



Cortical pain processing in migraine

Gianluca Coppola¹ · Vincenzo Parisi² · Antonio Di Renzo² · Francesco Pierelli^{1,3}

Received: 30 July 2019 / Accepted: 28 September 2019
© Springer-Verlag GmbH Austria, part of Springer Nature 2019

Abstract

Among painful disorders, migraine is distinguishable by its chronic pathology and episodic clinical manifestation. Only a small percentage of patients with migraine progress to a chronic form of migraine. Both peripheral and central portions of the trigeminal system are involved in the pathophysiology of migraine pain, as they are involved in the processes of peripheral and central sensitization, alongside various subcortical and cortical brain structures. This review focuses on clinical, neurophysiological, and neuroimaging data underscoring cortical pain processing in migraine. Data obtained from quantitative sensory testings are inconclusive and support the involvement of the peripheral portion of the trigeminovascular system as indirect evidence of peripheral sensitization, solely during the headache phase. The assessment of subjective pain intensity in response to several painful modalities has not been conclusive for the clear state of central sensitization in between migraine attacks but for the subclinical allodynia state that defines the boundary between behavioural responses and an irritable nervous state. Modulation of the brainstem and midbrain pain pathways, in conjunction with the thalamic and thalamocortical pathways, may be critical for the initiation and maintenance of migraine attacks. Several studies using different neuroimaging techniques have demonstrated that brains experiencing migraine undergo plastic changes in both microstructure and macrostructure and in the functioning of cortical networks, which may manifest early in the life of a patient with migraine. Further studies are required to understand how specific these results are to migraine relative to other painful disorders.

Keywords Pain · Migraine · Chronic · Neurophysiology · Neuroimaging · Quantitative sensory testing · Trigeminal system · Brainstem · Thalamus · Cortex

Introduction

According to the Global Burden of Disease Study, migraine is one of the four major leading causes of disability worldwide (Feigin et al. 2019). Among the various painful pathologies, migraine is distinguishable due to its chronic pathology and episodic manifestation. Annually, only 1–3% of the migraine population evolves from an episodic to a chronic form of this disease (Scher et al. 2003), i.e., headaches occur on at least 15 days a month for at least 3 months, with at least 8 headache days with evident migraine characteristics. The initially high headache frequency and the excessive use of

acute medication are major risk factors of migraine chronicity (Katsarava et al. 2004).

Several advances have been made in recent years in understanding the pathogenesis of migraine. Migraine is familial, suggesting a genetic vulnerability termed the “migraine threshold”, which is capable of determining brain characteristics that distinguish the brain of the migraineur from that of a non-migraineur (Sándor et al. 2002). Over the years, non-invasive neurophysiological techniques have revealed that the migraine brain is characterized by altered cortical responsiveness, malfunctioning of the mechanisms of pain control, and altered cortical pain processing (Coppola et al. 2013a). These functional properties of the brain are observed, especially during the pain-free phase, and are the underlying properties that, in the presence of exogenous or endogenous factors, can lead to the triggering of a migraine attack (de Tommaso et al. 2014). Due to advances in structural and functional neuroimaging techniques enabling the investigation of brain anatomy and function, substantial progress has been made in understanding

✉ Gianluca Coppola
gianluca.coppola@uniroma1.it

¹ Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Corso della Repubblica 79, 04100 Latina, Italy

² IRCCS-Fondazione Bietti, Rome, Italy

³ IRCCS-Neuromed, Pozzilli, IS, Italy

pain processing in patients who are affected by migraine (Sprengr and Borsook 2012).

This review focuses on clinical, neurophysiological, and neuroimaging data that provide information on cortical pain processing in migraine under the scope of providing a deeper understanding of how migraine affects the brain.

Peripheral sensitization in migraine

For migraine pain to occur, the involvement of the peripheral portion of trigeminal nociceptors in the dural and pial arteries and arterioles is necessary. This process involves the initiation of localized neuronal inflammation, involving leukocyte recruitment and mast cell degranulation. Factors that trigger this involvement have not been elucidated. This process can be apparent, in migraine with aura, or silent, in migraine without aura. Cortical spreading depression (CSD), the most likely culprit underscoring migraine aura, involves a wave of initial excitation and late depression of electrocortical activity that has been shown to open pannexin-1 megachannels in neurons exposed to stress (Karatas et al. 2013) and to activate the trigeminal system in animal models favouring release of vasoactive neuropeptides, like calcitonin gene-related peptide (CGRP), that promote neurogenic inflammation (Bolat et al. 2002). Nevertheless, whether and how CSD relates to the induction of migraine headaches remain a matter of debate. Although progression and pace of aura symptoms in the visual field and cortical retinotopic map suggest this, direct evidence that CSD causes aura symptoms in patients is scarce (Hadjikhani et al. 2001). For others, the involvement of the trigeminal nociceptive system is determined by the brainstem, the site of monoaminergic (adrenergic, cholinergic, serotonergic, and histaminergic) systems (Edvinsson et al. 1983; Bonvento et al. 1990) which along with the periaqueductal grey (PAG) inhibit pain in a descending manner. The brainstem also directly or indirectly regulates the degree of cortical activation via the thalamus (Mesulam 1990) and modulates neurovascular coupling, thus regulating blood flow and vascular permeability (Goadsby et al. 1982). This is important for CSD initiation and peripheral sensitization, which, in turn, may initiate a migraine attack (Goadsby and Akerman 2012). Some researchers have argued that when meningeal nociceptive receptors are sensitized, they become responsive to imperceptible rhythmic fluctuations in intracranial pressure (pulsation) produced by normal arterial pulsation. This mechanical hypersensitivity may mediate the pulsating quality of headaches and associated worsening during coughing, bending, or other physical activities that increase intracranial pressure (Burstein et al. 2004). Interestingly, in a neurophysiological study in a single chronic migraineur experiencing throbbing sensations even after headache resolution, researchers demonstrated a high

association between the overall amount of alpha range EEG activity/power and its modulation by throbbing intensity and rhythm, thus proving a potential central neural signature of pain quality (Mo et al. 2013). Despite the latter, several studies have attempted to verify direct or indirect signs of peripheral sensitization in migraineurs.

Various studies have used quantitative sensory testing to assess pain perception in various phases of the migraine cycle. Comparing the ictal to the interictal phase in episodic and chronic migraine patients, it has been observed that the pain threshold (PT) to mechanical and cold stimuli was reduced ipsilateral to the headache side (forehead) at the very beginning of an attack, spreading contralaterally and even extracephalically (forearm) during the delayed headache phase (Burstein et al. 2000a, b). Recently, with the scope of identifying signs of localized neural inflammation, researchers have applied ultrasmall superparamagnetic particles of iron oxide-enhanced 3 T MRI—a macrophage biomarker—to investigate the walls of cerebral arteries, dura mater, and regions of interest within the brain parenchyma of migraineurs during provoked attacks, revealing the absence of signs of localized macrophage-mediated neural inflammation. In animal models, this activates the perivascular trigeminal nociceptors that densely innervate the dural and cerebral arteries (Khan et al. 2019). These findings refute the idea that sterile inflammation of the walls of cerebral arteries and brain parenchyma plays a role in migraine pathophysiology.

Decreased cold PT over the forehead during the headache phase was confirmed by another independent group, and it was unrelated to the aura and headache side (Sand et al. 2008a; Uglem et al. 2017a). Contradictory results were obtained with regards to the preictal phase of migraines, when both lower—compared to the interictal phase—(Sand et al. 2008a) and normal (Engstrøm et al. 2013; Uglem et al. 2017a) PT values were reported. However, the authors do not rule out the possibility that PTs may decrease significantly when patients are tested close to an attack (Schwedt et al. 2015; Uglem et al. 2017a).

Most studies have been performed during the intercritical period of migraines. Their findings are contradictory and inconclusive, as both lower (Schoenen et al. 1991; Sandrini et al. 2002; Fernández-de-las-Peñas et al. 2008, 2009, 2010; Schwedt et al. 2011, 2015; Zappaterra et al. 2011; Grossi et al. 2011; Engstrøm et al. 2013; Florencio et al. 2015; Palacios-Ceña et al. 2016)—mostly to mechanical or thermal painful stimuli—and normal (Bovim 1992; Göbel et al. 1992; Bishop et al. 2001; Weissman-Fogel 2003; Katsarava et al. 2003; Ayzenberg et al. 2006; Buchgreitz et al. 2006, 2008; Coppola et al. 2007; Sand et al. 2008a; Gierse-Plogmeier et al. 2009; Perrotta et al. 2010; Teepker et al. 2011; Beese et al. 2015; de Tommaso et al. 2015) PT values between migraineurs and healthy controls were observed.

The results obtained by studying adolescents are also contradictory, since either a significant reduction (Zohsel et al. 2006; Ferracini et al. 2014; de Tommaso et al. 2016) or no difference (Anttila et al. 2002; Metsahonkala et al. 2006; Nahman-Averbuch et al. 2019) in the PT was observed during the intercritical period when compared to healthy subjects. Normal pressure and cold PTs were observed in elderly migraine patients in one study (Uthakhpur et al. 2009). Even when episodic migraine becomes chronic, uncertainty about the PT value remains, since both normal or significantly reduced mechanical, thermal, and electrical PTs (Cooke et al. 2007; Perrotta et al. 2010; Schwedt et al. 2011; Zappaterra et al. 2011; Grossi et al. 2011; Palacios-Ceña et al. 2016) have been detected.

Overall, PT data obtained from episodic and chronic migraine in adolescents, adults, and elderly patients are inconclusive. These data support the involvement of the peripheral portion of the trigeminovascular system solely during the headache phase.

Central sensitization in migraine

Direct (via tissue injury) or indirect (via sterile or neurogenic inflammation) involvement of peripheral trigeminal nerve endings can trigger a long-lasting increase in the excitability of spinal cord neurons, profoundly changing the gain of the somatosensory system and leading to pain hypersensitivity. Overall, this transient or persistent brain state is termed “central sensitization” and refers to an enhancement in cortical excitability responsible for plastic adaptive changes in the “salient network” (previously known as the “pain neuromatrix”) (Iannetti and Mouraux 2010). It results in decreased nociceptive thresholds and increased responsiveness to noxious and innocuous peripheral stimuli, i.e., increased subjective perception of pain intensity (PPI) and expansion of the receptive fields of central nociceptors (Woolf 2011). According to this definition, the reduction in painful thresholds observed during a migraine attack can also be part of the clinical manifestation of a central sensitization process.

