Altered processing of sensory stimuli in patients with migraine

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Abstract | Migraine is a cyclic disorder, in which functional and morphological brain changes fluctuate over time, culminating periodically in an attack. In the migrainous brain, temporal processing of external stimuli and sequential recruitment of neuronal networks are often dysfunctional. These changes reflect complex CNS dysfunction patterns. Assessment of multimodal evoked potentials and nociceptive reflex responses can reveal altered patterns of the brain's electrophysiological activity, thereby aiding our understanding of the pathophysiology of migraine. In this Review, we summarize the most important findings on temporal processing of evoked and reflex responses in migraine. Considering these data, we propose that thalamocortical dysrhythmia may be responsible for the altered synchronicity in migraine. To test this hypothesis in future research, electrophysiological recordings should be combined with neuroimaging studies so that the temporal patterns of sensory processing in patients with migraine can be correlated with the accompanying anatomical and functional changes.

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Introduction

Migraine is the most prevalent neurological disorder in the general population, with a cumulative lifetime incidence of 43% in women and 18% in men.[1] The episodic form of migraine is characterized by recurrent headache attacks, which are often accompanied by nausea, vomiting photophobia or phonophobia.[2] Some patients develop chronic migraine (at least 15 days of headache per month, including at least 8 days with typical migraine attacks).[2] In about 20% of patients, migraine attacks are preceded by or associated with an aura composed of transient focal neurological symptoms, such as scintillating scotomata (blurred areas in the visual field), paraesthesias or language disturbances. As interictal symptoms and overt brain lesions are absent, migraine is commonly considered to be a prototypic functional brain disorder.

The common migraine types, migraine with and without aura, are determined by complex interactions between multiple additive genetic, environmental, hormonal and endogenous (cognitive and emotional) factors.[3] These factors modify dynamic interactions between various brain areas and components that define the individual's level of susceptibility to migraine. The susceptibility level fluctuates and at times becomes sufficiently intense to precipitate a migraine attack. The neural components involved in susceptibility to migraine include the cerebral cortex, brainstem, hypothalamus and thalamus, as well as peripheral and central portions of the trigeminovascular system—the main pain-signalling system of the brain. The relative importance and exact sequence of activation of these structures during a migraine attack might vary with the migraine type, and remains a topic for extensive research.[3,4]

The temporal precision and noninvasiveness of electrophysiological methods make them particularly well-suited to study of the cyclic functional brain changes associated with migraine.[5] Investigators using these techniques have demonstrated that the migrainous brain has altered functioning between migraine attacks, and that this brain dysfunction undergoes cyclic changes up to initiation of the attack.[6] Various electrophysiological parameters have been studied in migraine research, including multimodal evoked potentials, steady-state visual evoked responses, noxious evoked cortical responses, and nociceptive reflexes. The results have provided three main sets of observations, which were consistent across most studies. First, between attacks, a stimulus-frequency-dependent increase occurs in photic driving and synchronization of EEG alpha (8–13 Hz) and beta (13–30 Hz) rhythms. Second, the interictal migrainous brain is characterized by a habituation (or adaptation) deficit of cortical evoked responses to repetitive, non-noxious sensory stimuli—this deficit normalizes during an attack. Third, responses or reflexes evoked by noxious stimuli also fail to habituate interictally, but this abnormality does not reverse during an attack. It should, however, be noted that not all studies confirmed these results.

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Key points

- Migraine is the most prevalent neurological disorder in the general population and exerts a considerable societal burden; in some patients, migraine becomes unremittingly chronic
- Electrophysiological studies can characterize the abnormal functioning of the migrainous brain between, immediately before and during attacks, and aid monitoring of the effects of therapeutic interventions
- Most electrophysiological studies of migraine describe functional changes between attacks, including hyperresponsivity to repeated sensory stimuli with abnormal temporal processing, malfunctioning sequential recruitment of neuronal networks, and impaired habituation
- The abnormalities of sensory processing vary over the migraine cycle: they worsen preictally but tend to disappear during the attack; furthermore, the abnormalities differ between episodic and chronic migraine
- Refined neurophysiological investigations suggest that the cyclic brain dysfunctions in migraine might be related to an abnormal cross-talk between thalamus and cortex (thalamocortical dysrhythmia)
- Understanding the dysfunction of temporal information processing in migraine paves the way for novel acute and preventive therapies, including pathophysiology-based neuromodulatory techniques

In this Review, we describe the data on alterations of neuronal processing in patients with migraine, affecting habituation, potentiation, summation, sequential dipolar source activation, and synchronization. We provide an overview of these neurophysiological studies and describe the novel methods used to explore functional brain connectivity in the migrainous brain. We pay particular attention to the temporal dimension of these abnormalities, which seems crucial to understanding the functional brain changes in migraine and their clinical correlates.

EEG changes induced by visual stimuli

Increased photic driving

Many studies have focused on steady-state visual evoked potentials (SSVEPs), which are the EEG response to repetitive visual stimulation. SSVEPs are not generated by amplitude modulation; instead, they primarily result from phase alignment of the ongoing background EEG activity[7] with the changes in frequency of the repetitive stimulus. This phenomenon, called photic driving, reflects the tendency of cortical neurons to synchronize their firing with the frequency of the visual stimuli.

