Chapter 17
Neurophysiological Model of Migraine Pathophysiology: Bringing the Past into the Future

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Abbreviations

ACh	Acetylcholine
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CNV	Contingent negative variation
CSD	Cortical spreading depression
EEG	Electroencephalography
EP	Evoked potential
mDNA	Mithochondrial DNA
nDNA	Nuclear DNA
PAG	Periaqueductal grey matter
PET	Positron emission tomography
rTMS	Repetitive transcranial magnetic stimulation
SSRIs, SNRIs	Serotonin and serotonin-norepinephrine reuptake inhibitors

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tDCS	Transcranial direct current stimulation
TRPA1	Transient receptor potential ankyrin 1
TVS	Trigeminovascular system (TVS)

17.1 Introduction

The definition of a migraine attack as 'nerve-storms' made by Liveing [1] is perhaps, as also pointed out by Oliver Sacks [2], the best metaphor to describe the sequence of symptoms starting 24–48 h before and lasting up to 24 h after the aura and headache phases, which characterizes the overt manifestation of the migraine syndrome. Migraine is indeed a complex of symptoms that can be triggered by diverse factors, amongst which are alcoholic beverages, stress, sleep disturbances and weather conditions [3] including lightning storms [4]. Such triggers are not causes, however, because for a factor to be possibly causal, it must be present also outside of an attack as a predisposing factor.

Genes could cause the fertile ground that predisposes to the recurrence of migraine attacks. The 'holy grail' of migraine genetics has not yet been found, however, probably because the migraine predisposition is not linked to a single gene, but to multiple genetic peculiarities that, taken individually, cause subtle non-pathogenic anomalies, but perturb the brain's equilibrium allowing triggers to ignite an attack, when they occur in combination [5]. Although mutations of single genes are not found in the common forms of migraine, contrary to familial hemiplegic migraines, it is well known that migraine runs in the family with a predominant maternal transmission.

Neurophysiology had the primacy of unraveling for the first time that in migraine the brain has peculiar functional characteristics even between attacks, i.e. when the patient is completely, or almost completely, asymptomatic.

In this book several chapters illustrate how the migraine brain has been explored with virtually all hitherto available neurophysiological methods. Various functional abnormalities were detected not only at the cortical level, as the general clinical hypersensitivity of the migraine could suggest, but also, albeit subtle, at the spinal (Perrotta, Chap. 8; Vollono, Chap. 7; Uglem, Chap. 11), brainstem (Vollono, Chap. 7) and thalamic and thalamocortical levels (Coppola and Pierelli, Chap. 6).

The first conclusion emerging from these studies is, therefore, that there is a global dysfunction of sensory information processing in the nervous system of migraine patients for all sensory modalities, except for the olfactory one (Chen et al., Chap. 2; Coppola and Magis, Chap. 3).

The second neurophysiological hallmark is that most of these abnormalities are reversible, as they are evident outside of a migraine attack, but either improve or sometimes worsen just before, i.e. during the premonitory phase, or during an attack (Sand et al., Chap. 1; Coppola and Magis, Chap. 3, Chen et al., Chap. 2; Coppola

and Pierelli, Chap. 6), possibly accompanied by abnormal sensorimotor integration (Boran et al., Chap. 9). Pharmacological therapies can often contribute to the normalization of cortical activities.

The third distinguishing feature of migraine is that neurophysiological responses are in part different when evoked by noxious or innocuous stimuli, likely because of a central sensitization in pain processing (Coppola and Magis, Chap. 3; de Tommaso et al., Chap. 10). Whether or not these alterations are due to a general deficit in pain inhibition by the endogenous pain control systems both at spinal and brainstem (Vollono, Chap. 7; Perrotta, Chap. 8) and frontal levels (de Tommaso et al., Chap. 10) remains to be determined [6]. Further studies are necessary to determine the causal link between the functional abnormalities during wakefulness and the alterations in quality and structure of sleep detected with polysomnography (Engstrøm and Rains, Chap. 5).

Fourth, although it is commonly postulated that the migraine aura is caused by cortical spreading depression, there is to date only indirect evidence in favor of this phenomenon from neuroimaging and, partly, from neurophysiological studies (Ambrosini and Coppola, Chap. 14).

Fifth, the abnormalities in information processing of painful or innocuous stimuli found in adult migraineurs can also be found in adolescents and even in subjects defined as being 'at risk for migraine' because they are born from parents affected by migraine and hence probably carry a higher genetic load (Coppola et al., Chap. 12; Valeriani and Gazerani, Chap. 15).

Sixth, the recurrence of cephalic pain is associated with cognitive disturbances and leads to behavioural, often ineffective, strategies to avoid pain, which is reflected in abnormalities of neurophysiological responses to cognitive tasks (Mickleborough et al., Chap. 4). In fact, various cognitive dysfunctions have been described in the various phases of the migraine cycle [7–13] and worsen when migraine becomes chronic [14–16].