Compared to the interictal period, increased subjective PPI with frank cutaneous allodynia was described during the early and late phases of migraine in two studies by the same research group, which was further decreased in both the ipsilateral and contralateral forehead, as well as the ipsilateral forearm (Burstein et al. 2000a, b). When other researchers followed the various phases of the migraine cycle, they discovered an inverse ‘U’-shaped pattern in subjectively judging PPI: a progressive linear increase of subjective PPI during the pain-free period, an abrupt decrease during the prodromal phase, and a further increase during the headache and post-headache phase (Uglen et al. 2017a, b).

Another way to judge subjective PPI is to verify the threshold of pain perception in response to a painful CO₂ laser or contact heat stimulus and record the resulting cortical response, termed pain-related evoked potentials (PREPs). Using a CO₂ laser as test stimulation source decreased basic PTs and increased cortical amplitudes during spontaneous or experimentally induced migraine attacks in the bilateral cephalic (supraorbital) and extra-cephalic (hand) areas ipsilateral to the headache side compared to those in the interictal phase (de Tommaso et al. 2002, 2004a, b 2005e). These effects were still present 2 h after intake of either almotriptan or lysine acetylsalicylate, although treatment provided relief from headaches (de Tommaso et al. 2005e). It is interesting to note that this neurophysiological behaviour closely mimics the activation pattern of the brainstem in neuroimaging, as it increases during an attack and remains elevated even after pain relief induced by injection of sumatriptan (Weiller et al. 1995). It is well known that nociceptive afferents, regardless of origin (cephalic or extracephalic), are able to activate brainstem nuclei that play a relevant role in mediating and maintaining central sensitization (Zambreanu et al. 2005; Lee et al. 2008).

With the exception of a few studies (de Tommaso et al. 2015; Vecchio et al. 2016), the vast majority of articles in which PPI are studied in response to contact heat irritating gaseous ammonia (Moulton et al. 2008, 2011; Stanke-witz et al. 2011, 2013; Russo et al. 2012a, 2017a; Schwedt et al. 2014), or laser (de Tommaso et al. 2005f, 2007; Di Clemente et al. 2013) stimulations do not report significant differences between migraineurs during the pain-free phase and healthy subjects. No differences in PPI were detected even after distracting tasks (de Tommaso et al. 2005f, 2008), after central (de Tommaso et al. 2010; Vecchio et al. 2016) or peripheral neuromodulation (Vecchio et al. 2018a, b), and during the premenstrual phase of the hormonal cycle (de Tommaso et al. 2009).

Nevertheless, using paradigms specifically designed to emphasize central sensitization processes such as the administration of capsaicin and the wind-up phenomenon, some authors have observed an increase in subjective values of PPI in response to both laser (de Tommaso et al. 2005c, 2007) and mechanical, electrical, or thermal stimuli, especially in patients with higher attack frequency (Weissman-Fogel 2003; Gierse-Plogmeier et al. 2009; Perrotta et al. 2010).

Overall, the assessments of subjective PPI in response to several painful modalities are not conclusive for a clear state of central sensitization in between migraine attacks but rather for a subclinical allodynia state that is at the boundary between behavioural responses and irritable nervous state.

Descending pain control systems in migraine

The application of heterotopic pain-conditioning stimulation is a well established and validated *in vivo* model for studying conditioned pain modulation. The latter is mediated by aminergic and opioidergic signalling in the brainstem (PAG) and prefrontal cortical structures. Many studies on migraine have reported defective conditioning of sensory noxious and innocuous responses by endogenous pain control (de Tommaso et al. 2007; Coppola et al. 2010b; Nahman-Averbuch et al. 2013, 2019; Fabjan et al. 2014; Guy et al. 2018; Kislser et al. 2018; Williams et al. 2019; Bogdanov et al. 2019), with one exception (Teepker et al. 2014). Altered turnover of monoamines, opioids, or acetylcholine released by brainstem nuclei may underlie aberrant central pain modulation in migraine, as suggested by several seminal pharmacological studies (Sicuteri 1976; Mascia et al. 1998; Leone et al. 2000; Nicolodi et al. 2002; Hamel 2007). Some of these neurotransmitter abnormalities are corroborated by both neuroimaging and neurophysiological methods. PET studies using radio-labelled 5-hydroxytryptamine (5-HT) receptor ligands or the 5-HT precursor tryptophan disclosed various abnormalities in migraine patients, including normalization of increased 5-HT synthesis after sumatriptan administration (Sakai et al. 2008), increased 5-HT_{1A} receptor availability in pontine nuclei (Demarquay et al. 2011) during an attack, and decreased 5-HT_{1B} receptor binding in various cortical areas involved in pain processing between attacks (Deen et al. 2018). In the latter study, the authors also found a positive correlation between time evolved since the last attack and 5-HT_{1B} receptor density in the dorsal raphe and midbrain, presumably related to downregulation of these receptors during the attack in response to increased brain serotonin. Nonetheless, reduced neuronal density and increased iron deposition within midbrain areas, including the dorsolateral pons and PAG, were observed during migraine (Welch et al. 2001; Marciszewski et al. 2018b; Domínguez et al. 2019), with fluctuations depending on the migraine cycle (Meylakh et al. 2018; Marciszewski et al. 2018a). Using diffusion tensor imaging (DTI), a recent study has reported that immediately prior to an attack, mean diffusivity decreased in the spinal trigeminal nucleus, dorsomedial/dorsolateral pons, and midbrain periaqueductal grey matter/nucleus cuneiform, and increased again immediately following the migraine attack (Marciszewski et al. 2019). Migraineurs showed age-related metabolic changes in the brainstem (especially the posterior pons) and other areas associated with learning and memory (hippocampus, fusiform gyrus, and parahippocampus) unrelated to disease duration or migraine days (Lisicki et al. 2019).

Malfunctioning subcortical control of neural processing in the cerebral cortex is thought to be responsible for

the functional cortical abnormalities frequently observed interictally in migraine. Lack of habituation to repetitive stimuli in brainstem auditory-evoked potentials (Sand et al. 2008b) and event-related cognitive potentials (Evers et al. 1999) was found to be related to platelet serotonin content during the migraine cycle. The intensity dependence of auditory-evoked potentials, which is inversely related to synaptically released serotonin in the central nervous system (CNS) (Wutzler et al. 2008), was reported to be stronger in interictal migraine compared to that in healthy controls (Wang et al. 1996; Ambrosini et al. 2003). Reduced brainstem activation in migraine may cause a lower interictal thalamic/thalamocortical drive, as recently confirmed by analysis of high-frequency oscillatory activities in multichannel somatosensory-evoked potentials (Porcaro et al. 2017). Moreover, like that for the brainstem, reduced thalamic control of cortical processing may also contribute to both lack of sensory habituation (Coppola et al. 2012) and paradoxical responses obtained after non-invasive brain neuromodulation, such as increased or decreased responses to inhibiting or activating transcranial magnetic stimulation, respectively (Brighina et al. 2005, 2011; Pierelli et al. 2013). Altered thalamic control in migraine may contribute to abnormal connectivity patterns between cerebral networks, as recently shown with structural and functional MRI connectivity studies during (Coppola et al. 2016b; Amin et al. 2018) and between (Wang et al. 2016; Coppola et al. 2016c) attacks. These abnormalities may be due to subtle plastic morphofunctional changes within thalamic nuclei in migraine between attacks (Coppola et al. 2014; Magon et al. 2015; Hodkinson et al. 2016b) that seem to be dependent on the time point at which patients are recorded during the migraine cycle (Coppola et al. 2014). The dependence of morphological and functional patterns of migrainous brain change on attack occurrence, time point during the interictal period, and migraine chronification was previously illustrated with neurophysiological (Kropp and Gerber 1998; Judit et al. 2000; Siniatchkin et al. 2000; Katsarava et al. 2003; Coppola et al. 2010a, 2013b, c, 2016a; Mehnert et al. 2019), psychophysiological (Shepherd et al. 2011; Nguyen et al. 2014), and neuroimaging methods (Moulton et al. 2011; Stankewitz et al. 2011, 2013; Coppola et al. 2015, 2016b, c; Deen et al. 2018). Aberrant functional activity in subcortical structures may be also the source of origin of some migraine accompanying symptoms. For instance, malfunctioning structures located within the brainstem may be the source of origin of phonophobia (medial olivocochlear system) (Joffily et al. 2016), photophobia (caudal trigeminal brainstem) (Okamoto et al. 2009), and osmophobia (rostral part of the pons) (Stankewitz and May 2011). Even an abnormal filtering of relevant sensory information at the level of different thalamic

nuclei seems to play a major role in determining some of the symptoms that accompany and sometimes precede a migraine attack, such as photophobia (pulvinar) (Noseda et al. 2010), extracephalic allodynia (several, mostly posterior thalamic nuclei) (Burstein et al. 2010), and vestibular symptoms (mediodorsal thalamic complex) (Russo et al. 2014). Whether CGRP released prior and during migraine attacks exerts in patients the same central and peripheral actions that cause migraine-like light aversion in animal models remains to be determined (Mason et al. 2017).

Unlike innocuous cortical-evoked responses, PREP amplitudes do not decrease in response to repetitive presentation of noxious stimuli irrespective of the phase of the migraine cycle, being deficient between (Valeriani et al. 2003; de Tommaso et al. 2005a) or during attacks (de Tommaso et al. 2005b), and even when migraines become chronic (Ferraro et al. 2012). This is probably because noxious stimuli are considered potentially threatening to the CNS, such that clear mechanisms of habituation are lacking. By contrast, they trigger cortical inhibitory antinociceptive systems that reduce the response amplitude, a mechanism that is dysfunctional in migraine. This hypothesis is supported by functional MRI studies in which decreased activity to thermal stimuli over time is accompanied by increased BOLD activity in the subgenual anterior cingulate cortex (Bingel et al. 2007), which is able to induce analgesia, since it plays a major role in the central descending opioidergic pain control system (Casey et al. 2000). Nonetheless, monoaminergic systems may also play a role in decreasing/increasing behavioural responses to pain, as blocking post-synaptic dopamine D2 receptors of the mesolimbic system with haloperidol increased, rather than decreased, cortical responses to consecutive painful electrical stimulations (Bauch et al. 2017).

Overall, modulation of brainstem and midbrain pain pathways, in synergy with thalamic and thalamocortical pathways, may be one of the critical factors for the initiation and maintenance of migraine attacks and its accompanied symptomatology.