Although normal brain activity is entrained by repetitive low-frequency (±10 Hz) light stimuli, increased photic driving has been described in response to medium-frequency (±20 Hz) light stimuli in patients with migraine, and is called the H response.[8] SSVEPs to flash stimuli in the medium-frequency range confirmed increased photic driving in individuals with migraine, without any relation to migraine severity or duration.[9,10] This observation was interpreted as hyper-responsivity of the brain to visual stimuli. Further analysis showed that in patients with migraine, SSVEP amplitude was less stable over time than in controls.[11] Fluctuation of increased photic drive over the migraine cycle has also been reported.[10,12] This instability, changes over the migraine cycle, and methodological differences probably explain some of the contradictory results reported in the literature.[12]

Another interesting aspect of visually induced changes in EEG recordings is that they might differ between migraine types. Some SSVEP studies found no differences between migraine with and without aura,[13] but one study showed that interhemispheric SSVEP asymmetry was increased in about half of patients affected by migraine with aura, whereas in those with migraine without aura, the amplitude of the second harmonic was increased.[14] Another group found an increased amplitude of the second harmonic in both migraine groups, but an augmented amplitude of the fourth harmonic at high spatial frequency only in patients who had migraine with aura.[15] The investigators interpreted their results as reflecting increased responsivity of the primary visual cortex in both types of migraine, albeit with extension of this increased responsivity to include secondary visual areas in migraine with aura. This hypothesis is being further tested in studies of EEG mapping during intermittent visual stimulation, as described below.

Increased synchronization

The role of neuronal networks in determining responsivity of the brain to visual stimulation can be assessed comprehensively by studying the synchronization and causal connections of different brain areas using nonlinear analysis methods. In healthy individuals, the oscillatory activity in the alpha range is suppressed during flicker stimulation, possibly as a result of desynchronization.[16] By contrast, in patients who have migraine without aura, the alpha rhythm remains highly synchronized across different brain areas during visual stimulation.[17] This pattern does not depend on the alpha amplitude, but pertains to the synchrony of temporal activation and dynamic interactions (such as functional connectivity) between brain areas,[18] and to their modification by sensory stimuli. Some researchers have suggested that functional connectivity is determined by both corticocortical and thalamocortical loops.[19] The mechanisms underlying temporal synchrony of EEG rhythms are not simply a result of the balance between excitatory and inhibitory inputs. Anticonvulsants, for instance, modulate alpha rhythm synchronization differentially: topiramate, an established migraine-preventing drug, has no effect on alpha oscillations, whereas levetiracetam, which might also be effective in migraine prevention, reduces alpha synchronization.[20] Low-frequency repetitive transcranial magnetic stimulation (rTMS), which has been studied as a preventive treatment in migraine and is thought to inhibit the underlying occipital cortex, has no effect on alpha phase synchronization.[21]

Oscillatory properties of neuronal networks can be accurately assessed by measuring the directed flow of information between their components, using Granger causality[22,23] or dynamic causal modelling,[24] both of which measure effective connectivity. Granger causality detects connectivity only in linear data; however, a modified version, kernel Granger causality,[23]can be used to infer direct dynamic influences from nonlinear signals such as EEG data. In a preliminary study, individuals who had migraine without aura showed

increased phase synchronization in the alpha band and reduced connectivity during intermittent flash stimulation, whereas those who had migraine with aura displayed clear desynchronization in the beta frequency range and increased connectivity during visual stimulation (Figure 1).[25] Given that brain activation is now described in terms of increased connectivity of different functional brain networks, visual stimulation seems to induce a more vigorous cortical activation and spread of information in migraine with aura than in migraine without aura (which is characterized by weak interaction between cortical regions), possibly because of a prevalent resonance of rhythmic activity generated at subcortical and thalamic levels.[22]

Evoked responses to non-noxious stimuli

Impaired habituation

Habituation—a response decrement as a result of repeated stimulation[26]—is a multifactorial process. The properties and characteristics of habituation[27] have been revised and refined,[28] but the underlying neural mechanisms are still not completely understood. Habituation has multiple roles, ranging from pruning of irrelevant information to protection of the cerebral cortex against overstimulation. This phenomenon has been studied to disentangle the neuronal substrates of behaviour, learning processes, and processing of CNS information in health and disease.[29–32]

The majority of interictal evoked potential studies in patients with migraine support the notion that the migrainous brain is characterized by impaired habituation to repetitive stimuli. The habituation deficit is observed across several sensory modalities, and is usually accompanied by a normal to low amplitude of early responses in averaged data. Lack of habituation is the most prominent (and probably genetically determined) consequence of the functional brain abnormality that characterizes many migraine patients between attacks.[33] Of note, the abnormal visual information processing that occurs in migraine between attacks corresponds neither to sensitization nor to dishabituation (that is, restoration to the full strength of a response previously weakened by habituation). It is accompanied by initially decreased or normal amplitude of response after a small number of stimuli, followed by a stable amplitude, or even a transient amplitude increase (potentiation).[34–43]

The first evidence for altered interictal habituation in patients with migraine came from studies of contingent negative variation (CNV), a slow event-related cortical response representing higher mental functions.[44–47] Subsequently, deficient habituation was demonstrated for another event-related potential, P300, which is elicited in the process of decision-making after visual[48] or auditory[49,50] stimulation. Deficient habituation was also subsequently described for several other modality-specific evoked potentials: pattern-reversal visual evoked potentials (VEPs),[33–42] visual evoked magnetoencephalographic (MEG) responses,[43] auditory evoked potentials (AEPs),[51,52] and somatosensory evoked potentials (SSEPs).[53–55] Several other studies, however, were