Seventh, it seems obvious, but cannot be taken for granted, that all these functional alterations can determine transient or lasting plastic changes at the synaptic level (Coppola and Antal, Chap. 13). This can be responsible for changes in synchrony of temporal activation and in functional dynamic connectivity between brain areas and for their modification by sensory stimuli (Sand et al., Chap. 1; Chen et al., Chap. 2; Coppola and Magis, Chap. 3; de Tommaso et al., Chap. 10). These plastic synaptic modifications may be at the basis of the micro- and macro-structural changes of cerebral white and grey matter that have been identified since several years with modern neuroimaging techniques [6].

Eighth, we have only recently gained some insight in the neuroanatomical correlates of the various ictal and interictal dysfunctions, evidenced by neurophysiology. Several recent studies show how the cerebral hyperresponsiveness observed with evoked potentials in migraine is associated with macro-structural changes, abnormal functional connectivity or a mismatch between the increased neural activity and brain energy availability in patients between attacks (Lisicki and Chen, Chap. 16).

17.2 Neurophysiological Model of Migraine Pathophysiology

As evidenced by the numerous neurophysiological studies performed over the migraine cycle, migraine is not a static brain disorder, but instead a disorder with a protean pathophysiological signature that changes depending on the phase of its cycle. It involves the nervous system in many ways and at various sites (see Fig. 17.1).

In a neurophysiological model of migraine pathophysiology, genetic predisposition, due to peculiarities in nuclear (nDNA) and/or mitochondrial (mDNA) DNA, has a pivotal role. As mentioned before, asymptomatic 'at-risk' subjects have the same neurophysiological pattern as interictal migraineurs [17–19]. Moreover, the neurophysiological responses of parents correlate closely with those of their children [20]. In chronic migraine, there is a close relationship between genetic polymorphisms, neurophysiological patterns and acute medication overuse [21, 22]. Unlike in familial hemiplegic migraine, the genetic basis of the aura in the common forms of migraine aura remains elusive; the neurobiological link between the aura and activation of the trigeminovascular system also remains speculative in humans. Interestingly, visually induced electrical and biochemical brain responses as well as neuromuscular junction safety factor differ between patients with strictly visual auras and those with complex neurological auras [23–26].

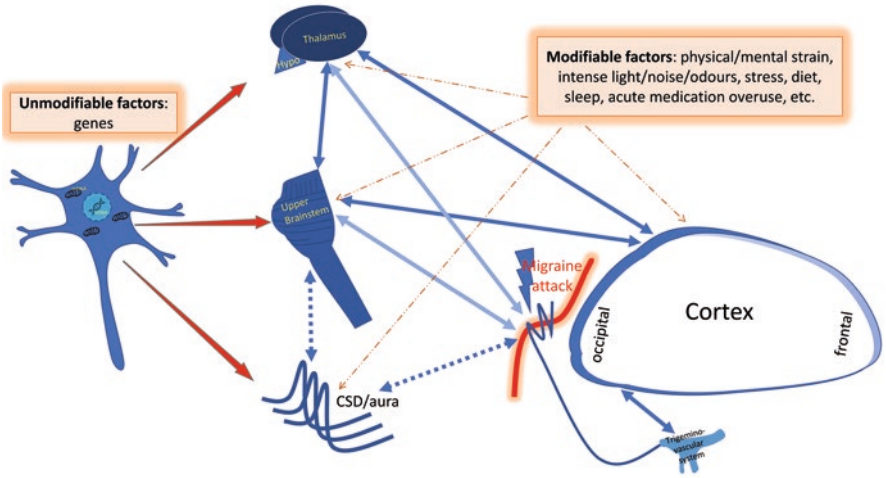

Fig. 17.1 Schematic representation of the pathophysiological model of migraine developed according to the data provided by neurophysiological studies. The figure shows the areas of the nervous system involved, their link (with a continuous line when evident, with a dotted line when only hypothesized) to form a cybernetic system. In the figure are also represented some of the possible non-modifiable and modifiable factors able to disrupt the system and determine the activation of the cerebral visceral alarm system par excellence, the trigeminal-vascular system. The final product is the triggering of a migraine attack, which tries to rebalance the system. In chronic migraine this system never stops being re-balanced because the TVS is always active (daily headache) and reinforced by the central sensitization process. See the text for more explanations

The proteins certain genes code for set the level of excitability of different brain structures. In migraineurs, for instance, they may influence the propensity to develop peripheral and/or central sensitization, they may reduce the efficiency of pain control systems from the frontal lobes to the upper brainstem, or more generally, they may alter the synaptic hyperpolarization/depolarization activity that underlies neuronal plasticity, i.e. learning and memory functions. These are precisely functions that are altered in migraine, such as habituation to sensory stimuli and short- and long-term adaptation processes induced by non-invasive transcranial brain stimulation. The studies analysing high-frequency EEG/EP oscillations indicate that thalamic activation of sensory cortices is abnormal in migraine and thalamocortical afferents are known to be under the tonic control of the brainstem and limbic system. This type of functional alteration is called 'thalamocortical dysrhythmia', which is likely to be responsible for the general hyperresponsiveness of the migraine brain [27].

