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 malfunctioning. These changes reflect complex CNS dysfunction patterns. Assessing the altered temporal patterns of the brain's electrophysiological activity, using multimodal evoked potentials and nociceptive reflex responses, can aid in understanding 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 of temporal patterns of sensory processing in patients with migraine should be combined with neuroimaging studies of the accompanying anatomical and functional changes.

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Key points

- Migraine is the most prevalent neurological disorder in the general population and a considerable societal burden. Its episodic form consists of paroxysmal attacks separated by remissions of variable duration, but in some patients migraine becomes unremittingly chronic
- Migraine is a functional brain disorder caused by interplay between a genetic predisposition and hormonal/environmental factors. Electrophysiological studies are able to identify the abnormal functioning of the migrainous brain between, just before and during attacks and to monitor the effect of therapeutic interventions
- Most electrophysiological studies in migraineurs are characterised between attacks, by hyperresponsivity to repeated sensory stimuli with abnormal temporal processing of brain

responses, malfunctioning sequential recruitment of neuronal networks and deficit of habituation

- These abnormalities of sensory processing vary over the migraine cycle: they worsen pre-ictally but tend to disappear during the attack; they 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

Introduction

Migraine is the most prevalent neurological disorder in the general population: its cumulative lifetime incidence is 43% in women and 18% in men.[1] Its episodic form 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, which 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 non-invasiveness of electrophysiological methods is 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: multimodal evoked potentials, steady-state visual evoked responses, noxious evoked cortical responses, and nociceptive reflexes. Their results have provided three major 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, which normalizes during an attack. Third, noxious evoked responses or reflexes 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.

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.

H1: EEG changes induced by visual stimuli

H2: 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 migraine patients SSVEP amplitude was less stable over time than in controls[11]. Fluctuation of increased photic driving over the migraine cycle has also been reported.[10,12] 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.

H2: 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 non-linear analysis methods. In healthy individuals, the alpha activity 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, i.e. 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) that has been tried as 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 its components, using Granger causality[22,23] or dynamic causal modeling,[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 non-linear signals such as EEG data. In a preliminary study, individuals who had migraine without aura showed increased phase synchronization in the alpha band during intermittent flash stimulation and reduced connectivity, 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]

H1: Evoked brain responses to non-noxious stimuli

H2: 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 irrelevant information to protection of the cerebral cortex against overstimulation. It has been studied to investigate the neuronal substrates of behaviour, learning processes, and treatment 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 usually accompanied by a normal to low amplitude of early responses in averaged data. Lack of habituation is the most prominent (probably genetically determined) consequence of the functional brain abnormality that characterises 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 (restoration to 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 (VEP),[33–42] visual evoked magnetoencephalographic (MEG) responses,[43] auditory evoked potentials (AEP)[51,52] and somatosensory evoked potentials (SSEP).[53–55]

However, several other studies were 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 is not constant in the same patient with migraine. It varies not only over the migraine cycle (interictal, preictal and ictal), but also within the interictal state, becoming more or less profound with decreasing time respectively to the next or from the previous attack.[65] Moreover, genetic variants can have an effect on habituation profiles.[66,67] Finally, spontaneous clinical worsening or improving of attack frequency can influence the baseline level of thalamocortical activation,[68,69] and hence the degree of habituation in patients with migraine.[55]

H2: Variation over the migraine cycle

H3: 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 several hours before the aura or the headache by the so-called prodromal or premonitory symptoms. Moreover, attack frequency varies over the patient's lifetime. It is thus 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 AEP, 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 not caused by a single determinant factor, but by a complex interplay between intrinsic cerebral, hormonal and environmental factors acting on a genetically predisposed nervous system. Disentangling this interplay is a challenge for future research, and will be a prerequisite for the development of novel effective therapies.

H3: 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 normal.

H2: 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 has a similar maximal activation range of sensory cortices, but a variable level of baseline activation. During repetitive stimulation, the maximum activation level (the ceiling) is reached rapidly and the response amplitude decreases rapidly (habituates) In subjects with a normal baseline activation while habituation is delayed or absent when baseline activation is low.[88] The first two of these mechanisms would be expected to give rise to a high initial response amplitude, indicating genuine hyperexcitability, and a linear decrease of habituation. By contrast, 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 understanding of the abnormal information processing in migraine. Amplitude of early HFOs embedded in the common SSEPs, 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, remain normal[89] or decreased[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 also been reported in patients with migraine between attacks.[91] These disparate findings may be a result of differences in recording parameters and selection of patients.