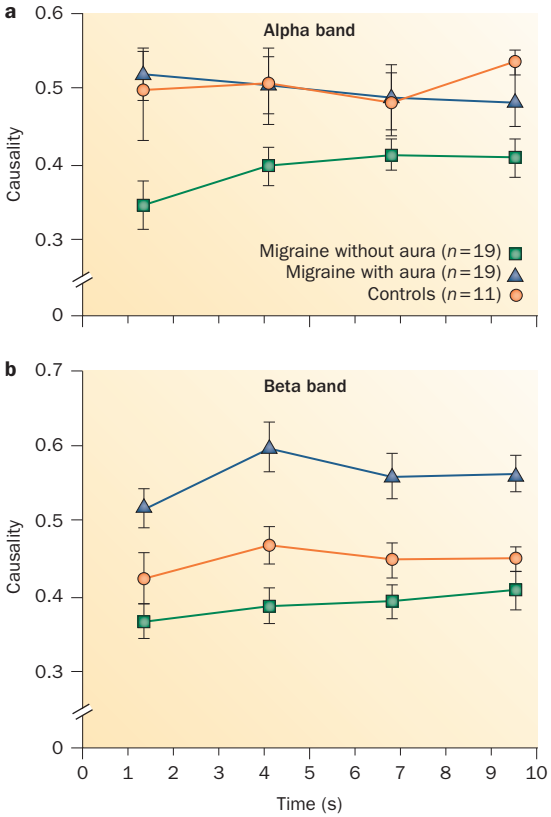


Figure 1 | Temporal evolution in effective connectivity, as revealed by kernel Granger causality analysis of averaged EEG data. Recordings were taken from patients with migraine and healthy controls during a 10 s flash stimulation at a 21 Hz frequency. **a** | In the alpha band, causal/effective connections across scalp derivations are weaker in individuals with migraine without aura than in those with migraine with aura or individuals with no migraine (healthy controls). **b** | By contrast, individuals with migraine with aura have increased causality across cortical areas in the beta band. This phenomenon might be subtended by increased cortical activation in migraine with aura during visual stimulation. The figure is based on data from a study by de Tommaso *et al.*[25]

not able to reproduce these results and found no habituation deficit in individuals with migraine, possibly because of differences in the methods used or selection of patients.[56–62]

The reasons for the discrepant results of habituation studies are not fully understood. Insufficient blinding of the investigator has been suggested as a possible culprit;[63] however, since the same researchers have found the same result (that is, normal habituation) in individuals with migraine in both blinded and nonblinded studies,[57] and lack of habituation has also been reported in a blinded study, this factor is unlikely to be the sole cause.[64] Factors directly related to the pathophysiology of migraine are probably involved. For instance, the habituation deficit does not remain constant in individuals with migraine. The deficit varies over the migraine cycle: it is profound during the interictal state, normalizes briefly before and during the attack and increases again a few days after the attack.[65] Moreover, genetic variants can have an

effect on habituation profiles.[66,67] Finally, spontaneous clinical worsening or improvement of attack frequency can influence the baseline level of thalamocortical activation[68,69] and, hence, the degree of habituation in patients with migraine.[55]

Variation over the migraine cycle

Episodic migraine

Episodic migraine is, by definition, a cyclic disorder. The attack itself is not an abrupt event, but the result of a sequential process that might start as the so-called prodromal or premonitory symptoms several hours before the aura or the headache. Moreover, attack frequency varies over the patient's lifetime. It is, therefore, of major pathophysiological interest to study the changes in brain responsivity associated with various stages of the migraine cycle. During the days preceding an attack, CNV and P300 habituation is minimal, and the amplitude of these responses is maximal.[70,71] Within the 12–24 h immediately preceding an attack, and during the attack, habituation of evoked potentials normalizes. This pattern has been shown for CNV,[36,70,71] VEP,[57,72] and SSEP[61] amplitudes, and for visual P300 latency.[73] The R2 component recorded during blink reflexes—evoked by an electrical stimulus delivered with a classic non-nociceptive surface electrode—showed a habituation deficit in patients before a migraine attack,[76] although in another study only slight habituation abnormalities were found interictally.[77] In a longitudinal study of brainstem AEPs, habituation of wave IV–V amplitude was deficient in patients with migraine, but did not change over the migraine cycle.[78]

To our knowledge, no single satisfactory explanation exists for the cyclic nature of episodic migraine, except for the one related to the ovarian cycle and variations in sex hormone levels. Nonetheless, various experimental data suggest some interesting avenues for further research. For instance, cortical responsivity is cyclic in individuals with migraine,[71] and varies in parallel with changes in platelet serotonin content.[73] The periodicity of neurophysiological brain activity might also be related to psychophysical, genetic[66,79] or metabolic factors,[80] or to the biorhythms of hypothalamic activity.[81] Migraine periodicity might thus be the result of several interacting biological cycles. Indeed, the migraine cycle is probably caused not by a single determining factor, but by a complex interplay between intrinsic cerebral, hormonal and environmental factors acting on a genetically predisposed nervous system. Disentanglement of this interplay is a challenge for future research, and will be a prerequisite for the development of effective novel therapies.

Chronic migraine

Cortical responsivity is different in episodic and chronic migraine. For instance, the initial amplitude of visual MEG responses (P100m) was greater in chronic migraine than in interictal episodic migraine.[82] Moreover, these responses show substantial habituation (comparable to that of healthy controls) to repetitive stimuli,[82] which contrasts with the interictal habituation deficit observed in episodic migraine. Interestingly, the habituation deficit reappears when patients evolve from chronic to episodic migraine.[83] Since the response pattern in chronic migraine is indistinguishable from that observed during migraine attacks,[43,51–62,70–72] our research group has suggested that patients with chronic migraine are locked in an ictal-like state.[84]