Unfortunately, clinical neurophysiology methods have provided little information on another diencephalic structure, the hypothalamus, that has received renewed attention during the last 5 years [28]. Modern neuroimaging studies support indeed with reasonable certainty the historical view [29] of the hypothalamus as a cerebral structure playing a crucial role in the periodicity of migraine attacks, its anterior part being more active up to 48 h before an attack during the pre-ictal phase when premonitory symptoms may occur [28, 30, 31]. An abnormal activation of the anterior hypothalamus also appears to be present during chronic migraine [32–34], confirming that chronic migraine could be considered, brain activity-wise, as a never-ending attack [35]. The hypothalamus is anatomically connected to the two most important pain control areas, the one located in the frontal lobes [36] and the one located in the midbrain [28, 37], and therefore has antinociceptive functions [38]. In addition, the neuroendocrine (orexinergic and non-orexinergic) hypothalamic system that is critically involved in coordinating appropriate physiological and behavioural responses to aversive and threatening stimuli [39, 40] like headache may be involved in this pathophysiological model. We speculate that the hypothalamus, together with the trigeminovascular system (TVS), the major alarm system of brain viscera, forms an important neural system designed to maintain brain homoeostasis by regulating homoeostatic needs, such as energy balance, osmoregulation and emotional response [41]. Whether the visual cortex that is also activated preictally in most imaging studies [28, 30, 31] and both directly or indirectly connected with the hypothalamus has a primary or secondary role in initiation of the migraine attack remains to be determined.

The high level of cortical responsivity between attacks of migraine is extremely energy-consuming for the brain [42]. A combined interictal study of VEP and FDG-PET has shown that in the visual cortex of migraineurs neuronal activation by far exceeds glucose uptake, and thus metabolic supply, during visual stimulation [43]. A mismatch between cerebral energy demands and energy reserve can lead to a critical disequilibrium able to activate the hypothalamo-TVS homoeostatic system and to ignite the migraine attack [42]. In a cybernetic system, like the human brain, the ignition of this system, whilst generating the headache and associated symptoms

of an attack, can be considered as the only means to bring the brain back into balance, i.e. to avoid 'rupture' of cerebral homoeostasis. In chronic migraine, this hypothalamo-TVS system in a certain way 'never stops' being active [35]. This is likely favoured by unmodifiable factors, such as the genotypes mentioned above, and persisting, though modifiable, factors, such as behavioural alterations like overuse of symptomatic drugs and biorhythm imbalances, for example, due to insufficient physical activity, forced rupture of circadian rhythms or inadequate dietary habits. All these factors are likely to contribute to an increase in oxidative stress, promote a persistent pro-inflammatory state and alter basal metabolism [44], all contributing in an additive way to unbalance the cerebral cybernetic system and thus increase the propensity for activation of the hypothalamo-TVS system.

17.3 Possible Therapeutic Interventions Based on Neurophysiological Evidence

Various targets for therapeutic intervention in this construct of migraine pathogenesis are schematized in Fig. 17.2.

As mentioned above, migraine affects the nervous system at multiple levels, from the first sensory division of the trigeminal nerve to the cortex, through the brainstem aminergic nuclei (raphe, locus coeruleus), diencephalon, basal forebrain (nucleus basalis) and periaqueductal grey matter (PAG). The subcortical structures seem to play a key role both in the interictal cortical hyperresponsive sensory processing and in attack generation. Not only the brainstem structures but also the diencephalon, hypothalamus and thalamus are actively involved in preparing and starting the migraine attack [31]. Therefore, drugs acting at these CNS sites might mitigate both attacks and subcortico-cortical neurophysiological abnormalities.

There is convincing evidence from neurophysiological and functional imaging studies that central nervous system changes precede the activation of the TVS. Although the pain is most likely generated in the peripheral portion of the TVS, notable via the release of calcitonin gene-related peptide (CGRP) in meningeal sensory afferents [45], neurophysiological signs of peripheral trigeminal sensitization between attacks are scarce and subtle, whilst there is robust evidence of central sensitization (Uglem, Chap. 11). Because of their high molecular weight, the novel anti-migraine monoclonal antibodies blocking CGRP transmission act in principle exclusively in the peripheral portion of the TVS, and yet they have a prophylactic effect. It is of interest in future neurophysiological studies to verify if they exert a pure peripheral effect or are also able to modify central areas involved in migraine pathophysiology, such as the hypothalamus or periventricular organs where the blood-brain barrier is lacking. If the former is the case, the monoclonal CGRP/rec mAbs may act as a long-lasting attack treatment rather than as a genuine preventive treatment supposed to mitigate the interictal central nervous system dysfunctions that may lead to a migraine attack.