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 10Hz 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 to healthy controls. Taken together, these studies indicate a dysfunction in thalamocortical oscillatory networks, and patients with migraine might, therefore, be considered to have thalamocortical dysrhythmia (Figure 2).

The thalamocortical dysrhythmia theory postulates that when an anatomical or functional disconnection of the thalamus from subcortical areas is present, the rhythmic thalamocortical activity may 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 this hypothesis. In agreement with 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 also 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) activities, chiefly over temporo-occipital areas,[96,97] which similarly concords with the thalamocortical dysrhythmia theory.

H2: 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 an 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 AEP (IDAP) is expressed by the amplitude–stimulus intensity slope of the cortical N1–P2 wave where N1 is the greatest negative component between 60 and 150 msec post-stimulus and P1 the greatest positivity between 120 and 200 msec. Interestingly, IDAP correlates inversely with central serotonin activity 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,[100,57] IDAP is significantly increased interictally compared to 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 is positively correlated 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.

H1: Processing of noxious stimuli

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

Pain disorders are commonly accompanied by central sensitization that 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 an 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" in animal experiments.[111]

H2: The nociceptive flexion reflex

The nociceptive flexion or withdrawal reflex (NWR) is a reliable measure of spinal nociception, as demonstrated by the facts that it requires Aδ fibre activation, that the reflex threshold is related to the pain perception threshold, and that the reflex magnitude positively correlates 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 NMDA 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, that triggers an attack in many migraineurs at delay of several hours, induces within 120 min a transitory facilitation of temporal summation of the NWR, in those patients who will develop a migraine attack (Figure 3).[119]

In individuals with chronic headache, such as MOH evolving from episodic migraine, the threshold for temporal summation of the NWR is markedly reduced compared to that in controls or patients with episodic migraine, which indicates a strong facilitation in the temporal processing of pain.[118] In patients with MOH, the suppressing effect of supraspinal diffuse noxious inhibitory control (DNIC) (Box 2) on temporal summation of the NWR is deficient.[118] This effect, which in humans is termed conditioned pain modulation,[120] can be tested by the 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 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]

H2: Nociceptive trigeminal evoked responses

The nBR is obtained in orbicularis oculi muscles by stimulating the supraorbital nerve via a concentric high-density electrode, which activates mainly 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 (LEP, 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] The Aδ fibre input generates cortical potentials, called respectively LEP or contact-heat evoked potentials (CHEP). The N2–P2 component of LEP and CHEP is thought to be generated in the posterior part of the anterior cingulate cortex and in bilateral insula.[124]

Compared to 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 LEP 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 LEP can be explained by the different methodology used, which involves stimulation of different nociceptive afferents.[129]

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

Nonlinear analysis of ongoing EEG changes shows 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 to healthy individuals, although their averaged LEP appear 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 (non averaged) nociceptive evoked potentials, refined neurophysiological techniques and the 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 medication overuse headache, pain-related cortical potentials to electrical forehead or forearm stimulation were facilitated, but not the nBR.[134]

H1: Migraine pathogenesis from the neurophysiological perspective

Given the results of the abovedescribed neurophysiological studies, the pathogenesis of migraine seems to be driven by a complex dysfunction of thalamocortical connectivity and temporal activation of neuronal networks. Thalamocortical dysrhythmia might also explain the phenomena observed in patients with migraine 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 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 dysrythmia has been proposed to underlie other functional brain disorders.[140,141] Theta and beta overactivation on the EEG, suggestive of thalamocortical dysrhythmia, was found in the cortical “pain matrix” of patients with chronic neuropathic pain, and was attenuated together with the pain in 6 patients treated by central lateral thalamotomy.[142] The anatomical correlates of thalamocortical dysrhythmia in migraine remain to be analysed further with modern neuroimaging methods. A functional MRI (fMRI) study in people with migraine revealed a lack of habituation of the BOLD (Box 2) signal during repetitive trigeminal nociceptive stimulation in areas of the pain matrix (anterior insula and middle cingulate gyrus).[143] Interestingly, this difference with 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.[40] (Fig. 4)