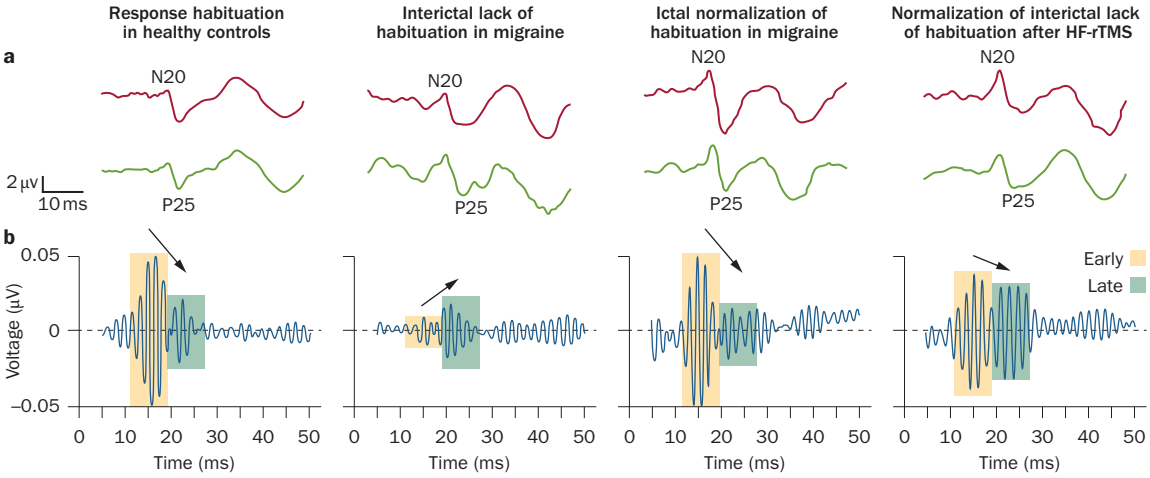
The most prevalent factor associated with the transition from episodic to chronic migraine is acute medication overuse. In medication overuse headache (MOH), the cortical response pattern suggests that the brain is locked in a preictal state, characterized by an increased amplitude of responses to intermittent stimuli (sensitization) and a consistent deficit of habituation to continuous or repetitive stimuli.[54] This pattern might vary with the class of drug overused. In triptan overusers, the initial SSEP amplitude is normal, whereas it is increased in overusers of NSAIDs and in those overusing drugs from both classes.[54,85] In both groups of overusers, however, SSEP habituation was abnormal.

Possible mechanisms of habituation

Genetic predisposition is likely to influence the brain's responsivity patterns, although its effects are variable between patients and migraine types. In migrainous child–parent pairs, habituation of evoked potentials has a clear familial pattern.[66,71] Moreover, in asymptomatic individuals who have a first-degree relative with migraine, and are thus at risk of developing migraine during their lifetime, cortical evoked potentials[79] and nociceptive blink reflexes[86] (nBRs, discussed under processing of noxious stimuli below) showed amplitude and habituation abnormalities similar to those found interictally in people with migraine.

The neural mechanisms underlying habituation and its impairment in patients with migraine remain poorly understood.[87] In theory, habituation deficits could be due to increased excitatory mechanisms, decreased activity of inhibitory interneurons, or reduced baseline activation of sensory cortices according to the 'ceiling' theory. This theory postulates that an individual's sensory cortices have variable baseline activation levels, but their maximum activation level (the ceiling) remains constant. During repetitive stimulation, the maximum activation level is reached rapidly, and subsequently the response amplitude decreases sharply (habituation) in individuals with normal baseline activation, while habituation is delayed or absent in individuals in whom baseline activation is low.[88] Both increased cortical excitability and decreased activity of inhibitory neurons would be expected to give rise to a high initial response amplitude, indicating genuine hyperexcitability, and a linear decrease on habituation. The ceiling theory can also account for the normal or decreased initial amplitude and the nonlinear and cyclic changes in habituation.

Studies of high-frequency oscillations (HFOs) embedded in evoked cortical responses have contributed to our understanding of the abnormal information processing in migraine. The amplitude of early HFOs embedded in



Thalamocortical drive	Intact	Decreased	Increased	Increased
Cortical activation	Intact	Not affected	Not affected	Increased

Figure 2 | Cortical response patterns during the migraine cycle. This schematic overview shows amplitude changes in the N20–P25 component of averaged EEG recordings in patients with migraine and healthy controls. **a** | HFOs and **b** | somatosensory evoked potentials. In healthy controls (panel 1), the N20–P25 component habituates, and early HFOs (reflecting thalamocortical drive) are greater than late HFOs (generated by intrinsic cortical activation). In patients with migraine between attacks (panel 2), habituation is absent and early HFOs are reduced, although late HFOs are normal. During a migraine attack (panel 3), habituation and early HFOs normalize. After 10 Hz HF-rTMS is applied over the somatosensory cortex in patients with episodic migraine (panel 4), the interictal lack of habituation reverses, and both early and late HFOs increase. Abbreviations: HFO, high-frequency oscillation; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation.

the common SSEPs, which is thought to reflect spiking activity in thalamocortical cholinergic afferents, is decreased interictally in patients with migraine and normalizes during attacks, whereas that of late HFOs, which probably reflect the activity of inhibitory cortical interneurons, remains normal[89] or decreases[90] between attacks. Moreover, a reduction in amplitude of early HFOs is associated with worsening of the clinical course of migraine.[68] Contrasting with these results, increased amplitudes of early and late HFOs has been reported between attacks in patients with migraine.[91] These disparate findings might be a result of differences in recording parameters and patient selection.

In patients with migraine, activation of the sensorimotor cortex induced by 10 Hz rTMS increased the amplitude of early and late HFOs in SSEPs, and induced habituation of the broadband SSEP.[55] rTMS significantly increased the amplitude of late HFOs, but had no effect on either early HFOs or habituation of the broadband SSEP in nonmigrainous controls, probably because their thalamocortical activity was already maximal at baseline.[55] These observations support the hypothesis that the habituation deficit in patients with migraine is due to reduced thalamic activation and, hence, reduced baseline activation of sensory cortices. Concordant data indicate that the interictal habituation deficit and low initial amplitude of VEPs in individuals with migraine normalizes after 10 Hz rTMS over the visual cortex.[36] Further evidence that control of thalamocortical activity is abnormal in people with migraine between attacks is suggested by the marked reduction in sensory gating of P50 middle-latency AEPs[92] and the significant habituation deficit in late visual-evoked high-frequency activity (oscillations in the gamma range, 20–35 Hz),[93] in comparison with healthy controls. Taken together, these studies indicate dysfunction of thalamocortical oscillatory networks, and patients with migraine might, therefore, be considered to have thalamocortical dysrhythmia (Figure 2).