Cerebral plastic changes related to migraine

As part of the central sensitization process, the cortical topographical representation of pain, elicited using laser stimuli, changes plastically in both episodic (de Tommaso et al. 2004a) and chronic (de Tommaso et al. 2005d) migraineurs compared to that in healthy subjects.

Neuroimaging techniques are increasingly used today to assess plastic changes in the brain in response to the more or less frequent occurrence of migraine pain.

Several studies were performed in episodic migraine patients between attacks using functional MRI in response

to noxious stimuli delivered over trigeminal or extratrigeminal areas. Overall, they demonstrated an increased BOLD response in brain areas involved in nociception/antinociception, affective, and cognitive features related to pain processing (insula, middle cingulate and anterior cingulate [ACC] cortices, secondary somatosensory cortex, amygdala, cerebellum, caudate nuclei, motor and premotor areas, temporal pole, lentiform nuclei, posterior thalamus, fusiform gyrus, subthalamic nucleus, hypothalamus, pre- and post-central gyrus, visual areas, hippocampus, parahippocampal gyrus, dorsolateral prefrontal cortex [DLPFC], and perigenual part of the ACC) (Moulton et al. 2011; Stankewitz et al. 2011, 2013; Schwedt et al. 2014; Mathur et al. 2016; Russo et al. 2017a, b, 2019; Schulte et al. 2017) and reduced BOLD activation within the brainstem (trigeminal nucleus caudalis and nucleus cuneiformis) (Stankewitz et al. 2011; Schulte and May 2016). Furthermore, parts of the pain-induced BOLD signal changes were not related to the presence of depression or anxiety (Schwedt et al. 2014). Conversely, the time to the next attack was positively correlated with activation strength within the trigeminal nuclei (Stankewitz et al. 2011), and the headache intensity was negatively related to the middle prefrontal cortex and posterior cingulate cortex (PCC) and positively related to bilateral insula activation (Mathur et al. 2016). Attack frequency was related to activation strength within several brain areas (middle cingulate, insula, fusiform gyrus, hippocampus, DLPFC, precentral gyrus, PAG, and cerebellum) (Moulton et al. 2011; Schwedt et al. 2014; Mathur et al. 2016; Mehnert and May 2017), whereas years with migraine were correlated positively with activation strength in the fusiform gyrus (Schwedt et al. 2014), negatively with that in the superior temporal gyrus (Mathur et al. 2016), and positively with that in the cerebellum (Russo et al. 2019). A study explored the effect of the beta-blocker metoprolol on the cerebral pain processing and reported that BOLD signal intensity in the hypothalamus increased under metoprolol during pain compared to that under placebo (Hebestreit and May 2017).

Functional abnormalities within brain structures have been described of migraine attacks. An enhanced BOLD signal was observed in response to noxious stimuli within the temporal lobe structures (Moulton et al. 2011), dorsal parts of the pons (Stankewitz et al. 2011), posterior hypothalamus (Schulte et al. 2017), and cerebellum (Mehnert and May 2017). Notably, the spinal trigeminal nucleus activation seems to fluctuate during the migraine cycle; it was slightly greater during the preictal state in migraine patients than in healthy subjects, but it was significantly enhanced in the preictal state compared to the interictal scans. Spinal trigeminal nucleus activation was decreased during an acute attack compared to that during the preictal period (Stankewitz et al. 2011) when it is more strongly activated by visual sensory load (Schulte et al. 2018) (Fig. 1). Nonetheless, during

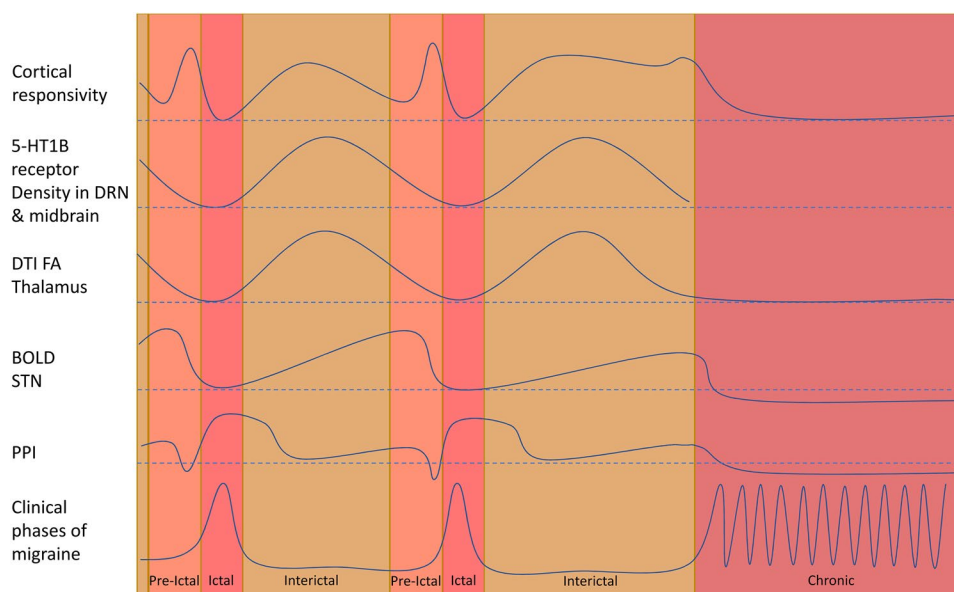


Fig. 1 Schematic representation of the results provided by the studies that found a correlation between different clinical, morphological, or functional variables and the number of days elapsed since the last migraine attack. During the interictal phase, the BOLD activity of the spinal trigeminal nucleus (STN) decreases, while the fractional anisotropy (FA) of the thalami, the 5-HT_{1B} receptor density in the dorsal raphe nuclei (DRN) and the midbrain, and the cortical responsiveness, measured by recording evoked potentials (EPs) to different sensory modalities, increase progressively with increasing time since the last attack and in parallel with a decrease in the subjective perception of pain intensity (PPI), a measure of central sensitization. During the

preictal phase, when PPI suddenly decreases, STN BOLD activation and cortical hyper-responsiveness reach their maximum, whereas thalamic FA and 5-HT_{1B} receptor density in the DRN and in the mid-brain approach their minimum. During the headache phase, when PPI reaches its maximum increase, STN BOLD activity, as well as thalamic FA and 5-HT_{1B} receptor density in the DRN and midbrain, are at their lowest values and cortical hyper-responsiveness normalizes. During a chronic migraine, at the time when PPI is normal or at the lower limits of normality, STN BOLD activity normalizes, as does thalamus FA (personal data) and cortical responsiveness

attacks, and even more so with aggravation and chronification of attacks, migraineurs have increased μ -opioid receptor-mediated neurotransmission in pain perception and modulating brain regions, such as the caudate, thalamus, amygdala, and parahippocampus (Jassar et al. 2019).

One study examined a patient with mixed migraine with and without aura longitudinally every day for 30 days using painful olfactory stimuli (gaseous ammonia) as a functional task in MRI during the ictal phase compared with preictal and interictal phases (Schulte and May 2016). In this patient, the hypothalamus was significantly more active immediately before the headache phase when it also showed the greatest functional coupling with the spinal trigeminal nuclei. During the ictal state, the hypothalamus was functionally coupled with the dorsal rostral pons (Schulte and May 2016), an area considered to be the location of a “generator” of the attack (Weiller et al. 1995; Bahra et al. 2001; Stankewitz and May 2011).

Whether these structural and functional alterations in brain areas devoted to the processing of nociceptive/antinociceptive information are related to aberrant white fibre bundles and/or to alterations in neuronal density of grey matter remains to be determined.

Several studies have characterized white-matter diffusion changes in migraine patients with and without aura, with variable involvement of diffusive metrics of the visual, trigeminal, somatosensory tracts, thalamus, PAG, and corpus callosum (Rocca et al. 2003, 2008; Granziera et al. 2006, 2014; DaSilva et al. 2007; Schmitz et al. 2008; Yuan et al. 2012; Szabó et al. 2012, 2018; Yu et al. 2013; Coppola et al. 2014). In some studies, these interictal changes in cortical synaptic connectivity patterns may directly depend on the recurrence of migraine attacks (Schmitz et al. 2008; Yuan et al. 2012; Szabó et al. 2018) and on the general level of neuroinflammation measured as the interictal plasma levels of pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) (Veréb et al. 2018). This may restructure neural circuits and may, in turn, change the neuronal density of the grey matter.

Indeed, there are several reports of grey-matter morphometric changes in migraine patients, the majority of which occur in areas coincidentally involved in the transmission and processing of pain (Rocca et al. 2006; Kim et al. 2008; Schmidt-Wilcke et al. 2008; Schmitz et al. 2008; Valfrè et al. 2008; Liu et al. 2013; Hougaard et al. 2014; Soheili-Nezhad et al. 2019). Most of these morphological abnormalities were

related to the frequency of attacks and duration of migraine (Kim et al. 2008; Schmitz et al. 2008; Valfrè et al. 2008; Rocca et al. 2014) but not with the side of aura (Messina et al. 2013; Hougaard et al. 2014).

In addition, the volume of the grey matter in migraine fluctuates over time depending on the cycle of migraine (Coppola et al. 2015) and longitudinal changes in attack frequency (Messina et al. 2018). Nevertheless, abnormal grey-matter volume in areas ascribable to pain processing (Schmidt-Wilcke et al. 2008; Valfrè et al. 2008; Bilgic et al. 2016; Lai et al. 2016; Neeb et al. 2017) and multi-sensory integration (Lai et al. 2016) has also been consistently observed in chronic migraine, sometimes depending on the duration of the disorder and consumption of acute medication (Coppola et al. 2017). In fact, altered structural integrity and functional connectivity of various areas belonging to the descending pain modulatory system such as the periaqueductal grey (Riederer et al. 2013; Michels et al. 2017; Chen et al. 2017a, b) and thalamic nuclei (Chen et al. 2017d) have been repeatedly identified in patients with medication overuse headache (MOH). Moreover, the orbito-frontal cortex was less connected both metabolically (Fumal et al. 2006) and functionally to the spinal trigeminal nucleus and cerebellum (Mehnert et al. 2018) in patients with MOH before drug withdrawal, whereas these connections normalized after drug discontinuation (Fumal et al. 2006; Mehnert et al. 2018).

As with other chronic pain conditions, the physiopathology of migraine has also been linked to activation of the glial system. Activation of glia in areas belonging to the salient network and visual system was detected using integrated PET/MRI brain scans with [^{11}C]PBR28, a radioligand that binds to the 18 kDa translocator protein (a marker of glial activation) in migraine with aura patients, although outside the aura and headache phase (Albrecht et al. 2019).