It has not yet been demonstrated whether the different synchronicity and deficient habituation characterizing neuronal responses to external stimuli in migraine play a role in the cortical predisposition to spreading depression, or any other phenomenon able to activate the trigeminovascular system and induce a migraine attack. It is also not proven (though it would intuitively seem possible) that the abnormal temporal processing of nociceptive information predisposes to migraine attacks, central sensitization and possibly chronic migraine. 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 anti-migraine drugs,[107] both of which also decrease attack frequency, is indirect evidence that the brain dysfunction between attacks may predispose patients to recurrent attacks. Considering that the cerebral energy reserve (ATP content) is significantly lower in migraineurs between attacks compared to healthy subjects[80], it is tempting to speculate that the cortical hyperresponsivity may contribute to disrupt the brain’s metabolic homeostasis by enhancing energy demands and to start up the biochemical cascade that leads to the migraine attack.[6]

H1: 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] It was suggested[147] that these alterations might reflect maladaptive plastic changes driven by dysfunctions in multimodal exogenous and endogenous task processing. 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 from or to the last migraine attack, and seemed to mimic the cyclic neurophysiological changes described above.[149]

Collectively, these observations suggest that searching for optimal methods of influencing the cortical temporal processing of exogenous stimuli that can trigger a migraine attack, or of 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, and of other pharmacological or non-pharmacological 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, non-invasive cortical neuromodulation techniques such as rTMS and transcranial direct current stimulation (tDCS) have already been assessed in clinical trials. Several studies 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 (i.e.inhibitory) tDCS over the occipital cortex had no significant preventive effect, although the latter intervention did reduce attack intensity compared to 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 determining which pharmacological and non-pharmacological 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 by 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 anatomic and functional changes associated with migraine and its subtypes.

H1: Conclusions

Most data described here suggest that the cortical processing of non-noxious and noxious sensory stimuli is different between patients with migraine and healthy controls. 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 are different not only 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, it is unlikely that the brain dysfunctions can simply be explained by an imbalance between excitatory and inhibitory circuits.[87] We propose that thalamocortical dysrhythmia may be the culprit for abnormal central processing of non-noxious and noxious sensory stimuli in migraine patients and that it might be itself caused by a genetically determined, inadequate control of the thalamus and cortex by monoaminergic (serotonergic) projections originating in the brain stem (Fig. 4). We further postulate that the cortical hyperresponsivity to sensory stimuli may contribute causally to migraine attack repetition because it favours an excessive energy expenditure in a brain with a reduced energy reserve.

In order 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 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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Figure 1

Temporal evolution in effective connectivity (causality-ordinate) as revealed by kernel Granger causality analysis of averaged EEG data from patients with migraine and healthy controls during a 10-sec flash stimulation (abscissa) at a 21Hz frequency. In the alpha band (a), causal/effective connections across scalp derivations are reduced in migraine without aura compared to migraine with aura or healthy controls, while in the beta band (b) migraine with aura patients have increased causality across cortical areas. This phenomenon may be subtended by an increase of cortical activation in migraine with aura during visual stimulation.

Data used to generate this Figure were obtained from de Tommaso *et al*.[25]

Figure 2

Schematic overview showing 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 10Hz 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.

Figure 3

Facilitation of the temporal summation threshold of the biceps femoris nociceptive withdrawal reflex is markedly more facilitated by glyceryltrinitrate administration (versus placebo) in patients with migraine than in healthy controls. Data for these graphs were obtained from Perrotta *et al*., 2011.[119] Abbreviations: NWR, nociceptive withdrawal reflex; TST, temporal summation threshold, GTN, glyceryltrinitrate; Plb, placebo.

Figure 4

The migraine headache (1) is due to activation of the trigeminovascular system (TVS), the major pain-signalling system in the brain. The migraine aura is caused by cortical spreading depression (CSD) that may or may not activate the trigeminovascular sytem. Genetic channelopathies (2) predispose to CSD in the rare Familial/Sporadic Hemiplegic forms of migraine (FHM).