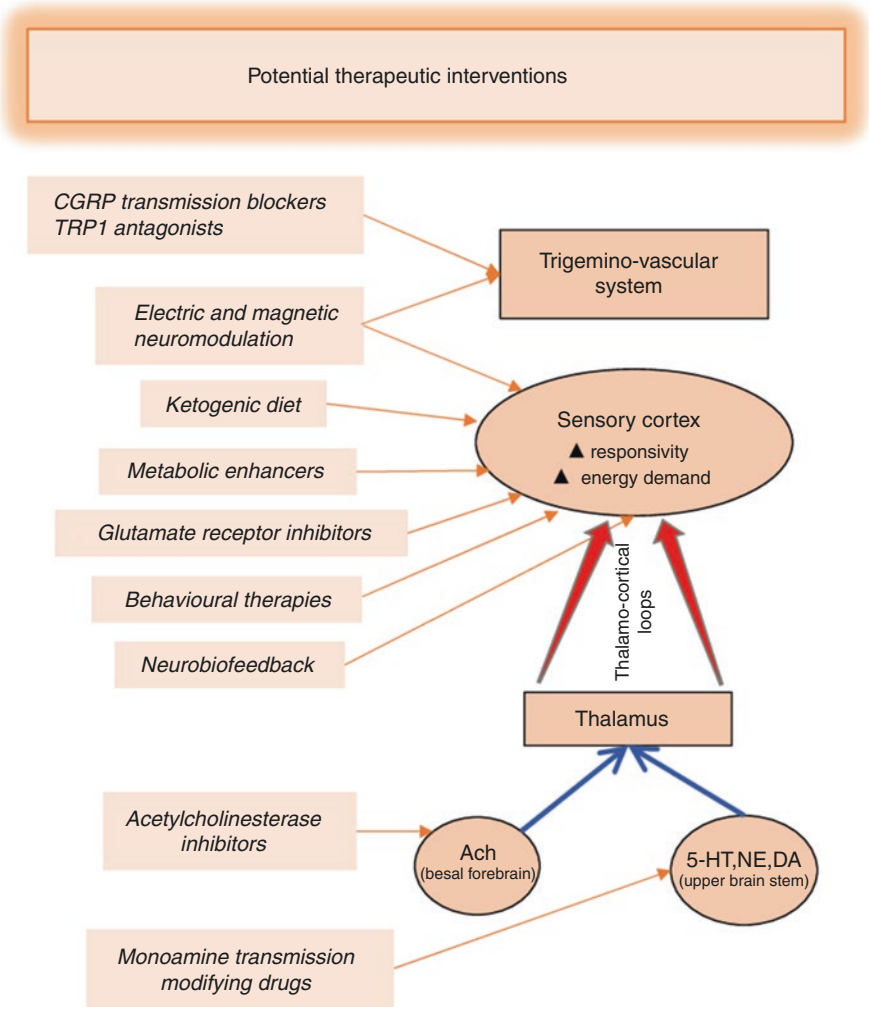

Fig. 17.2 Schematic representation of the brainstem-thalamocortical network and trigeminovascular system thought to be relevant for migraine pathogenesis and the potential therapeutic interventions

A disturbance of the serotonin metabolism has been described in migraine patients [46]. The efficacy of the serotonin transmission-modifying drugs in both the acute and prophylactic treatment of migraine is well accepted.

Amongst the monoamine reuptake inhibitors, a pharmacological class used in migraine prophylaxis, the tricyclic agent amitriptyline is the only with some evidence for efficacy. By contrast, the selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs, SNRIs) have not been found to be consistently effective in migraine, but available information is too scarce to allow any definitive

conclusion. Nevertheless, these agents were shown to have specific effects on cortical responsivity [47, 48], suggesting that more studies in migraine prophylaxis may be worthwhile [49].

Interactions between serotonin and other monoamines, such as acetylcholine, have been described in animal models [50–52], indicating that the serotonergic system could be only one of the possible targets for migraine treatment. As a matter of fact, thalamocortical projections supposed to be dysfunctioning in migraine (Coppola and Pierelli, Chap. 6) are chiefly cholinergic, and in neurophysiological studies acetylcholine (ACh) can influence cortical responsivity in animals [53, 54] and in humans as far as thalamocortical activity [55] or cortical inhibitory functions are concerned [56]. Interestingly, in animals, ACh significantly increases firing in nociceptive afferents of meningeal trigeminal nerves [57] whilst muscarinic receptor activation decreases overall the excitatory/inhibitory ratio and inhibits both initiation and propagation of cortical spreading depression [58]. Nicolodi et al. found in an open-label proof-of-concept study that a 2-month treatment with donepezil, a second-generation acetylcholinesterase inhibitor, reduced the frequency of migraine attacks, cumulative hours with headache and pain severity; its efficacy was superior to that of propranolol [59]. Acetylcholinesterase inhibitors could contribute to stabilize the aminergic innervation of the thalamus and cortex and to inhibit cortical spreading depression. Placebo-controlled trials of acetylcholinesterase inhibitors in migraine prevention are thus worthwhile.