Because morphometric changes in the micro- and macrostructure of the brain may reflect a restructuring of local neural circuits through changes in neuronal connections via branching and crossing of dendritic trees and/or changes in cortical synaptic connectivity and plasticity. It is plausible that in the presence of these extensive abnormalities in the brain micro- and macrostructures associated with migraine, the communication between areas related to the cortical pain processing is equally altered.

Over the last decade, several fMRI studies on migraine have assessed the resting-state functional connectivity in different brain networks, suggesting that this neurological condition is associated with brain functional connectivity alterations. The intrinsic connectivity within brain areas anchored to the default mode network (DMN), which is involved in self-referential orientation and monitoring, was reduced during the interictal period of migraine without aura patients compared to that in healthy subjects (Tessitore et al.

2013; Hubbard et al. 2014; Hodkinson et al. 2016a; Yu et al. 2017a; Faragó et al. 2017; Yang et al. 2018). Moreover, the DMN itself was observed to be more connected with the executive control network and insula (Xue et al. 2012) but less connected with prefrontal and temporal regions (Tessitore et al. 2013), as well as the visuospatial system (Coppola et al. 2016c). Conversely, in migraine with aura patients, the DMN functional intrinsic connectivity was increased between attacks (Faragó et al. 2017). The intraregional connectivity of the executive control network (ECN) was diminished in migraineurs when scanned between attacks (Yu et al. 2017a; Yang et al. 2018), and the ECN itself was less interconnected with the middle frontal gyrus, dorsal ACC (Russo et al. 2012b; Tessitore et al. 2015), and precuneus (Li et al. 2017). Visual areas are known to be deeply involved in migraine pathophysiology, and their intrinsic connectivity was reduced (Hodkinson et al. 2016a; Soheili-Nezhad et al. 2019), especially within the visuospatial (Hubbard et al. 2014), ventral (Lisicki et al. 2018), and dorsal attention (Yang et al. 2018) systems, the latter being, in turn, less interconnected with the DMN (Coppola et al. 2016c) of patients affected by migraines without aura. Intriguingly, a recent study found that visual cortical hyper-responsiveness in episodic migraine patients, as assessed with single-trial visual evoked potentials, was proportional to grey-matter volume in the visual cortex and the right temporoparietal junction, an area belonging to the ventral attention network. The latter was, in turn, strongly interconnected with a series of areas involved in attention control to incoming salient events, such as headache, finally providing for the first time a unique link between structural and functional abnormalities within the migraine brain (Lisicki et al. 2018). In migraine with aura, intrinsic connectivity within the attention, medial and lateral visual systems (Faragó et al. 2017), advanced visual network (Russo et al. 2019), and lingual gyrus (Tedeschi et al. 2016) was enhanced between attacks. Compared to those in healthy subjects, areas within the sensorimotor (Hubbard et al. 2014; Hodkinson et al. 2016a; Yang et al. 2018), auditory (Hodkinson et al. 2016a; Yang et al. 2018), and cingulo-opercular (Yang et al. 2018) networks were less functionally connected in migraine without aura patients.

Areas anchored to the salience network/pain neuromatrix, mostly involved in detection and integration of salient sensory cues, showed less functional connectivity in both episodic migraine without aura patients (Yang et al. 2018) and in chronic migraine (CM) patients with and without medication overuse (Androulakis et al. 2017) compared to that in healthy subjects. Moreover, the salience network showed a greater degree of centrality (a measure of network importance) in CM than in episodic migraine. Connectivity strength of the salience network to the hypothalamus was more pronounced, while its connectivity to the dorsal raphe nuclei was attenuated in CM compared to that in episodic

migraines (Lee et al. 2019). The limbic system, which supports various functions including emotion, conduct, motivation, and long-term memory, was more connected in episodic migraine without aura patients but less connected in CM compared to that in healthy subjects (Chen et al. 2017c).

In our previous fMRI study performed in CM patients without previous history of medication overuse, the analysis of independent components revealed abnormalities in the functional connectivity between large-scale neurocognitive networks, specifically between the DMN, dorsal attention system (DAS), and ECN compared to those in healthy controls (Coppola et al. 2019).

Few studies have examined the brain of migraineurs during attacks using resting-state fMRI. During the initial 6 h of a spontaneous migraine attack, we (Coppola et al. 2016b) observed that the executive control network and dorsoventral attention system were significantly less interconnected. Moreover, in healthy subjects, but not in migraine patients, greater strength of the dorsoventral attention system was associated with lower bilateral thalamic diffusivity values. In patients, greater strength of the executive control network was associated with fewer monthly migraine days (Coppola et al. 2016b). In a companion article by the same group of researchers, these patients showed stronger functional connectivity between brain areas anchored to the DMN, i.e., between the medial prefrontal cortex (MPFC) and posterior cingulate cortex, and between the MPFC and bilateral insula. Furthermore, the strength of MPFC-to-insula connectivity was negatively correlated with pain intensity (Coppola et al. 2018). Amin et al. studied cerebral resting-state functional connectivity in the very early phase preceding a migraine-like headache induced by the administration of PACAP38 (Amin et al. 2016). In the early headache phase, PACAP, but not vasoactive intestinal polypeptide that has no attack-triggering effect, changed connectivity patterns in a priori selected salience, sensorimotor, and default mode networks (Amin et al. 2016). During spontaneous migraine attacks, the same authors also found evidence for abnormal network connectivity between the thalamus and several pain-modulating and -encoding cortical areas, such as the superior parietal lobule, insular cortex, primary motor and premotor cortices, supplementary motor area, and orbitofrontal cortex (Amin et al. 2018). Interestingly, non-pharmacological treatment with kinetic oscillation stimulation in the nasal cavity gave rise to a downregulated pattern of resting-state connectivity in a group of migraineurs during attacks (Li et al. 2016a).

Overall, the huge amount of studies conducted with neuroimaging techniques have clearly shown that migraine is accompanied by changes at multiple levels in the brain, from the synaptic level, as shown by DTI and voxel-based morphometry (VBM) studies, to the level of large-scale neuronal networks. In fact, the analysis of resting-state MRI data in

various subgroups of migraine patients and in various phases of the migraine cycle unravelled the involvement of neurocognitive networks directly (salience network) or indirectly (executive, auditory, visual, and visuo-attentive networks) related to pain–cognition interactions. This activity of large-scale neuronal networks could be the consequence of the attack recurrence. However, it could also reflect an intrinsic vulnerability of the migraine brain and constitute the pathophysiological basis of the inability to cope with the cognitively demanding conditions of daily activities due to the presence or expectation of migraine pain.

To clarify the influence of clinical migraine severity on plastic changes in functional networks related to pain–cognition, several authors have performed regression analyses for various patient groups.

In episodic migraine patients between attacks, the average pain intensity correlated negatively with functional connectivity between the right ACC–PCC in migraine without aura (Yu et al. 2017a), with abnormal inflows to the right posterior thalamus from the right DLPFC (Wang et al. 2016), reduced connectivity within the middle frontal gyrus (Russo et al. 2012b), and connectivity changes between the anterior insula and occipital areas (Niddam et al. 2016). In CM, average pain intensity was correlated positively with the strength of DAS connectivity and negatively with the strength of ECN connectivity (Coppola et al. 2019). Interestingly, decreased visual analogue scale scores after treatment with acupuncture correlated negatively with functional connectivity of the right frontoparietal network (Li et al. 2015, 2017) and with changes in functional connectivity among the PAG, rostral ACC, and ventral striatum (Li et al. 2016b). Duration of migraine disease correlated negatively with the strength of both intrinsic connectivity and causal influences from the fronto-insular cortex (FIC) to the ACC (Yu et al. 2012, 2017a), insular subregions (Yu et al. 2017b), and functional connectivity values in the prefrontal cortex, putamen, caudate nucleus (Gao et al. 2016), right nucleus accumbens, and bilateral caudate (Yuan et al. 2013). Conversely, it correlated positively to functional connectivity of the bilateral PAG with bilateral thalamus and putamen, left pallidum, and right medial orbitofrontal gyrus (Chen et al. 2017a); functional connectivity between the dorsal ACC and DLPFC/orbitofrontal cortex (Jin et al. 2013); greater connectivity between the DMN/ECN and insula (Xue et al. 2012); and increased average regional homogeneity values in the thalamus, brainstem, and temporal pole (Zhao et al. 2013). The mean monthly frequency of migraine attacks correlated negatively with the increased strength of causal influences from the rFIC to the right DLPFC (Yu et al. 2017a) and positively with connectivity between the left middle frontal gyrus and medial PFC (Niddam et al. 2016), functional connectivity between the bilateral caudate and left insula (Yuan et al. 2013), and connectivity between the PAG

and several cortical areas primarily involved in nociception and somatosensory processing (dorsomedial PFC, primary somatosensory area, primary motor cortex, ACC, parahippocampal gyrus, amygdala, DLPFC, angular gyrus, and medial thalamus Mainero et al. 2011). The parameter time interval to the nearest migraine attack was positively correlated with connectivity between the left middle frontal gyrus and medial prefrontal cortex in MO, and was correlated with seeds in the posterior cingulate and several regions within the DMN, including the ventral medial prefrontal cortex, bilateral hippocampi, and a region in the middle occipital gyrus in the migraine with aura (Niddam et al. 2016).

Genetic predisposition may play a role in both abnormal brain morphology and its connectivity patterns, since grey-matter volumetric abnormalities in adults within the salience network (Rocca et al. 2014) and widespread abnormal resting-state functional connectivity (Colon et al. 2019) were also observed in paediatric patients/adolescents affected by migraine.

Overall, neuroimaging studies have demonstrated that the migraine brain undergoes plastic changes in both the microstructure and macrostructure of the brain and in the functioning of cortical networks, all of which are under the influence of medication overuse. In some cases, these changes may be related to the severity of the clinical migraine presentation. The observation that morphofunctional abnormalities of the migraine brain can be proportional to the subjective perception of headache severity may provide an opportunity to objectively determine the pain intensity perceived by the patient bypassing verbal assessment (Mouraux and Iannetti 2018). Further studies are necessary to prove that these abnormalities manifest themselves early in the migraine patient's life, representing an inherited phenotypic manifestation of the disorder.