The challenge in migraine research is to determine what causes CSD, and what, besides CSD, can activate the TVS in the more common forms of migraine. Neurophysiological studies described in this review have contributed to disentangle some of the complex pathomechanisms in migraine. They have shown that interictal abnormalities of sensory processing might predispose the migrainous brain to an attack. 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 brain stem monoaminergic nuclei (5). Cortical hyperresponsivity combined with a decreased mitochondrial energy reserve favours metabolic strain and rupture of metabolic homeostasis(6). This may trigger CSD in the cortex and, via subcortical chemosensitive structures, TVS activation. There is evidence for upper brain stem activation during migraine attacks. Whether this is due to collateral projections from the trigeminal nociceptive pathway, to chemosensing of the metabolic dysequilibrium or to input from hypothalamus and limbic system remains to be determined. Activation of the monoaminergic nuclei may explain why cortical hyperresponsivity normalizes during an attack. The migraine attack is associated with sensitization of central nociceptive pathways (7) which can be detected by abnormalities of noxious evoked cortical and subcortical responses. The latter abnormalities amplify and persist in chronic migraine (8) where the neurophysiological pattern is that of a «never-ending attack ».

Common genetic variants set the « migraine threshold » by modulating a number of different physiological mechanisms: oxidative stress, neuroinflammation, neurotransmission, metabolism..

As described in the text, the neurophysiological abnormalities vary between patients, over the migraine cycle, under the influence of preventive anti-migraine medications and with migraine chronification.

Dashed lines indicate connections for which there is little or no experimental evidence yet.

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 (& ictal) changes in non-noxious sensory evoked potentials

- Trend for low amplitude averaged responses to small numbers of repeated stimuli
- Deficient habituation during prolonged stimulus repetition (normalizes during attack)
- Increased intensity dependence of auditory evoked potentials

Interictal (& 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

- High amplitude averaged cortical responses to small numbers of repeated non-noxious or noxious stimuli
- Normal habituation of non noxious sensory evoked responses
- Deficient habituation of noxious sensory evoked responses

Box 2: Glossary

Granger causality/Kernel Granger causality: operative definition of causality for linear/nonlinear systems

Diffuse noxious inhibitory control (DNIC): pain inhibition by a heterotopic painful stimulation