The thalamocortical dysrhythmia theory postulates that when anatomical or functional disconnection of the thalamus from subcortical areas is present, the rhythmic thalamocortical activity might change to favour low-frequency activity (mainly 4–7 Hz theta waves). At the cortical level, this change will result in reduced firing rates of excitatory pyramidal cells at the beginning of stimulation, and of fast-spiking inhibitory interneurons during stimulus repetition.[94,95] Reduced firing of fast-spiking interneurons leads to disinhibition of adjacent cortical columns, which is reflected by a progressive rise in high-frequency gamma band oscillations—the so-called edge effect.[95] This theory could explain both the reduced thalamic and thalamocortical activity observed with HFOs, and the rise in late visual-evoked gamma band oscillations.

Several findings support the thalamocortical dysrhythmia theory. Short-range lateral inhibition in the visual cortex is more pronounced in migraine patients than in healthy volunteers at the beginning of the stimulus session.[65] Moreover, short-range lateral inhibition in the visual cortex increases over successive responses in people with migraine, but remains unchanged in

healthy controls.[65] Several quantitative EEG studies in individuals with migraine have shown a widespread increase in slow (mostly theta) oscillatory activity, chiefly over temporo-occipital areas,[96,97] which similarly concords with the thalamocortical dysrhythmia theory.

Amplitude–stimulus intensity function

Another time-related modality of stimulus processing that seems to be altered in people with migraine is the progressive amplitude adaptation of cortical responses to repetitive stimuli of increasing intensity, which is referred to as the amplitude–stimulus intensity function. When stimuli are delivered at increasing intensity, the evoked cortical responses increase in certain individuals, but decrease in others.[98] This so-called augmenting–reducing response has been widely studied, mainly in the context of auditory stimuli. The intensity dependence of AEPs (IDAP) is expressed by the amplitude–stimulus intensity slope of the cortical N1–P2 wave, where N1 is the greatest negative component 60–150 ms post-stimulus and P1 is the greatest positivity from 120–200 ms. Interestingly, IDAP correlates inversely with central serotonergic transmission, as evaluated indirectly by biochemical and pharmacological methods.[99]

Although the grand average of long-latency AEPs has normal latency and amplitude in patients with migraine,[57,100] IDAP is significantly increased interictally compared with healthy volunteers in most[51,52,72]—although not all[57]—studies. IDAP normalizes the day before and during the migraine attack, similarly to VEP habituation.[72] In fact, the interictal increase in IDAP in people with migraine can be attributed to a habituation deficit of the cortical response to high-intensity auditory stimuli.[52] IDAP is also strongly influenced by sensory overload.[101] Indeed, when IDAP is assessed during intense flash stimulation, two subgroups of patients with migraine can be identified—one reacts to the stimulus by a decrease in IDAP, as do controls, whereas the other reacts by an increase in IDAP. The underlying neurobiological basis of this difference between clinically similar patients is unknown, but might be related to differences in genetic background and/or brain connectivity.

An increased IDAP (that is, an augmenting pattern) suggests the presence of decreased central serotonergic transmission.[102,103] A high IDAP correlates positively with clinical symptoms of major depression[104] that are thought to be associated with decreased serotonergic signalling, and normalizes in depressed patients treated with selective serotonin reuptake inhibitors.[105] IDAP abnormalities also correlate with personality traits thought to be associated with decreased serotonergic transmission in individuals with migraine.[106] Treatment with migraine-preventing drugs such as β-blockers, which increase serotonergic transmission, normalizes the increased interictal IDAP in patients with migraine.[107] All things considered, the increased IDAP in migraine could be secondary to reduced activity of raphe cortical monoaminergic pathways, which causes low baseline activation levels of auditory cortices.

Processing of noxious stimuli

Another feature that is present in patients with migraine concerns the altered processing of nociceptive stimuli, which has been studied using nociceptive trigeminal and biceps femoris reflexes, as well as thermonociceptive-induced cortical evoked responses.

The nociceptive flexion reflex

Pain disorders are commonly accompanied by central sensitization, which amplifies the CNS response to painful stimuli. This amplification also occurs during migraine attacks[108] and worsens with increasing attack frequency.[109] One mechanism underlying central sensitization is the activity-dependent change in excitability of central nociceptors, which results in abnormal amplification of pain sensation in physiological nociception—a phenomenon referred to as temporal summation of pain stimuli[110] that is equivalent to 'wind-up' phenomenon (facilitation of wide-dynamic-range nociceptive neurons located in the deep laminae of the spinal cord dorsal horn and the spinal trigeminal nucleus after constant-intensity stimulation of C fibres) in animal experiments.[111]

The nociceptive flexion or withdrawal reflex (NWR) is a reliable measure of spinal nociception, as demonstrated by the fact that it requires Aδ-fibre activation, that the reflex threshold is related to the pain perception threshold, and that the reflex magnitude correlates positively with pain intensity ratings.[112,113] Temporal summation of pain develops in parallel with temporal summation of the NWR of the lower limbs, reflected by a progressive increase in magnitude of the NWR after constant-intensity electrical stimulation (which activates both Aδ and C fibres,[113–115] and is inhibited by *N*-methyl-D-aspartate receptor antagonists).[116] Interestingly, descending pain control systems modulate temporal summation of the NWR,[117] and might be dysfunctional in a number of chronic pain disorders, including migraine. For example, studies of temporal summation of the NWR in people with migraine show facilitation of temporal pain processing between attacks.[118] Administration of a nitric oxide donor, such as glyceryl trinitrate, induces transitory facilitation of temporal summation of the NWR within 120 min in patients who will go on to develop a glyceryl trinitrate-triggered migraine attack several hours later (Figure 3).[119]