Conclusions

The aforementioned experimental studies clearly suggest that brain structures implicated in migraine pathophysiology, such as the brainstem nuclei (monoaminergic nuclei, PAG, spinal trigeminal nucleus); hypothalamic and thalamic nuclei; and somatosensory, salient, and visual area cortices should not be considered as isolated culprits for dysfunction but as a network of functionally interconnected, mutually influencing cerebral areas. Regardless of the primary site of dysfunction, all areas to which it is connected can, in turn, be influenced by a domino effect. This explains why determining the primary ictal dysfunction is a challenge in patients in whom sequential studies are notoriously difficult and why the concept of the “migraine generator” recently switched from the dorsal pons (Weiller et al. 1995) to the hypothalamus (Schulte and May 2016).

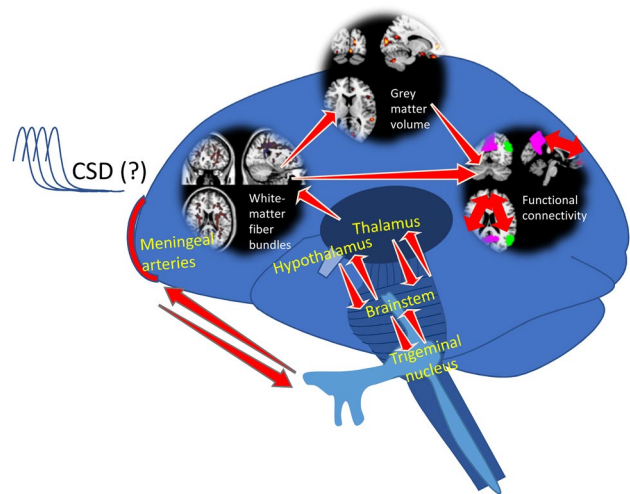


Fig. 2 Schematic representation of the possible pain processing model in migraine. Migraine may involve irritation of meningeal perivascular nociceptive trigeminal nerve endings. It is not known whether this involvement is initiated by cortical spreading depression (CSD), manifested in migraine with aura or silent in migraine without aura, or by abnormal activation either of the spinal trigeminal nucleus or the descending pain control systems at the brainstem or midbrain levels. Abnormalities at these levels could activate the autonomic nervous system (the hypothalamus), especially shortly before and during an attack. However, they could also impede to correctly filter out sensory information afferent to the CNS through the thalamus. These morphofunctional abnormalities in subcortical structures could, in turn, be responsible for abnormalities in the microstructure of white-matter fibre bundles, as well as for the altered grey-matter neuronal density in brain areas devoted to processing salient information such as pain. In turn, the presence of these alterations in the micro- and macrostructures of the brain could be the backbone architecture of the changes in resting functional connectivity maps observed during all migraine phases, which ultimately represent the anatomical bases of ‘central sensitization’ process

From the studies summarized above emerges a marginal role of the peripheral portion of the trigeminal system, reinforcing the concept that the CNS mechanisms that sustain migraine headaches do not consist solely of a bottom–up process involving a painful focus, located within the brainstem and midbrain, which modifies inputs to the next higher level (thalamus and cerebral cortex). Indeed, several CNS regions and networks mediate subtle forms of plasticity by adjusting neural maps downstream and consequently altering all the modulatory mechanisms at the origin of sensory perceptions. Disturbances in normal sensory processing within these large-scale neuronal networks could lead to maladaptive changes, impaired trigeminovascular functions, and consequently modifications in subjective pain perception, which ultimately comprise the ‘central sensitization’ process (Fig. 2). These concepts may unite the ‘bottom–up’ and ‘top–down’ mechanisms of trigeminal nociception and pain. These concepts should be taken into account in the future development of therapeutic strategies aimed at improving

the quality of life of patients experiencing craniofacial dysfunctions due to sustained or chronic headaches.

Acknowledgements The contributing authors associated with the G. B. Bietti Foundation were supported by the Italian Ministry of Health and the Fondazione Roma.

References

- Albrecht DS, Mainero C, Ichijo E et al (2019) Imaging of neuroinflammation in migraine with aura. *Neurology* 92:e2038–e2050. <https://doi.org/10.1212/WNL.0000000000007371>
- Ambrosini A, Rossi P, De Pasqua V et al (2003) Lack of habituation causes high intensity dependence of auditory evoked cortical potentials in migraine. *Brain* 126:2009–2015. <https://doi.org/10.1093/brain/awg206>
- Amin FM, Hougaard A, Magon S et al (2016) Change in brain network connectivity during PACAP38-induced migraine attacks: a resting-state functional MRI study. *Neurology* 86:180–187
- Amin FM, Hougaard A, Magon S et al (2018) Altered thalamic connectivity during spontaneous attacks of migraine without aura: a resting-state fMRI study. *Cephalalgia* 38:1237–1244. <https://doi.org/10.1177/0333102417729113>
- Androulakis XM, Rorden C, Peterlin BL, Krebs K (2017) Modulation of salience network intranetwork resting state functional connectivity in women with chronic migraine. *Cephalalgia*. <https://doi.org/10.1177/0333102417748570>
- Anttila P, Metsähonkala L, Mikkelsen M et al (2002) Muscle tenderness in pericranial and neck-shoulder region in children with headache. A controlled study. *Cephalalgia* 22:340–344
- Ayzenberg I, Obermann M, Nyhuis P et al (2006) Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures. *Cephalalgia* 26:1106–1114. <https://doi.org/10.1111/j.1468-2982.2006.01183.x>
- Bahra A, Matharu MS, Buchel C et al (2001) Brainstem activation specific to migraine headache. *Lancet* 357:1016–1017
- Bauch EM, Andreou C, Rausch VH, Bunzeck N (2017) Neural habituation to painful stimuli is modulated by dopamine: evidence from a pharmacological fMRI study. *Front Hum Neurosci* 11:630. <https://doi.org/10.3389/fnhum.2017.00630>
- Beese LC, Putzer D, Osada N et al (2015) Contact heat evoked potentials and habituation measured interictally in migraineurs. *J Headache Pain* 16:1
- Bilgic B, Kocaman G, Arslan AB et al (2016) Volumetric differences suggest involvement of cerebellum and brainstem in chronic migraine. *Cephalalgia* 36:301–308. <https://doi.org/10.1177/0333102415588328>
- Bingel U, Schoell E, Herken W et al (2007) Habituation to painful stimulation involves the antinociceptive system. *Pain* 131:21–30. <https://doi.org/10.1016/j.pain.2006.12.005>
- Bishop KL, Holm JE, Borowiak DM, Wilson BA (2001) Perceptions of pain in women with headache: a laboratory investigation of the influence of pain-related anxiety and fear. *Headache* 41:494–499
- Bogdanov VB, Bogdanova OV, Viganò A et al (2019) Increased cerebral responses to salient transitions between alternating stimuli in chronic migraine with medication overuse headache and during migraine attacks. *Cephalalgia* 39:988–999. <https://doi.org/10.1177/0333102418825359>
- Bolay H, Reuter U, Dunn AK et al (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med* 8:136–142. <https://doi.org/10.1038/nm0202-136>
- Bonvento G, Lacombe P, MacKenzie ET et al (1990) Differential effects of electrical stimulation of the dorsal raphe nucleus and of cervical sympathectomy on serotonin and noradrenaline concentrations in major cerebral arteries and pial vessels in the rat. *J Cereb Blood Flow Metab* 10:123–126
- Bovim G (1992) Cervicogenic headache, migraine, and tension-type headache. Pressure-pain threshold measurements. *Pain* 51:169–173
- Brighina F, Giglia G, Scalia S et al (2005) Facilitatory effects of 1 Hz rTMS in motor cortex of patients affected by migraine with aura. *Exp Brain Res* 161:34–38. <https://doi.org/10.1007/s00221-004-2042-7>
- Brighina F, Cosentino G, Vigneri S et al (2011) Abnormal facilitatory mechanisms in motor cortex of migraine with aura. *Eur J Pain* 15:928–935
- Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R (2006) Frequency of headache is related to sensitization: a population study. *Pain* 123:19–27. <https://doi.org/10.1016/j.pain.2006.01.040>
- Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R (2008) Increased pain sensitivity is not a risk factor but a consequence of frequent headache: a population-based follow-up study. *Pain* 137:623–630. <https://doi.org/10.1016/j.pain.2007.10.023>
- Burstein R, Cutrer MF, Yarnitsky D (2000a) The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain* 123(Pt 8):1703–1709
- Burstein R, Yarnitsky D, Goor-Aryeh I et al (2000b) An association between migraine and cutaneous allodynia. *Ann Neurol* 47:614–624
- Burstein R, Collins B, Jakubowski M (2004) Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Ann Neurol* 55:19–26. <https://doi.org/10.1002/ana.10786>
- Burstein R, Jakubowski M, Garcia-Nicas E et al (2010) Thalamic sensitization transforms localized pain into widespread allodynia. *Ann Neurol* 68:81–91. <https://doi.org/10.1002/ana.21994>
- Casey KL, Svensson P, Morrow TJ et al (2000) Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol* 84:525–533. <https://doi.org/10.1152/jn.2000.84.1.525>
- Chen Z, Chen X, Liu M et al (2017a) Disrupted functional connectivity of periaqueductal gray subregions in episodic migraine. *J Headache Pain* 18:36. <https://doi.org/10.1186/s10194-017-0747-9>
- Chen Z, Chen X, Liu M et al (2017b) Texture features of periaqueductal gray in the patients with medication-overuse headache. *J Headache Pain* 18:14. <https://doi.org/10.1186/s10194-017-0727-0>
- Chen Z, Chen X, Liu M et al (2017c) Altered functional connectivity architecture of the brain in medication overuse headache using resting state fMRI. *J Headache Pain* 18:25. <https://doi.org/10.1186/s10194-017-0735-0>
- Chen Z, Jia Z, Chen X et al (2017d) Volumetric abnormalities of thalamic subnuclei in medication-overuse headache. *J Headache Pain* 18:82. <https://doi.org/10.1186/s10194-017-0791-5>
- Colon E, Ludwick A, Wilcox SL et al (2019) Migraine in the young brain: adolescents vs. young adults. *Front Hum Neurosci* 13:87. <https://doi.org/10.3389/fnhum.2019.00087>
- Cooke L, Eliasziw M, Becker WJ (2007) Cutaneous allodynia in transformed migraine patients. *Headache* 47:531–539. <https://doi.org/10.1111/j.1526-4610.2006.00717.x>
- Coppola G, Di Clemente L, Fumal A et al (2007) Inhibition of the nociceptive R2 blink reflex after supraorbital or index finger stimulation is normal in migraine without aura between attacks. *Cephalalgia* 27:803–808. <https://doi.org/10.1111/j.1468-2982.2007.01323.x>
- Coppola G, Currà A, Di Lorenzo C et al (2010a) Abnormal cortical responses to somatosensory stimulation in medication-overuse headache. *BMC Neurol*. <https://doi.org/10.1186/1471-2377-10-126>

