific medications and interindividual covariates. However, it was relevant in detecting the unmet needs in migraine subgroups experiencing inadequate responses to acute treatment [149].

A study has calculated individual differences of hemodynamic measurements such as heart rate, skin temperature, electrodermal activity, and peripheral capillary oxygen saturation, and associated these measurements with efficiency of clinical outcomes [150]. The models could predict the onset of migraine 52 minutes prior to the attack, so that treatment response would be more effective. This type of study is still in the exploratory stage and must be applied to a much larger cohort of migraine subjects as well as tested with different migraine causal factors.

6 Conclusions and future research

Migraine is a complicated disorder with various causal factors and interindividual differences that make treatment complicated. Specific brain structural variability at baseline could depict subjects with pain disorders that would respond to therapy. Future research is warranted regarding longitudinal studies on causal factors of migraine, new techniques used to treat migraineurs, and emphasis on the importance of considering interindividual differences when conducting research studies and treating migraine patients.

Conflict of interests

The authors declare that they have no conflict of interests.
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References


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