In individuals with chronic headache, such as MOH in the setting of episodic migraine, the threshold for temporal summation of the NWR is markedly reduced compared with that in controls or in patients with episodic migraine, which indicates strong facilitation in the temporal processing of pain.[118] In patients with MOH, the pain-suppressing effect of supraspinal diffuse noxious inhibitory control (pain inhibition by heterotopic painful stimulation) on temporal summation of the NWR is deficient.[118] This effect, which in humans is termed conditioned pain modulation,[120] can be tested by heterotopic application of a painful cold stimulus.[119] The deficits in conditioned pain modulation or supraspinal diffuse noxious inhibitory control and facilitation of temporal summation of the NWR normalize after

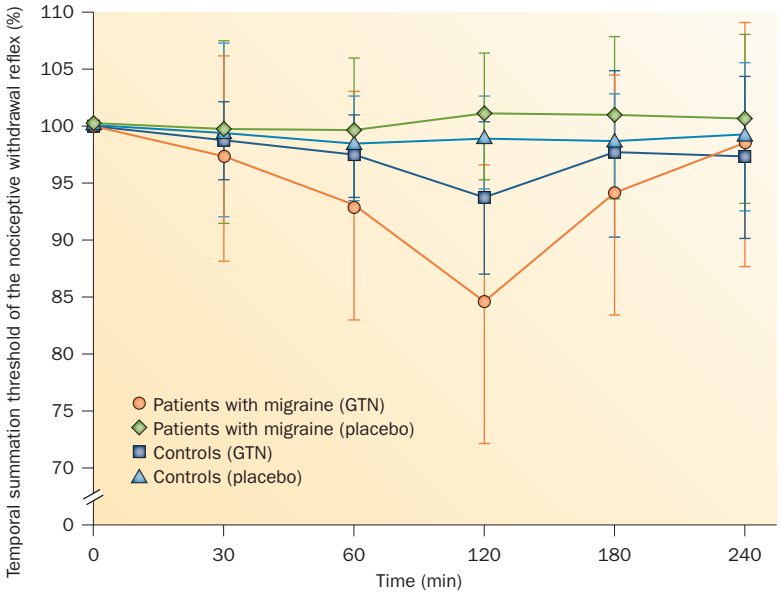


Figure 3 | Facilitation of temporal pain processing between migraine attacks. Facilitation of the temporal summation threshold of the biceps femoris nociceptive withdrawal reflex is markedly more facilitated by glyceryl trinitrate administration (versus placebo) in patients with migraine than in healthy controls. Abbreviation: GTN, glyceryl trinitrate. Permission obtained from John Wiley and Sons, West Sussex (UK), *Eur. J. Pain* **15**, 482–490 (2011).

drug withdrawal, which could be related to the reduction in activity of anandamide hydrolase (also known as fatty acid amide hydrolase) and, hence, slowing of the degradation of endocannabinoids.[121]

Nociceptive trigeminal evoked responses

The nBR is evoked in orbicularis oculi muscles by stimulating the supraorbital nerve via a concentric high-density electrode, which mainly activates Aδ afferents. This reflex is mediated via interneurons of the spinal trigeminal nucleus. Migraine is characterized by an interictal deficit of nBR habituation during both short[74] and long[38] series of stimuli. nBR habituation normalizes during migraine attacks,[74] and individuals at risk of developing migraine lack nBR habituation deficits,[86] whereas habituation of nociceptive laser-evoked potentials (LEPs, discussed further below) remains deficient.[75] Patients with migraine also show temporal summation of the nBR.[122]

Brief radiant heat pulses generated by CO_2 laser stimulation or contact thermode-delivered stimuli excite Aδ and C fibre thermonociceptors in superficial skin layers.[123] In turn, the Aδ fibre input generates LEPs or contact-heat evoked potentials (CHEPs) in the cortex. The N2–P2 component of LEPs and CHEPs is thought to be generated in the posterior part of the anterior cingulate cortex and in the bilateral insula.[124]

Compared with healthy controls and people with episodic migraine between attacks, the brain distribution of LEP is shifted rostrally in patients with migraine during an attack[125] and in patients with chronic migraine.[126] This anterior shift of activation contrasts with the posterior shift of LEPs observed during capsaicin-induced neuropathic pain in healthy volunteers,[127] and with the caudal displacement of cortical evoked potentials in the cingulate gyrus after intramuscular nociceptive stimulation of the trapezius muscle in patients with migraine.[128] This difference with the data on LEPs can be explained by the different methodologies used, which involved stimulation of different nociceptive afferents.[129]

Similarly to the cortical evoked potentials elicited by non-noxious stimuli, LEPs[75,130] and CHEPs[131] show habituation deficits in patients with migraine between attacks. However, in contrast with non-noxious cortical evoked potentials, the lack of habituation of LEPs persists during the attack, and is associated with an increased N2–P2 amplitude.[132]

Nonlinear analysis of ongoing EEG changes reveals subtle changes in the cortical response to painful laser stimuli in patients with migraine.[133] For example, individuals with episodic migraine have markedly reduced predictability of their EEG rhythms after the laser stimulus compared with healthy individuals, although their averaged LEPs seem normal; however, the averaging technique used to extract evoked potentials from the background EEG signals might neglect subtle changes in the processing of pain by the brain. Future studies using analysis of single (nonaveraged) nociceptive evoked potentials, refined neurophysiological techniques and a combination of neurophysiological and imaging methods will help to characterize the pathophysiological features of central processing of pain in patients with migraine. In chronic migraine and MOH, pain-related cortical potentials as a response to electrical forehead or forearm stimulation were facilitated, but no change was observed in the nBR.[134]

Thalamocortical dysrhythmia in migraine

Given the results of the above-described neurophysiological studies, the pathogenesis of migraine seems to be driven by complex dysfunction of thalamocortical connectivity and temporal activation of neuronal networks. Thalamocortical dysrhythmia might also explain the phenomena observed in patients with migraine who are treated with transcranial neuromodulation techniques—for instance, the increased variability of dynamic changes in excitability[135] or the paradoxical homeostatic cerebral plasticity.[136–138] In a proof-of-concept study, the plastic cortical changes induced by rTMS were found to be inversely related to thalamocortical activation.[139] This observation suggests that the paradoxical effects observed after rTMS in patients with migraine might be a consequence of abnormal thalamocortical drive, which impairs short-term and long-term changes in cortical synaptic effectiveness, and finally leads to maladaptive responses. Taken together, the dysfunctions found in the migrainous brain suggest an impairment of thalamocortical control of temporal activation of different neuronal networks.[48]