Many neurophysiological [60, 61] and neuroimaging [62–64] studies suggest that the glutamatergic neurotransmission is abnormal in migraine. Genes that are involved in glutamate signaling may be implicated in migraine [65]. Glutamate receptor inhibitors possess antinociceptive properties in animal models of trigeminovascular nociception [66] and hence are promising drugs for acute migraine treatment [67]. There is some evidence in favour of an association between certain glutamate receptor polymorphisms and somatosensory evoked responses in chronic migraine with medication overuse headache [22].

Another path to explore is the metabolic facet of migraine pathophysiology. MR spectroscopy, PET scan and blood studies of glucose and insulin metabolism have established that the mitochondrial energy metabolism is altered in the brain of migraine patients between attacks [68]. This is supported by therapeutic trials of so-called metabolic enhancers (nutraceuticals) acting on the respiratory chain [69] and of ketogenic diet [70]. The latter, besides enhancing mitochondrial metabolism, is able to modulate cortical excitability, as illustrated by the normalization of visual and somatosensory evoked potentials in episodic migraine patients after 1 month of ketogenic diet [71, 72]. Further studies are necessary to determine if the neurophysiological patterns can predict the therapeutic response and if the normalization of cortical evoked responses is due to an enhancement of inhibitory circuits or a reduction in excitatory activity, or to an effect on both.

As mentioned above, external trigger factors likely contribute to an increase in oxidative stress that may promote a persistent pro-inflammatory state and alter the basal energetic metabolism of the migrainous brain [44, 68]. Sensory neurons of the trigeminal nerve express transient receptor potential ankyrin 1 (TRPA1)

cation channels, which are of particular interest in migraine since they sense a large series of reactive by-products of oxidative stress and seem to contribute to the transition from an acute to a chronic pain condition [73]. TRPA1 activators can trigger migraine attacks and analgesic and specific anti-migraine drugs are able to inhibit or desensitize TRPA1 channels. Novel TRPA1 antagonists may represent a new class of drugs to mitigate the oxidative stress response and to treat migraine [74].

For clinical practice, it is of interest that non-pharmacological strategies are able to modulate cortical pre-activation levels and excitability and can be useful in migraine prophylaxis. Contingent negative variation (CNV) biofeedback, a psychophysiological intervention, was effective in treating migrainous children [75]. Although the effect could be related to other factors than the self-regulation, it suggests that further therapeutic trials of neurofeedback are worthwhile in migraine, including adult migraineurs.

Other means to modify activity and metabolism of cortical neurons are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), both of which can induce long-lasting modifications of cortical excitability. These neuromodulatory methods have shown promising results in treating major depression [76, 77]. Unfortunately, despite the great interest in these methods, the results obtained so far in the acute or preventive treatment of migraine are scarce and partly contradictory [78]. Peripheral nerve neurostimulation such as cervical vagus nerve stimulation or external trigeminal neurostimulation can also be effective as adjunctive therapies in migraine [79]. Further studies are needed to determine whether these non-invasive neurostimulation methods are more effective if they are selected and adapted according to the interictal peripheral and cortical neurophysiological profile of migraine patients, as demonstrated in a proof-of-concept study [80] and in other functional brain disorders [81].

17.4 Perspectives on Neurophysiology in Migraine

More than 3000 years passed since the first description by Hippocrates of migraine as a periodic syndrome encompassing aura, hemicranial pain and associated gastrointestinal symptoms: ‘he seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck....vomiting, when it became possible, was able to divert the pain and render it more moderate’ [82]. But only about 150 years have passed since the first recognition of migraine as a paroxysmal brain disorder by Liveing: ‘A form of centrencephalic seizure, the activity of which is projected rostrally upon the cerebral hemi-spheres, and peripherally via the autonomic nervous system’ [29].

The temporal resolution of modern neurophysiological techniques, in combination with the high spatial resolution of modern MRI techniques, has enabled

neuroscientists to make giant strides in understanding the pathophysiology of migraine. Given the progress made since 1959, when Golla and Winter [83] used old-fashioned four-channel EEG to study the brain in migraine, the time is ripe for substantial advances in disentangling its multiple pathophysiological facets. Progress in the next few years will largely depend on a better understanding of the mechanisms underlying cortical hyperresponsivity in migraineurs, of the underpinnings of its variations over the migraine cycle and of its relation with brainstem-thalamocortical rhythms and activity of subcortico-(thalamo-)cortical aminergic pathways. It will also be necessary to disentangle the link between the fluctuations in cortical responsivity and the activation of the hypothalamo-TVS pathway, as well as the link between the latter and the migraine aura. It is of uttermost importance to gather more data on the geno-phenotype correlations in the various migraine forms. Moreover, since migraine has many comorbidities, ranging from psychiatric to chronic pain disorders, it is of fundamental importance to acquire more information on possible electrophysiological links with the various comorbid disorders, jointly with a better clinical characterization of patients. Finally, the link between metabolic factors, cortical spreading depression and TVS activation needs to be clarified, in particular with regard to the possible role of the oxygen/ATP sensing system, involving hypoxia-inducible factor (HIF), and to the role of metalloproteinases able to break down the blood-brain barrier and to allow brain-derived factors accessing the TVS system.