BOLD: blood oxygen level dependent

AEP: auditory evoked potentials

IDAP: intensity dependence of **auditory evoked potentials**

VEP: visual evoked potentials

SSVP: steady state visual evoked potential

SSEP: somato-sensory evoked potential

HFO: high frequency oscillations

MOH: medication overuse headache

NWR: nociceptive withdrawal reflex

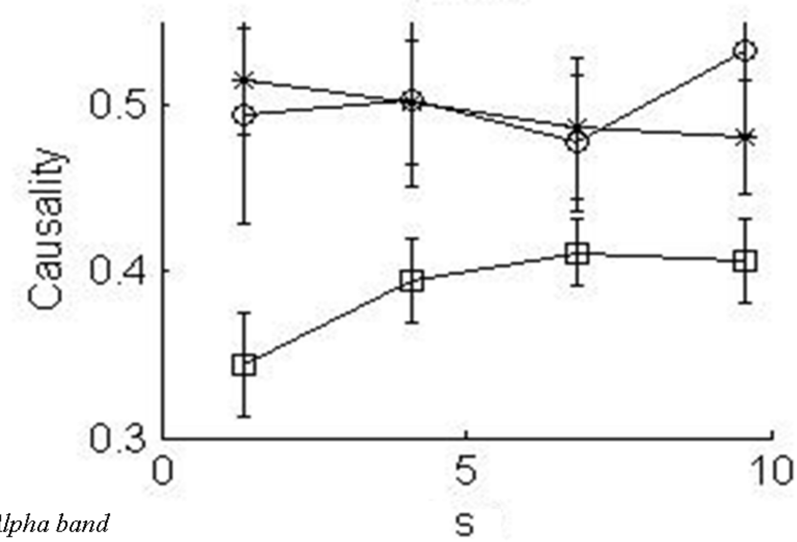
nBR: nociceptive blink reflex

LEP: laser evoked potentials

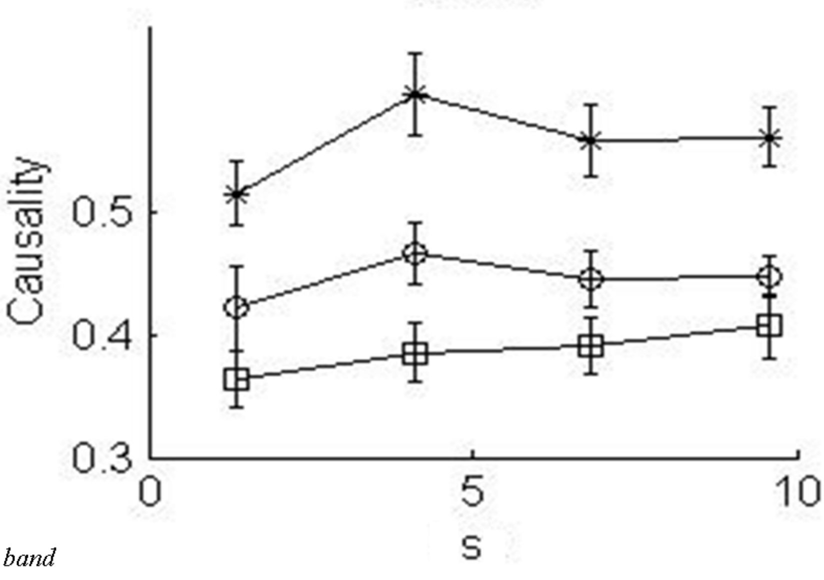
CHEP: contact heat evoked potentials

rTMS: repetitive transcranial magnetic stimulation

tDCS: transcranial direct current stimulation



Alpha band



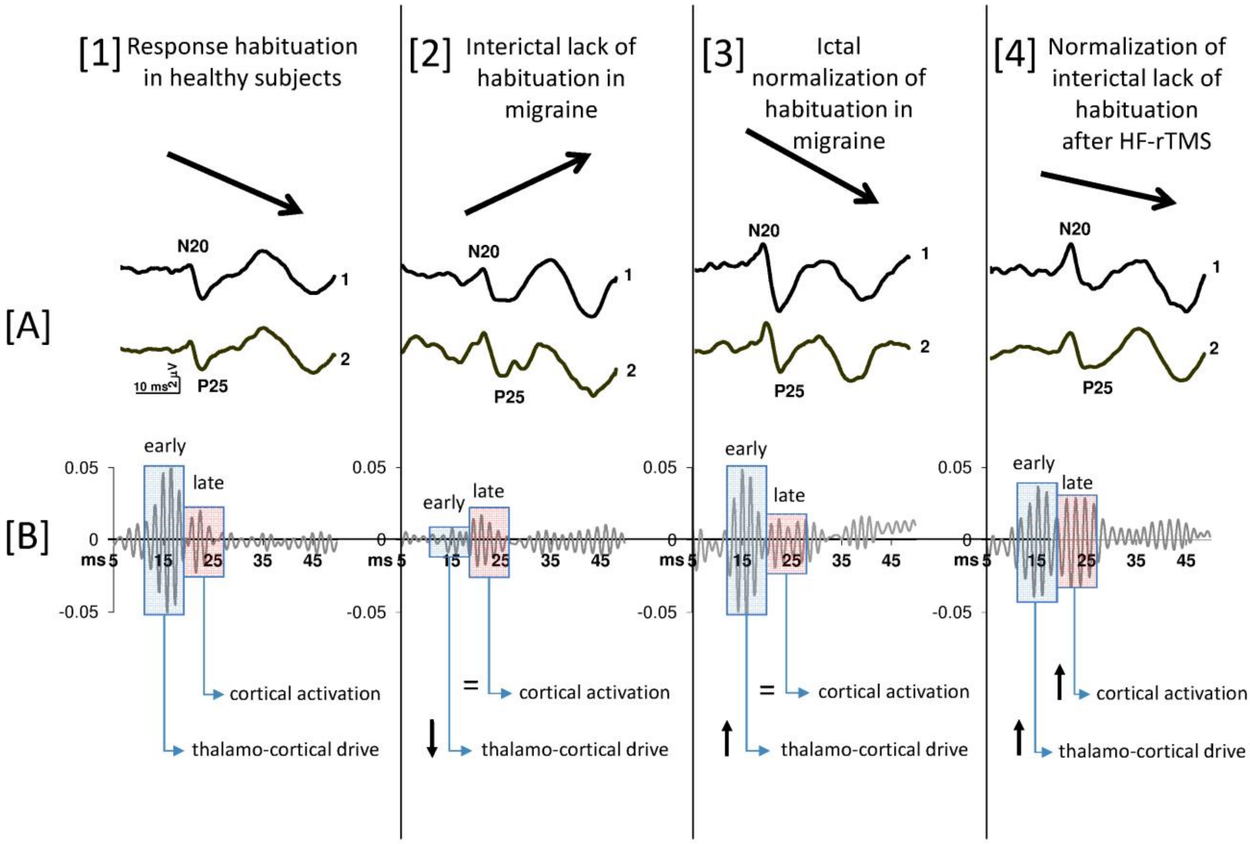