Thalamocortical dysrhythmia has also been proposed to underlie other functional brain disorders.[140,141] In patients with chronic neuropathic pain, overactivation in the theta and beta range —suggestive of

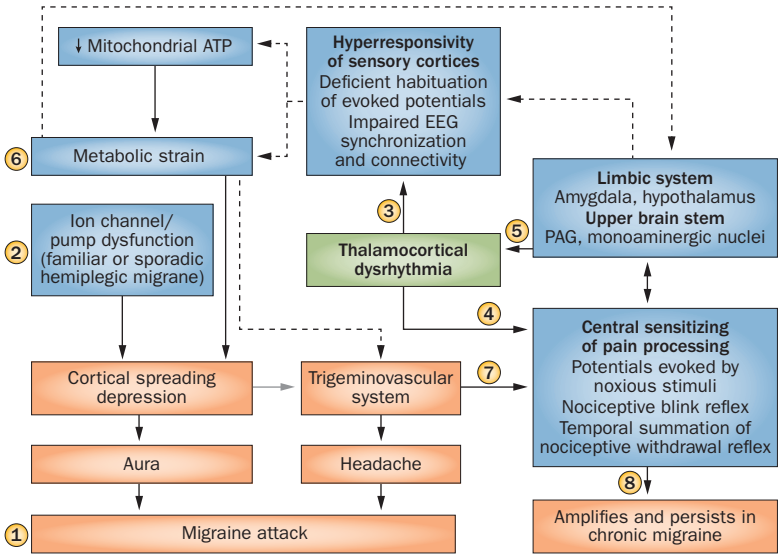


Figure 4 | A neurophysiological model of migraine pathogenesis. Activation of the trigeminovascular system—the main pain-signalling system in the brain—triggers migraine headache (1). The migraine aura is caused by CSD, which may or may not activate the trigeminovascular system. Genetic channelopathies (2) predispose to CSD in the rare familial and sporadic hemiplegic forms of migraine. Interictal thalamocortical dysrhythmia causes hyperresponsivity of sensory cortices (3) as well as abnormal pain processing (4). The thalamocortical dysrhythmia itself may be induced by decreased control from brainstem monoaminergic nuclei (5). Cortical hyperresponsivity combined with a decreased mitochondrial energy reserve favours metabolic strain (6). This process could trigger CSD in the cortex and, via subcortical chemosensitive structures, activate the trigeminovascular system. The migraine attack is associated with sensitization of central nociceptive pathways (7). Abnormalities of responses evoked by noxious stimuli amplify and persist in chronic migraine (8). Dashed lines indicate hypothetical connections, for which there is currently little or no experimental evidence. Abbreviations: CSD, cortical spreading depression; PAG, periaqueductal grey.

thalamocortical dysrhythmia—was found in the cortical 'pain matrix'. In six patients who were successfully treated by central lateral thalamotomy, the overactivity attenuated along with the pain.[142]

Further assessment with modern neuroimaging methods will be required to disentangle the anatomical correlates of thalamocortical dysrhythmia in migraine. A functional MRI (fMRI) study in people with migraine revealed a lack of habituation of the blood oxygen level-dependent signal during repetitive trigeminal nociceptive stimulation in areas of the pain matrix (anterior insula and middle cingulate gyrus).[143] Interestingly, this difference between patients with migraine and healthy controls was not found for olfactory stimuli, which the researchers attributed to the fact that olfaction is not relayed in the thalamus.

Our research group has proposed that hypofunctioning serotoninergic projections to the thalamus and cortex might cause functional disconnection of the thalamus, leading to thalamocortical dysrhythmia and reduced cortical habituation (Figure 4).[40]

It has not yet been demonstrated whether the altered synchronicity and deficient habituation of neuronal responses to external stimuli in migraine has a role in the cortical predisposition to spreading depression, or in other phenomena that are able to activate the trigeminovascular system and induce a migraine attack. Also, whether the abnormal temporal processing of nociceptive information predisposes to migraine attacks, central sensitization and, possibly, chronic migraine is not proven, but would intuitively seem probable. However, the fact that the interictal cortical hyperresponsivity to sensory stimuli in migraine can be alleviated by neurostimulation techniques[55] (see below) and by preventive antimigraine drugs, both of which also decrease attack frequency,[107] supports indirectly the hypothesis that the brain dysfunction between attacks could predispose patients to recurrent attacks. Considering that the cerebral energy reserve (ATP content) between attacks is significantly lower in individuals with migraine compared with healthy individuals,[80] it is tempting to speculate that the cortical hyperresponsivity might contribute to disruption of the brain's metabolic homeostasis by increasing energy demand, thereby initiating the biochemical cascade that leads to the migraine attack.[6]

Prospects for clinical research

The results of MRI studies suggest that migraine is associated with altered interictal functional connectivity in subcortical and cortical areas that are devoted to cognitive functions and pain processing.[144,145] Connectivity was stronger between the periaqueductal grey and several brain areas associated with pain processing, such as the prefrontal cortex, anterior cingulate and amygdala, areas that are very similar to brain regions implicated in neurophysiological data on sequential cortical activation during painful stimuli.[125,126,144,146] Diffusion-weighted MRI studies showed that microstructural alterations of white matter, and thus of functional connectivity, are present across the orbitofrontal cortex, insula, thalamus and dorsal midbrain.[147] These alterations might reflect maladaptive plastic changes driven by dysrupted exogenous and endogeneous multimodal task processing.[147] In another fMRI study, thalamic sensitization correlated with widespread mechanical allodynia during the migraine attack.[148] Moreover, in a diffusion tensor MRI study, our research group found dynamic ictal and interictal microstructural variations in the thalamus that were related to the time since the last migraine attack, and seemed to mimic the cyclic neurophysiological changes described above.[149]