- Coppola G, Currà A, Serrao M et al (2010b) Lack of cold pressor test-induced effect on visual-evoked potentials in migraine. *J Headache Pain* 11:115–121. <https://doi.org/10.1007/s10194-009-0177-4>
- Coppola G, De Pasqua V, Pierelli F, Schoenen J (2012) Effects of repetitive transcranial magnetic stimulation on somatosensory evoked potentials and high frequency oscillations in migraine. *Cephalalgia* 32:700–709. <https://doi.org/10.1177/0333102412446313>
- Coppola G, Di Lorenzo C, Schoenen J, Pierelli F (2013a) Habituation and sensitization in primary headaches. *J Headache Pain* 14:65. <https://doi.org/10.1186/1129-2377-14-65>
- Coppola G, Iacovelli E, Bracaglia M et al (2013b) Electrophysiological correlates of episodic migraine chronification: evidence for thalamic involvement. *J Headache Pain* 14:76
- Coppola G, Parisi V, Di Lorenzo C et al (2013c) Lateral inhibition in visual cortex of migraine patients between attacks. *J Headache Pain* 14:20. <https://doi.org/10.1186/1129-2377-14-20>
- Coppola G, Tinelli E, Lepre C et al (2014) Dynamic changes in thalamic microstructure of migraine without aura patients: a diffusion tensor magnetic resonance imaging study. *Eur J Neurol* 21:287. <https://doi.org/10.1111/ene.12296>
- Coppola G, Di Renzo A, Tinelli E et al (2015) Evidence for brain morphometric changes during the migraine cycle: a magnetic resonance-based morphometry study. *Cephalalgia* 35:783–791. <https://doi.org/10.1177/0333102414559732>
- Coppola G, Bracaglia M, Di Lenola D et al (2016a) Lateral inhibition in the somatosensory cortex during and between migraine without aura attacks: correlations with thalamocortical activity and clinical features. *Cephalalgia* 36:568–578. <https://doi.org/10.1177/0333102415610873>
- Coppola G, Di Renzo A, Tinelli E et al (2016b) Thalamo-cortical network activity during spontaneous migraine attacks. *Neurology* 87:2154–2160. <https://doi.org/10.1212/WNL.0000000000000327>
- Coppola G, Di Renzo A, Tinelli E et al (2016c) Thalamo-cortical network activity between migraine attacks: insights from MRI-based microstructural and functional resting-state network correlation analysis. *J Headache Pain* 17:100. <https://doi.org/10.1186/s10194-016-0693-y>
- Coppola G, Petolicchio B, Di Renzo A et al (2017) Cerebral gray matter volume in patients with chronic migraine: correlations with clinical features. *J Headache Pain* 18:115. <https://doi.org/10.1186/s10194-017-0825-z>
- Coppola G, Di Renzo A, Tinelli E et al (2018) Resting state connectivity between default mode network and insula encodes acute migraine headache. *Cephalalgia* 38:846–854. <https://doi.org/10.1177/0333102417715230>
- Coppola G, Di Renzo A, Petolicchio B et al (2019) Aberrant interactions of cortical networks in chronic migraine. *Neurology* 92:e2550–e2558. <https://doi.org/10.1212/wnl.0000000000000757>
- DaSilva AFM, Granziera C, Tuch DS et al (2007) Interictal alterations of the trigeminal somatosensory pathway and periaqueductal gray matter in migraine. *Neuroreport* 18:301–305. <https://doi.org/10.1097/WNR.0b013e32801776bb>
- de Tommaso M, Guido M, Libro G et al (2002) Abnormal brain processing of cutaneous pain in migraine patients during the attack. *Neurosci Lett* 333:29–32
- de Tommaso M, Guido M, Libro G et al (2004a) Topographic and dipolar analysis of laser-evoked potentials during migraine attack. *Headache* 44:947–960. <https://doi.org/10.1111/j.1526-4610.2004.04188.x>
- de Tommaso M, Libro G, Guido M et al (2004b) Nitroglycerin induces migraine headache and central sensitization phenomena in patients with migraine without aura: a study of laser evoked potentials. *Neurosci Lett* 363:272–275. <https://doi.org/10.1016/j.neulet.2004.04.029>
- de Tommaso M, Libro G, Guido M et al (2005a) Habituation of single CO₂ laser-evoked responses during interictal phase of migraine. *J Headache Pain* 6:195–198. <https://doi.org/10.1007/s10194-005-0183-0>
- de Tommaso M, Lo sito L, Di Fruscolo O et al (2005b) Lack of habituation of nociceptive evoked responses and pain sensitivity during migraine attack. *Clin Neurophysiol* 116:1254–1264. <https://doi.org/10.1016/j.clinph.2005.02.018>
- de Tommaso M, Losito L, Difruscolo O et al (2005c) Capsaicin failed in suppressing cortical processing of CO₂ laser pain in migraine patients. *Neurosci Lett* 384:150–155. <https://doi.org/10.1016/j.neulet.2005.04.086>
- de Tommaso M, Losito L, Difruscolo O et al (2005d) Changes in cortical processing of pain in chronic migraine. *Headache J Head Face Pain* 45:1208–1218. <https://doi.org/10.1111/j.1526-4610.2005.00244.x>
- de Tommaso M, Losito L, Libro G et al (2005e) Effects of symptomatic treatments on cutaneous hyperalgesia and laser evoked potentials during migraine attack. *Cephalalgia* 25:359–368. <https://doi.org/10.1111/j.1468-2982.2004.00866.x>
- de Tommaso M, Marinazzo D, Stramaglia S (2005f) The measure of randomness by leave-one-out prediction error in the analysis of EEG after laser painful stimulation in healthy subjects and migraine patients. *Clin Neurophysiol* 116:2775–2782. <https://doi.org/10.1016/j.clinph.2005.08.019>
- de Tommaso M, Difruscolo O, Sardaro M et al (2007) Effects of remote cutaneous pain on trigeminal laser-evoked potentials in migraine patients. *J Headache Pain* 8:167–174. <https://doi.org/10.1007/s10194-007-0385-8>
- de Tommaso M, Baumgartner U, Sardaro M et al (2008) Effects of distraction versus spatial discrimination on laser-evoked potentials in migraine. *Headache* 48:408–416. <https://doi.org/10.1111/j.1526-4610.2007.00857.x>
- de Tommaso M, Valeriani M, Sardaro M et al (2009) Pain perception and laser evoked potentials during menstrual cycle in migraine. *J Headache Pain* 10:423–429. <https://doi.org/10.1007/s10194-009-0150-2>
- de Tommaso M, Brighina F, Fierro B et al (2010) Effects of high-frequency repetitive transcranial magnetic stimulation of primary motor cortex on laser-evoked potentials in migraine. *J Headache Pain* 11:505–512. <https://doi.org/10.1007/s10194-010-0247-7>
- de Tommaso M, Ambrosini A, Brighina F et al (2014) Altered processing of sensory stimuli in patients with migraine. *Nat Rev Neurol* 10:144–155. <https://doi.org/10.1038/nrneurol.2014.14>
- de Tommaso M, Trotta G, Vecchio E et al (2015) Functional connectivity of EEG signals under laser stimulation in migraine. *Front Hum Neurosci* 9:640. <https://doi.org/10.3389/fnhum.2015.00640>
- de Tommaso M, Sciricchio V, Ricci K et al (2016) Laser-evoked potential habituation and central sensitization symptoms in childhood migraine. *Cephalalgia* 36:463–473. <https://doi.org/10.1177/0333102415597527>
- Deen M, Hansen HD, Hougaard A et al (2018) Low 5-HT_{1B} receptor binding in the migraine brain: a PET study. *Cephalalgia* 38:519–527. <https://doi.org/10.1177/0333102417698708>
- Demarquay G, Lothe A, Royet JP et al (2011) Brainstem changes in 5-HT_{1A} receptor availability during migraine attack. *Cephalalgia* 31:84–94
- Di Clemente L, Puledda F, Biasiotta A et al (2013) Topiramate modulates habituation in migraine: evidences from nociceptive responses elicited by laser evoked potentials. *J Headache Pain* 14:25. <https://doi.org/10.1186/1129-2377-14-25>
- Domínguez C, López A, Ramos-Cabrera P et al (2019) Iron deposition in periaqueductal gray matter as a potential biomarker