Beta band

□ *Migraine without aura n° 19*

* *Migraine with aura n° 19*

○ *Controls n° 11*

Figure 1F



[1] Response habituation in healthy subjects
[2] Interictal lack of habituation in migraine
[3] Ictal normalization of habituation in migraine
[4] Normalization of interictal lack of habituation after HF-rTMS
[A]
[B]
N20
P25
1
2
10 ms
2 µV
early
late
0.05
0
-0.05
ms
5
15
25
35
45
=
cortical activation
thalamo-cortical drive

Figure 2

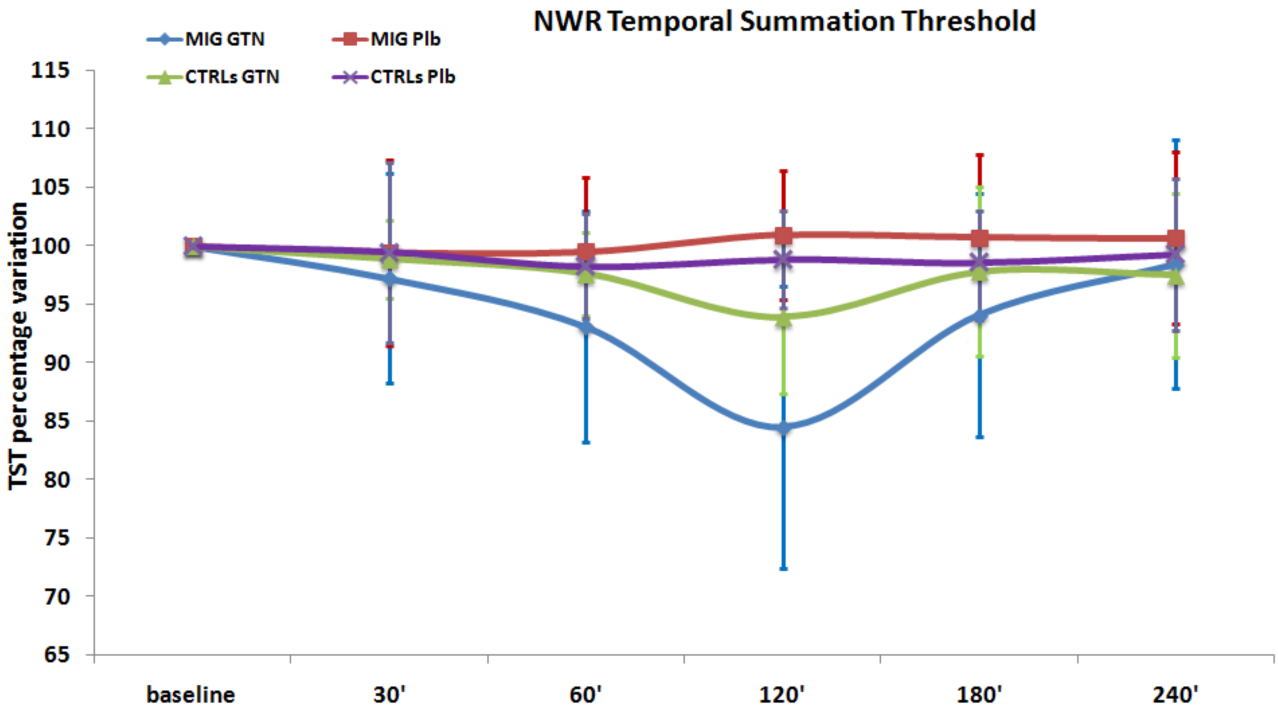

NWR Temporal Summation Threshold
MIG GTN
MIG Plb
CTRLs GTN
CTRLs Plb
TST percentage variation
115
110
105
100
95
90
85
80
75
70
65
baseline
30'
60'
120'
180'
240'