To conclude, given the multiple anatomical and functional peculiarities found in the brain of migraine patients even between attacks, we think it is time to move from the original definition of migraine as ‘non-organic central pain’ by Federigo Sicuteri [84] to that of ‘biobehavioural organic maladaptive central pain’, which incorporates the biological and behavioural aspects of the disorder, as well as the accompanying morpho-functional plastic alterations.

References

1. Liveing E. On megrim: sick-headache, and some allied disorders: a contribution to the pathology of nerve-storms. London: J. and A. Churchill; 1873.
2. Sacks O. Migraine. Berkeley, CA: University of California Press; 1992.
3. Kelman L. The Triggers or precipitants of the acute migraine attack. Cephalalgia. 2007;27:394–402.
4. Martin GV, Houle T, Nicholson R, et al. Lightning and its association with the frequency of headache in migraineurs: an observational cohort study. Cephalalgia. 2013;33:375–83.
5. Di Lorenzo C, Grieco GS, Santorelli FM. Migraine headache: a review of the molecular genetics of a common disorder. J Headache Pain. 2012;13:571–80.
6. Coppola G, Parisi V, Di Renzo A, et al. Cortical pain processing in migraine. J Neural Transm. 2020;127:551–66.
7. Farmer K, Cady R, Bleiberg J, et al. A pilot study to measure cognitive efficiency during migraine. Headache. 2000;40:657–61.
8. Farmer K, Cady R, Bleiberg J, et al. Sumatriptan nasal spray and cognitive function during migraine: results of an open-label study. Headache. 2001;41:377–84.

9. Gil-Gouveia R, Oliveira A, Martins I. Cognitive dysfunction during migraine attacks: a study on migraine without aura. Cephalalgia. 2015;35:662–74.
10. Koppen H, Palm-Meinders I, Kruit M, et al. The impact of a migraine attack and its after-effects on perceptual organization, attention, and working memory. Cephalalgia. 2011;31:1419–27.
11. Le Pira F, Lanaia F, Zappalà G, et al. Relationship between clinical variables and cognitive performances in migraineurs with and without aura. Funct Neurol. 2004;19:101–5.
12. Suhr JA, Seng EK. Neuropsychological functioning in migraine: clinical and research implications. Cephalalgia. 2012;32:39–54.
13. Yetkin-Ozden S, Ekizoglu E, Baykan B. Face recognition in patients with migraine. Pain Pract. 2015;15:319–22.
14. Santos-Lasaosa S, Viloria-Alebesque A, Morandeira-Rivas C, et al. Mnemonic complaints and chronic migraine. Rev Neurol. 2013;57:145–9.
15. Ferreira KS, Teixeira CT, Cáfaro C, et al. Chronic migraine patients show cognitive impairment in an extended neuropsychological assessment. Arq Neuropsiquiatr. 2018;76:582–7.
16. Gómez-Beldarrain M, Anton-Ladislao A, Aguirre-Larracoechea U, et al. Low cognitive reserve is associated with chronic migraine with medication overuse and poor quality of life. Cephalalgia. 2015;35:683–91.
17. Siniatchkin M, Kropp P, Gerber WD. Contingent negative variation in subjects at risk for migraine without aura. Pain. 2001;94:159–67.
18. Di Clemente L, Coppola G, Magis D, et al. Interictal habituation deficit of the nociceptive blink reflex: an endophenotypic marker for presymptomatic migraine? Brain. 2007;130:765–70.
19. Lisicki M, Ruiz-Romagnoli E, D'Ostilio K, et al. Familial history of migraine influences habituation of visual evoked potentials. Cephalalgia. 2017;37:1082–7.
20. Sándor PS, Afra J, Proietti-Cecchini A, et al. Familial influences on cortical evoked potentials in migraine. Neuroreport. 1999;10:1235–8.
21. Di Lorenzo C, Coppola G, Currà A, et al. Cortical response to somatosensory stimulation in medication overuse headache patients is influenced by angiotensin converting enzyme (ACE) I/D genetic polymorphism. Cephalalgia. 2012;32:1189–97.
22. Di Lorenzo C, Coppola G, Grieco G, et al. O041. GRIA3 (glutamate receptor, ionotropic, ampa 3) gene polymorphism influences cortical response to somatosensory stimulation in medication-overuse headache (MOH) patients. J Headache Pain. 2015;16:A49.
23. Ambrosini A, Maertens de Noordhout A, Schoenen J. Neuromuscular transmission in migraine: a single-fiber EMG study in clinical subgroups. Neurology. 2001;56:1038–43.
24. Ambrosini A, de Noordhout AM, Schoenen J. Neuromuscular transmission in migraine patients with prolonged aura. Acta Neurol Belg. 2001;101:166–70.
25. Sándor P, Dydak U, Schoenen J, et al. MR-spectroscopic imaging during visual stimulation in subgroups of migraine with aura. Cephalalgia. 2005;25:507–18.
26. Coppola G, Bracaglia M, Di Lenola D, et al. Visual evoked potentials in subgroups of migraine with aura patients. J Headache Pain. 2015;16:92.
27. Coppola G, Ambrosini A, Di Clemente L, et al. Interictal abnormalities of gamma band activity in visual evoked responses in migraine: an indication of thalamocortical dysrhythmia? Cephalalgia. 2007;27:1360–7.
28. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain. 2016;139:1987–93.
29. Pearce JMS. Migraine: a cerebral disorder. Lancet. 1984;324:86–9.
30. Maniyar F, Sprenger T, Monteith T, et al. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 2014;137:232–41.
31. Schulte LH, Mehnert J, May A. Longitudinal neuroimaging over 30 days: temporal characteristics of migraine. Ann Neurol. 2020;87:646–51.
32. Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine. Neurology. 2017;88:2011–6.
33. Lerebours F, Boulanouar K, Barège M, et al. Functional connectivity of hypothalamus in chronic migraine with medication overuse. Cephalalgia. 2019;39:892–9.