Collectively, these observations suggest that a search for optimal methods of influencing the cortical temporal processing of exogenous stimuli that can trigger a migraine attack, or methods for modulating endogenous trigeminal noxious inputs that lead to central sensitization and eventually chronic headache, could result in novel interventions for migraine prevention. The modes of action of anticonvulsants or antidepressants, as well as of other pharmacological or nonpharmacological interventions, such as neuromodulation methods, should be reconsidered in terms of their ability to normalize the complex abnormalities of brain connectivity and hyperresponsivity found in patients with migraine.[150] For example, noninvasive cortical neuromodulation techniques such as rTMS and transcranial direct current

Box 1 | Neurophysiological findings associated with migraine

Several abnormalities of sensory processing may be observed in patients with migraine:

Interictal light-induced EEG changes
- Stimulus-frequency-dependent increase in photic drive
- Alpha frequency synchronization and decrease in functional connectivity (in migraine without aura)
- Beta frequency desynchronization and increase in functional connectivity (in migraine with aura)

Interictal (and ictal) changes in non-noxious sensory evoked potentials
- Trend towards lower amplitude of averaged responses to brief sequences of repeated stimuli
- Deficient habituation during prolonged stimulus repetition (normalizes during attack)
- Increased intensity-dependence of auditory evoked potentials (normalizes during attack)

Interictal (and ictal) changes in noxious sensory evoked responses
- Deficient habituation of cortical evoked responses (persists during attack)
- Deficient habituation of nociceptive blink reflexes (normalizes during attack)
- Facilitation of temporal summation of the biceps femoris flexion reflex

Changes in chronic migraine
- Increased amplitude of averaged cortical responses to small numbers of repeated non-noxious and noxious stimuli
- Deficient habituation of sensory evoked responses to noxious stimuli despite normal habituation of sensory responses evoked by non-noxious stimuli

stimulation (tDCS) have already been assessed in clinical trials. Several studies have investigated the hypothesis that the cortex in patients with migraine patients is hyperexcitable between attacks. However, inhibitory low-frequency rTMS over the vertex had no superior therapeutic effect to sham stimulation,[151] and cathodal (inhibitory) tDCS over the occipital cortex had no significant preventive effect on migraine attacks , although the latter intervention did reduce attack intensity compared with placebo.[152] By contrast, in a pilot trial designed to assess an alternative hypothesis—that the visual cortex is not hyperexcitable *per se,* but, rather, insufficiently activated at baseline (as described above[87])—anodal (facilitatory) tDCS over the occipital cortex significantly decreased attack frequency and intensity when used as preventive therapy in patients with migraine.[150]

The challenge for future research, therefore, lies in identification of the precise anatomical structures and functional networks involved in migraine, and determination of which pharmacological and nonpharmacological interventions can optimally modulate the function of these areas and thereby improve temporal information processing. Such investigations will involve simultaneous recordings of the above-reported phenomena via neurophysiological and functional neuroimaging techniques, along with the application of nonlinear algorithms to model brain complexity.[153] Novel therapeutic interventions can then be tested for their capacity to normalize the anatomical and functional changes associated with migraine and its subtypes.

Conclusions

Most of the data described here suggest that the cortical processing of non-noxious and noxious sensory stimuli differs between patients with migraine and healthy controls (Box 1). The neuronal networks involved in sensory processing are characterized by different modalities of sequential recruitment under different environmental or endogenous conditions. The patterns of temporal activation have been analysed over a range of neuronal activities, from progressive changes of neuronal recruitment in the habituation or intensity dependence phenomena, to facilitation of noxious stimuli summation, and complex patterns of variability, phase synchronization and causality that are adapted to describe the properties of a chaotic and nonlinear system. These intricate processes not only differ between patients with migraine and healthy individuals, but also vary according to the phases of the migraine cycle in the same patient.

The mechanisms underpinning these complex changes are far from being understood, and how they fit into the puzzle of migraine pathogenesis is still unclear. Owing to their complexity, however, the brain dysfunctions are unlikely to be explained simply by an imbalance between excitatory and inhibitory circuits.[87] We propose that thalamocortical dysrhythmia could be the culprit for abnormal central processing of non-noxious and noxious sensory stimuli in patients with migraine, and that the thalamocortical dysrhythmia itself might be caused by genetically determined inadequate control of the thalamus and cortex by monoaminergic (serotonergic) projections originating in the brainstem (Figure 4). We further postulate that the cortical hyperresponsivity to sensory stimuli might contribute causally to migraine attack repetition, because it favours excessive energy expenditure in a brain with a reduced energy reserve.

To reduce discrepancies between studies, more attention should be paid to blinding of investigators, so that accurate clinical data and headache diaries can be collected before and during testing. In addition, prospective studies should be conducted to monitor patients' clinical fluctuations throughout the migraine cycle. It will also be of utmost importance to gather more data on the (neurophysiological) phenotype–genotype correlations in patients with the various migraine types. Finally, improved insight into the nature of the interictal dysfunction of temporal information processing in individuals with migraine will, we hope, pave the way for novel therapeutic targets, and could herald improved migraine management.

Review criteria

We initially searched the PubMed database to identify articles published up to June 2013. The search terms used were "migraine", "electroencephalography", "EEG", "evoked potentials", "habituation", "temporal summation", "nociceptive withdrawal reflex" and "blink reflex", alone and in combination. The literature search was updated using the additional keywords "migraine", "habituation" and "evoked potentials" to identify full-text papers written in English and published in peer-reviewed journals up to December 2013, using the PubMed and Google Scholar databases. Reviews were considered only when they introduced new concepts or hypotheses.

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Author contributions

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