Figure 3

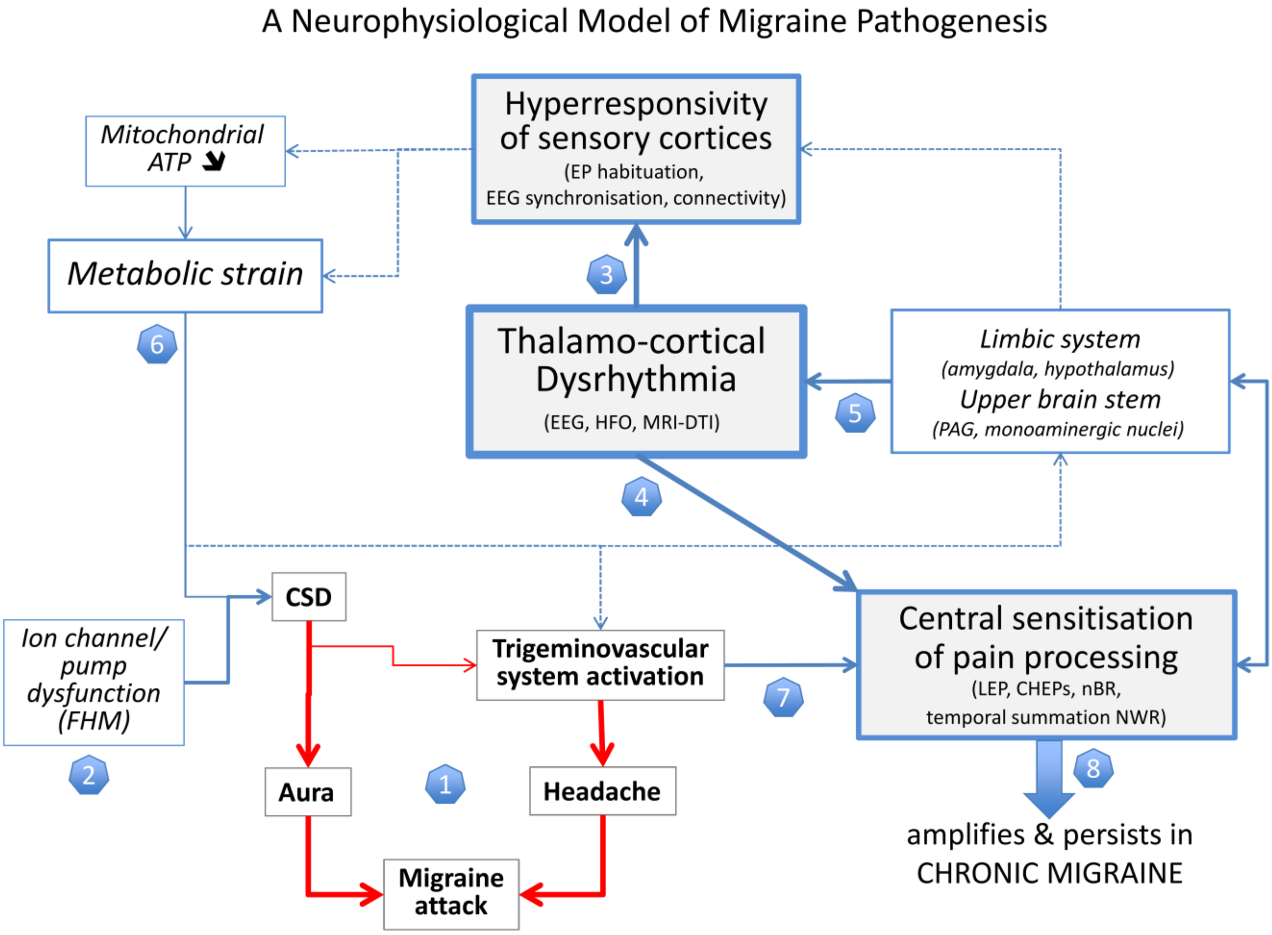


Figure 4