34. Coppola G, Di Renzo A, Petolicchio B, et al. Increased neural connectivity between the hypothalamus and cortical resting-state functional networks in chronic migraine. J Neurol. 2020;267:185–91.
35. Schoenen J. Is chronic migraine a never-ending migraine attack? Pain. 2011;152:239–40.
36. Jin J, Chen Q, Qiao Q, et al. Orexin neurons in the lateral hypothalamus project to the medial prefrontal cortex with a rostro-caudal gradient. Neurosci Lett. 2016;621:9–14.
37. Malick A, Strassman RM, Burstein R. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. J Neurophysiol. 2000;84:2078–112.
38. Razavi BM, Hosseinzadeh H. A review of the role of orexin system in pain modulation. Biomed Pharmacother. 2017;90:187–93.
39. James MH, Campbell EJ, Dayas CV. Role of the orexin/hypocretin system in stress-related psychiatric disorders. In: Geyer MA, et al., editors. Current topics in behavioral neurosciences. New York, NY: Springer; 2017. p. 197–219.
40. Grafe LA, Eacret D, Luz S, et al. Orexin 2 receptor regulation of the hypothalamic–pituitary–adrenal (HPA) response to acute and repeated stress. Neuroscience. 2017;348:313–23.
41. Matthews GA, Tye KM. Neural mechanisms of social homeostasis. Ann N Y Acad Sci. 2019;1457:5–25.
42. Schoenen J. Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behavior and trigeminovascular activation? Biomed Pharmacother. 1996;50:71–8.
43. Lisicki M, D'Ostilio K, Coppola G, et al. Evidence of an increased neuronal activation-to-resting glucose uptake ratio in the visual cortex of migraine patients: a study comparing 18FDG-PET and visual evoked potentials. J Headache Pain. 2018;19:49.
44. Borkum JM. Migraine triggers and oxidative stress: a narrative review and synthesis. Headache. 2016;56:12–35.
45. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. Cephalalgia. 2019;39:366–73.
46. Hamel E. Serotonin and migraine: biology and clinical implications. Cephalalgia. 2007;27:1293–300.
47. Nyrke T, Kangasniemi P, Lang AH, et al. Steady-state visual evoked potentials during migraine prophylaxis by propranolol and femoxetine. Acta Neurol Scand. 1984;69:9–14.
48. Ozkul Y, Bozlar S. Effects of fluoxetine on habituation of pattern reversal visually evoked potentials in migraine prophylaxis. Headache. 2002;42:582–7.
49. Wang F, Wang J, Cao Y, et al. Serotonin-norepinephrine reuptake inhibitors for the prevention of migraine and vestibular migraine: a systematic review and meta-analysis. Reg Anesth Pain Med. 2020;45:323–30.
50. Bianchi C, Siniscalchi A, Beani L. 5-HT(1A) agonists increase and 5-HT3 agonists decrease acetylcholine efflux from the cerebral cortex of freely-moving guinea-pigs. Br J Pharmacol. 1990;101:448–52.
51. Obata H, Saito S, Sasaki M, et al. Interactions of 5-HT2 receptor agonists with acetylcholine in spinal analgesic mechanisms in rats with neuropathic pain. Brain Res. 2003;965:114–20.
52. Ghelardini C, Galeotti N, Figini M, et al. The central cholinergic system has a role in the antinociception induced in rodents and guinea pigs by the antimigraine drug sumatriptan. J Pharmacol Exp Ther. 1996;279:884–90.
53. Carlton PL. Cholinergic mechanisms in the control of behavior by the brain. Psychol Rev. 1963;70:19–39.
54. Puigbò JY, Maffei G, Herreros I, et al. Cholinergic behavior state-dependent mechanisms of neocortical gain control: a neurocomputational study. Mol Neurobiol. 2018;55:249–57.
55. Restuccia D, Della Marca G, Valeriani M, et al. Influence of cholinergic circuitries in generation of high-frequency somatosensory evoked potentials. Clin Neurophysiol. 2003;114:1538–48.
56. Di Lazzaro V, Oliviero A, Pilato F, et al. Neurophysiological predictors of long term response to AChE inhibitors in AD patients. J Neurol Neurosurg Psychiatry. 2005;76:1064–9.
57. Shelukhina I, Mikhailov N, Abushik P, et al. Cholinergic nociceptive mechanisms in rat meninges and trigeminal ganglia: potential implications for migraine pain. Front Neurol. 2017;8:163.