- for chronic migraine. *Neurology* 92:e1076–e1085. <https://doi.org/10.1212/WNL.0000000000007047>
- Edvinsson L, Degueurce A, Duverger D et al (1983) Central serotonergic nerves project to the pial vessels of the brain. *Nature* 306:55–57
- Engström M, Hagen K, Bjørk MH et al (2013) Sleep quality, arousal and pain thresholds in migraineurs: a blinded controlled polysomnographic study. *J Headache Pain* 14:12
- Evers S, Quibeldey F, Grottemeyer KH et al (1999) Dynamic changes of cognitive habituation and serotonin metabolism during the migraine interval. *Cephalalgia* 19:485–491
- Fabjan A, Bajrović F, Musizza B et al (2015) Study of neurovascular coupling during cold pressor test in patients with migraine. *Cephalalgia* 35:692–701
- Faragó P, Tuka B, Tóth E et al (2017) Interictal brain activity differs in migraine with and without aura: resting state fMRI study. *J Headache Pain* 18:8. <https://doi.org/10.1186/s10194-016-0716-8>
- Feigin VL, Nichols E, Alam T et al (2019) Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 18:459–480. [https://doi.org/10.1016/S1474-4422\(18\)30499-X](https://doi.org/10.1016/S1474-4422(18)30499-X)
- Fernández-de-las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Pareja JA (2008) Side-to-side differences in pressure pain thresholds and pericranial muscle tenderness in strictly unilateral migraine. *Eur J Neurol* 15:162–168. <https://doi.org/10.1111/j.1468-1331.2007.02020.x>
- Fernández-de-las-Peñas C, Madeleine P, Cuadrado ML et al (2009) Pressure pain sensitivity mapping of the temporalis muscle revealed bilateral pressure hyperalgesia in patients with strictly unilateral migraine. *Cephalalgia* 29:670–676
- Fernández-de-las-Peñas C, Madeleine P, Caminero AB et al (2010) Generalized neck–shoulder hyperalgesia in chronic tension-type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle. *Cephalalgia* 30:77–86
- Ferracini GN, Stuginsk-Barbosa J, Dach F, Speciali JG (2014) A comparison pressure pain threshold in pericranial and extra-cephalic regions in children with migraine. *Pain Med* 15:702–709. <https://doi.org/10.1111/pme.12353>
- Ferraro D, Vollono C, Miliucci R et al (2012) Habituation to pain in “medication overuse headache”: a CO₂ laser-evoked potential study. *Headache* 52:792–807
- Florencio LL, Giantomassi MCM, Carvalho GF et al (2015) Generalized pressure pain hypersensitivity in the cervical muscles in women with migraine. *Pain Med* 16:1629–1634. <https://doi.org/10.1111/pme.12767>
- Fumal A, Laureys S, Di Clemente L et al (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain* 129:543–550. <https://doi.org/10.1093/brain/awh691>
- Gao Q, Xu F, Jiang C et al (2016) Decreased functional connectivity density in pain-related brain regions of female migraine patients without aura. *Brain Res* 1632:73–81. <https://doi.org/10.1016/j.brainres.2015.12.007>
- Gierse-Plogmeier B, Colak-Ekici R, Wolowski A et al (2009) Differences in trigeminal and peripheral electrical pain perception in women with and without migraine. *J Headache Pain* 10:249–254. <https://doi.org/10.1007/s10194-009-0118-2>
- Goadsby PJ, Akerman S (2012) The trigeminovascular system does not require a peripheral sensory input to be activated—migraine is a central disorder. Focus on “Effect of cortical spreading depression on basal and evoked traffic in the trigeminovascular sensory system”. *Cephalalgia* 32:3–5
- Goadsby PJ, Lambert GA, Lance JW (1982) Differential effects on the internal and external carotid circulation of the monkey evoked by locus coeruleus stimulation. *Brain Res* 249:247–254
- Göbel H, Weigle L, Kropp P, Soyka D (1992) Pain sensitivity and pain reactivity of pericranial muscles in migraine and tension-type headache. *Cephalalgia* 12:142–151
- Granziera C, DaSilva AFM, Snyder J et al (2006) Anatomical alterations of the visual motion processing network in migraine with and without aura. *PLoS Med* 3:e402. <https://doi.org/10.1371/journal.pmed.0030402>
- Granziera C, Daducci A, Romascano D et al (2014) Structural abnormalities in the thalamus of migraineurs with aura: a multiparametric study at 3 T. *Hum Brain Mapp* 35:1461–1468. <https://doi.org/10.1002/hbm.22266>
- Grossi DB, Chaves TC, Gonçalves MC et al (2011) Pressure pain threshold in the craniocervical muscles of women with episodic and chronic migraine: a controlled study. *Arq Neuropsiquiatr* 69:607–612
- Guy N, Voisin D, Mulliez A et al (2018) Medication overuse reinstates conditioned pain modulation in women with migraine. *Cephalalgia* 38:1148–1158. <https://doi.org/10.1177/0333102417727545>
- Hadjikhani N, Sanchez del Rio M, Wu O et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci* 98:4687–4692. <https://doi.org/10.1073/pnas.071582498>
- Hamel E (2007) Serotonin and migraine: biology and clinical implications. *Cephalalgia* 27:1293–1300
- Hebestreit JM, May A (2017) The enigma of site of action of migraine preventives: no effect of metoprolol on trigeminal pain processing in patients and healthy controls. *J Headache Pain* 18:116. <https://doi.org/10.1186/s10194-017-0827-x>
- Hodkinson DJ, Veggeberg R, Kucyi A et al (2016a) Cortico–cortical connections of primary sensory areas and associated symptoms in migraine. *eneuro*. <https://doi.org/10.1523/eneuro.0.0163-16.2016>
- Hodkinson DJ, Wilcox SL, Veggeberg R et al (2016b) Increased amplitude of thalamocortical low-frequency oscillations in patients with migraine. *J Neurosci* 36:8026–8036. <https://doi.org/10.1523/JNEUROSCI.1038-16.2016>
- Hougaard A, Amin FM, Hoffmann MB et al (2014) Structural gray matter abnormalities in migraine relate to headache lateralization, but not aura. *Cephalalgia* 35:3
- Hubbard CS, Khan SA, Keaser ML et al (2014) Altered brain structure and function correlate with disease severity and pain catastrophizing in migraine patients. *eNeuro*. <https://doi.org/10.1523/eneuro.0006-14.2014>
- Iannetti G, Mouraux A (2010) From the neuromatrix to the pain matrix (and back). *Exp Brain Res* 205:1–12
- Jassar H, Nascimento TD, Kaciroti N et al (2019) Impact of chronic migraine attacks and their severity on the endogenous μ -opioid neurotransmission in the limbic system. *NeuroImage Clin* 23:101905. <https://doi.org/10.1016/j.nicl.2019.101905>
- Jin C, Yuan K, Zhao L et al (2013) Structural and functional abnormalities in migraine patients without aura. *NMR Biomed* 26:58–64
- Joffily L, de Melo Tavares de Lima MA, Vincent MB, Frota SM (2016) Assessment of otoacoustic emission suppression in women with migraine and phonophobia. *Neurol Sci* 37:703–709. <https://doi.org/10.1007/s10072-016-2565-2>
- Judit A, Sandor PS, Schoenen J (2000) Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. *Cephalalgia* 20:714–719
- Karatas H, Erdener SE, Gursoy-Ozdemir Y et al (2013) Spreading depression triggers headache by activating neuronal Panx1 channels. *Science* (80-) 339:1092–1095. <https://doi.org/10.1126/science.1231897>

- Katsarava Z, Giffin N, Diener H-C, Kaube H (2003) Abnormal habituation of “nociceptive” blink reflex in migraine-evidence for increased excitability of trigeminal nociception. *Cephalalgia* 23:814–819
- Katsarava Z, Schneeweiss S, Kurth T et al (2004) Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology* 62:788–790
- Khan S, Amin FM, Fliedner FP et al (2019) Investigating macrophage-mediated inflammation in migraine using ultrasmall superparamagnetic iron oxide-enhanced 3 T magnetic resonance imaging. *Cephalalgia*. <https://doi.org/10.1177/0333102419848122>
- Kim JH, Suh SI, Seol HY et al (2008) Regional grey matter changes in patients with migraine: a voxel-based morphometry study. *Cephalalgia* 28:598–604
- Kisler LB, Granovsky Y, Coghill RC et al (2018) Do patients with interictal migraine modulate pain differently from healthy controls? A psychophysical and brain imaging study. *Pain* 159:2667–2677. <https://doi.org/10.1097/j.pain.0000000000001380>
- Kropp P, Gerber WD (1998) Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. *Neurosci Lett* 257:73–76
- Lai T-H, Chou K-H, Fuh J-L et al (2016) Gray matter changes related to medication overuse in patients with chronic migraine. *Cephalalgia* 36:1324–1333. <https://doi.org/10.1177/0333102416630593>
- Lee MC, Zambreanu L, Menon DK, Tracey I (2008) Identifying brain activity specifically related to the maintenance and perceptual consequence of central sensitization in humans. *J Neurosci* 28:11642–11649
- Lee MJ, Park BY, Cho S et al (2019) Increased connectivity of pain matrix in chronic migraine: a resting-state functional MRI study. *J Headache Pain* 20:29. <https://doi.org/10.1186/s10194-019-0986-z>
- Leone M, Attanasio A, Croci D et al (2000) The serotonergic agent m-chlorophenylpiperazine induces migraine attacks: a controlled study. *Neurology* 55:136–139
- Li K, Zhang Y, Ning Y et al (2015) The effects of acupuncture treatment on the right frontoparietal network in migraine without aura patients. *J Headache Pain* 16:33. <https://doi.org/10.1186/s10194-015-0518-4>
- Li T-Q, Wang Y, Hallin R, Juto J-E (2016a) Resting-state fMRI study of acute migraine treatment with kinetic oscillation stimulation in nasal cavity. *NeuroImage Clin* 12:451–459. <https://doi.org/10.1016/j.nicl.2016.08.014>
- Li Z, Liu M, Lan L et al (2016b) Altered periaqueductal gray resting-state functional connectivity in migraine and the modulation effect of treatment. *Sci Rep* 6:20298. <https://doi.org/10.1038/srep20298>
- Li Z, Lan L, Zeng F et al (2017) The altered right frontoparietal network functional connectivity in migraine and the modulation effect of treatment. *Cephalalgia* 37:161–176. <https://doi.org/10.1177/0333102416641665>
- Lisicki M, D’Ostilio K, Coppola G et al (2018) Brain correlates of single trial visual evoked potentials in migraine: more than meets the eye. *Front Neurol*. <https://doi.org/10.3389/fneur.2018.00393>
- Lisicki M, D’Ostilio K, Coppola G et al (2019) Age related metabolic modifications in the migraine brain. *Cephalalgia* 39:978–987. <https://doi.org/10.1177/0333102419828984>
- Liu J, Lan L, Li G et al (2013) Migraine-related gray matter and white matter changes at a 1-year follow-up evaluation. *J Pain* 14:1703–1708
- Magon S, May A, Stankewitz A et al (2015) Morphological abnormalities of thalamic subnuclei in migraine: a multicenter MRI study at 3 Tesla. *J Neurosci* 35:13800–13806
- Mainero C, Boshyan J, Hadjikhani N (2011) Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol* 70:838–845
- Marciszewski KK, Meylakh N, Di Pietro F et al (2018a) Changes in brainstem pain modulation circuitry function over the migraine cycle. *J Neurosci* 38:10479–10488. <https://doi.org/10.1523/JNEUROSCI.1088-18.2018>
- Marciszewski KK, Meylakh N, Di Pietro F et al (2018b) Altered brainstem anatomy in migraine. *Cephalalgia* 38:476–486. <https://doi.org/10.1177/0333102417694884>
- Marciszewski KK, Meylakh N, Di Pietro F et al (2019) Fluctuating regional brainstem diffusion imaging measures of microstructure across the migraine cycle. *eneuro*. <https://doi.org/10.1523/eneuro.0005-19.2019>
- Mascia A, Afra J, Schoenen J (1998) Dopamine and migraine: a review of pharmacological, biochemical, neurophysiological, and therapeutic data. *Cephalalgia* 18:174–182
- Mason BN, Kaiser EA, Kuburas A et al (2017) Induction of migraine-like photophobic behavior in mice by both peripheral and central CGRP mechanisms. *J Neurosci* 37:204–216. <https://doi.org/10.1523/JNEUROSCI.2967-16.2016>
- Mathur VA, Moayed M, Keaser ML et al (2016) High frequency migraine is associated with lower acute pain sensitivity and abnormal insula activity related to migraine pain intensity, attack frequency, and pain catastrophizing. *Front Hum Neurosci* 10:489. <https://doi.org/10.3389/fnhum.2016.00489>
- Mehnert J, May A (2017) Functional and structural alterations in the migraine cerebellum. *J Cereb Blood Flow Metab* 78:89. <https://doi.org/10.1177/0271678x17722109>
- Mehnert J, Hebestreit J, May A (2018) Cortical and subcortical alterations in medication overuse headache. *Front Neurol* 9:499. <https://doi.org/10.3389/fneur.2018.00499>
- Mehnert J, Bader D, Nolte G, May A (2019) Visual input drives increased occipital responsiveness and harmonized oscillations in multiple cortical areas in migraineurs. *NeuroImage Clin* 23:101815. <https://doi.org/10.1016/j.nicl.2019.101815>
- Messina R, Rocca MA, Colombo B et al (2013) Cortical abnormalities in patients with migraine: a surface-based analysis. *Radiology* 268:170–180. <https://doi.org/10.1148/radiol.13122004>
- Messina R, Rocca MA, Colombo B et al (2018) Gray matter volume modifications in migraine. *Neurology* 91:e280–e292. <https://doi.org/10.1212/WNL.0000000000005819>
- Mesulam MM (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 28:597–613. <https://doi.org/10.1002/ana.410280502>
- Metsahonkala L, Anttila P, Laimi K et al (2006) Extracerebral tenderness and pressure pain threshold in children with headache. *Eur J Pain* 10:581–585
- Meylakh N, Marciszewski KK, Di Pietro F et al (2018) Deep in the brain: changes in subcortical function immediately preceding a migraine attack. *Hum Brain Mapp* 39:2651–2663. <https://doi.org/10.1002/hbm.24030>
- Michels L, Christidi F, Steiger VR et al (2017) Pain modulation is affected differently in medication-overuse headache and chronic myofascial pain—a multimodal MRI study. *Cephalalgia* 37:764–779. <https://doi.org/10.1177/0333102416652625>
- Mo J, Maizels M, Ding M, Ahn AH (2013) Does throbbing pain have a brain signature? *Pain* 154:1150–1155. <https://doi.org/10.1016/j.pain.2013.02.013>
- Moulton EA, Burstein R, Tully S et al (2008) Interictal dysfunction of a brainstem descending modulatory center in migraine patients. *PLoS One* 3:10
- Moulton EA, Becerra L, Maleki N et al (2011) Painful heat reveals hyperexcitability of the temporal pole in interictal and ictal migraine states. *Cereb Cortex (New York, NY 1991)* 21:435–448
- Mouraux A, Iannetti GD (2018) The search for pain biomarkers in the human brain. *Brain* 141:3290–3307. <https://doi.org/10.1093/brain/awy281>