58. Zerimech S, Chever O, Scalmani P, et al. Cholinergic modulation inhibits cortical spreading depression in mouse neocortex through activation of muscarinic receptors and decreased excitatory/inhibitory drive. Neuropharmacology. 2020;166:107951.
59. Nicolodi M, Galeotti N, Ghelardini C, et al. Central cholinergic challenging of migraine by testing second-generation anticholinesterase drugs. Headache. 2002;42:596–602.
60. Coppola G, Vandenheede M, Di Clemente L, et al. Somatosensory evoked high-frequency oscillations reflecting thalamo-cortical activity are decreased in migraine patients between attacks. Brain. 2005;128:98–103.
61. Cosentino G, Fierro B, Vigneri S, et al. Impaired glutamatergic neurotransmission in migraine with aura? Evidence by an input-output curves transcranial magnetic stimulation study. Headache. 2011;51:726–33.
62. Zielman R, Wijnen JP, Webb A, et al. Cortical glutamate in migraine. Brain. 2017;140:1859–71.
63. Niddam DM, Lai KL, Tsai SY, et al. Neurochemical changes in the medial wall of the brain in chronic migraine. Brain. 2018;141:377–90.
64. Niddam DM, Lai KL, Tsai SY, et al. Brain metabolites in chronic migraine patients with medication overuse headache. Cephalalgia. 2020; https://doi.org/10.1177/0333102420908579.
65. Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 2016;48:856–66.
66. Ferrari A, Rustichelli C, Baraldi C. Glutamate receptor antagonists with the potential for migraine treatment. Expert Opin Investig Drugs. 2017;26:1321–30.
67. Chan K, MaassenVanDenBrink A. Glutamate receptor antagonists in the management of migraine. Drugs. 2014;74:1165–76.
68. Gross EC, Lisicki M, Fischer D, et al. The metabolic face of migraine—from pathophysiology to treatment. Nat Rev Neurol. 2019;15:627–43.
69. Lisicki M, Schoenen J. Metabolic treatments of migraine. Expert Rev Neurother. 2020;20:295–302.
70. Di Lorenzo C, Pinto A, Ienca R, et al. A randomized double-blind, cross-over trial of very low-calorie diet in overweight migraine patients: a possible role for ketones? Nutrients. 2019;11:1742.
71. Di Lorenzo C, Coppola G, Bracaglia M, et al. A ketogenic diet normalizes interictal cortical but not subcortical responsivity in migraineurs. BMC Neurol. 2019;19:136.
72. Di Lorenzo C, Coppola G, Bracaglia M, et al. Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet in migraine: a multimodal evoked potentials study. J Headache Pain. 2016;17:58.
73. Nassini R, Materazzi S, Benemei S, et al. The TRPA1 channel in inflammatory and neuropathic pain and migraine. Rev Physiol Biochem Pharmacol. 2014;167:1–44.
74. Benemei S, Fusi C, Trevisan G, et al. The TRPA1 channel in migraine mechanism and treatment. Br J Pharmacol. 2014;171:2552–67.
75. Siniatchkin M, Kropp P, Gerber WD. Neurofeedback—the significance of reinforcement and the search for an appropriate strategy for the success of self-regulation. Appl Psychophysiol Biofeedback. 2000;25:167–75.
76. McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018;79:35–48.
77. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128:56–92.
78. Schoenen J, Baschi R, Magis D, et al. Noninvasive neurostimulation methods for migraine therapy: the available evidence. Cephalalgia. 2016;36:1170–80.
79. Ambrosini A, D'Alessio C, Magis D, et al. Targeting pericranial nerve branches to treat migraine: current approaches and perspectives. Cephalalgia. 2015;35:1308–22.
80. Viganò A, D'Elia TS, Sava SL, et al. Transcranial direct current stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. J Headache Pain. 2013;14:23.

81. Khayyer Z, Ngaosuvan L, Sikström S, et al. Transcranial direct current stimulation based on quantitative electroencephalogram combining positive psychotherapy for major depression. J Integr Neurosci. 2018;17:89–96.
82. Pearce JMS. Historical aspects of migraine. J Neurol Neurosurg Psychiatry. 1986;49:1097–103.
83. Golla FL, Winter AL. Analysis of cerebral responses to flicker in patients complaining of episodic headache. Electroencephalogr Clin Neurophysiol. 1959;11:539–49.
84. Sicuteri F, Anselmi B, Del Bianco PL. Systemic non-organic central pain: a new syndrome with decentralization supersensitivity. Headache. 1978;18:133–6.