- Nahman-Averbuch H, Granovsky Y, Coghil RC et al (2013) Waning of “conditioned pain modulation”: a novel expression of subtle pronociception in migraine. *Headache J Head Face Pain* 53:1104–1115. <https://doi.org/10.1111/head.12117>
- Nahman-Averbuch H, Leon E, Hunter BM et al (2019) Increased pain sensitivity but normal pain modulation in adolescents with migraine. *Pain* 160:1019–1028. <https://doi.org/10.1097/j.pain.0000000000001477>
- Neeb L, Bastian K, Villringer K et al (2017) Structural gray matter alterations in chronic migraine: implications for a progressive disease? *Headache* 57:400–416. <https://doi.org/10.1111/head.13012>
- Nguyen B, Vingrys AJ, McKendrick AM (2014) The effect of duration post-migraine on visual electrophysiology and visual field performance in people with migraine. *Cephalalgia* 34:42–57
- Nicolodi M, Galeotti N, Ghelardini C et al (2002) Central cholinergic challenging of migraine by testing second-generation anticholinesterase drugs. *Headache* 42:596–602
- Niddam DM, Lai K-L, Fuh J-L et al (2016) Reduced functional connectivity between salience and visual networks in migraine with aura. *Cephalalgia* 36:53–66. <https://doi.org/10.1177/0333102415583144>
- Noseda R, Kainz V, Jakubowski M et al (2010) A neural mechanism for exacerbation of headache by light. *Nat Neurosci* 13:239–245
- Okamoto K, Thompson R, Tashiro A et al (2009) Bright light produces Fos-positive neurons in caudal trigeminal brainstem. *Neuroscience* 160:858–864. <https://doi.org/10.1016/j.neuroscience.2009.03.003>
- Palacios-Ceña M, Lima Florencio L, Natália Ferracini G et al (2016) Women with chronic and episodic migraine exhibit similar widespread pressure pain sensitivity. *Pain Med* 17:2127–2133. <https://doi.org/10.1093/pain/pnw056>
- Perrotta A, Serrao M, Sandrini G et al (2010) Sensitisation of spinal cord pain processing in medication overuse headache involves supraspinal pain control. *Cephalalgia* 30:272–284
- Pierelli F, Iacovelli E, Bracaglia M et al (2013) Abnormal sensorimotor plasticity in migraine without aura patients. *Pain* 154:1738–1742
- Porcaro C, Di Lorenzo G, Seri S et al (2017) Impaired brainstem and thalamic high-frequency oscillatory EEG activity in migraine between attacks. *Cephalalgia* 37:915–926. <https://doi.org/10.1177/0333102416657146>
- Riederer F, Gantenbein AR, Marti M et al (2013) Decrease of gray matter volume in the midbrain is associated with treatment response in medication-overuse headache: possible influence of orbitofrontal cortex. *J Neurosci* 33:15343–15349
- Rocca MA, Colombo B, Inglese M et al (2003) A diffusion tensor magnetic resonance imaging study of brain tissue from patients with migraine. *J Neurol Neurosurg Psychiatry* 74:501–503
- Rocca MA, Ceccarelli A, Falini A et al (2006) Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. *Stroke* 37:1765–1770
- Rocca MA, Pagani E, Colombo B et al (2008) Selective diffusion changes of the visual pathways in patients with migraine: a 3-T tractography study. *Cephalalgia* 28:1061–1068. <https://doi.org/10.1111/j.1468-2982.2008.01655.x>
- Rocca M, Messina R, Colombo B et al (2014) Structural brain MRI abnormalities in pediatric patients with migraine. *J Neurol* 261:350–357
- Russo A, Tessoro A, Esposito F et al (2012a) Pain processing in patients with migraine: an event-related fMRI study during trigeminal nociceptive stimulation. *J Neurol* 259:1903–1912. <https://doi.org/10.1007/s00415-012-6438-1>
- Russo A, Tessoro A, Giordano A et al (2012b) Executive resting-state network connectivity in migraine without aura. *Cephalalgia* 32:1041–1048
- Russo A, Marcelli V, Esposito F et al (2014) Abnormal thalamic function in patients with vestibular migraine. *Neurology* 82:2120–2126
- Russo A, Esposito F, Conte F et al (2017a) Functional interictal changes of pain processing in migraine with ictal cutaneous allodynia. *Cephalalgia* 37:305–314. <https://doi.org/10.1177/0333102416644969>
- Russo A, Tessoro A, Esposito F et al (2017b) Functional changes of the perigenual part of the anterior cingulate cortex after external trigeminal neurostimulation in migraine patients. *Front Neurol* 8:282. <https://doi.org/10.3389/fneur.2017.00282>
- Russo A, Tessoro A, Silvestro M et al (2019) Advanced visual network and cerebellar hyperresponsiveness to trigeminal nociception in migraine with aura. *J Headache Pain* 20:46. <https://doi.org/10.1186/s10194-019-1002-3>
- Sakai Y, Dobson C, Diksic M et al (2008) Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis. *Neurology* 70:431–439. <https://doi.org/10.1212/01.wnl.0000299095.65331.6f>
- Sand T, Zhitniy N, Nilsen KB et al (2008a) Thermal pain thresholds are decreased in the migraine preattack phase. *Eur J Neurol* 15:1199–1205
- Sand T, Zhitniy N, White LR, Stovner LJ (2008b) Brainstem auditory-evoked potential habituation and intensity-dependence related to serotonin metabolism in migraine: a longitudinal study. *Clin Neurophysiol* 119:1190–1200
- Sándor P, Ambrosini A, Agosti RM, Schoenen J (2002) Genetics of migraine: possible links to neurophysiological abnormalities. *Headache* 42:365–377
- Sandrini G, Proietti Cecchini A, Milanov I et al (2002) Electrophysiological evidence for trigeminal neuron sensitization in patients with migraine. *Neurosci Lett* 317:135–138
- Scher AI, Stewart WF, Ricci JA, Lipton RB (2003) Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 106:81–89
- Schmidt-Wilcke T, Gänssbauer S, Neuner T et al (2008) Subtle grey matter changes between migraine patients and healthy controls. *Cephalalgia* 28:1–4
- Schmitz N, Admiraal-Behloul F, Arkink EB et al (2008) Attack frequency and disease duration as indicators for brain damage in migraine. *Headache* 48:1044–1055
- Schoenen J, Bottin D, Hardy F, Gerard P (1991) Cephalic and extracephalic pressure pain thresholds in chronic tension-type headache. *Pain* 47:145–149
- Schulte LH, May A (2016) The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* 139:1987–1993. <https://doi.org/10.1093/brain/aww097>
- Schulte LH, Allers A, May A (2017) Hypothalamus as a mediator of chronic migraine. *Neurology* 88:2011–2016. <https://doi.org/10.1212/WNL.0000000000003963>
- Schulte LH, Allers A, May A (2018) Visual stimulation leads to activation of the nociceptive trigeminal nucleus in chronic migraine. *Neurology* 90:e1973–e1978. <https://doi.org/10.1212/WNL.0000000000005622>
- Schwedt TJ, Krauss MJ, Frey K, Gereau RW (2011) Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. *Cephalalgia* 31:6–12
- Schwedt TJ, Chong CD, Chiang C-C et al (2014) Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. *Cephalalgia* 34:947–958. <https://doi.org/10.1177/0333102414526069>
- Schwedt TJ, Zuniga L, Chong CD (2015) Low heat pain thresholds in migraineurs between attacks. *Cephalalgia* 35:593–599. <https://doi.org/10.1177/0333102414550417>

- Shepherd AJ, Wyatt G, Tibber MS (2011) Visual metacontrast masking in migraine. *Cephalalgia* 31:346–356
- Sicuteri F (1976) Hypothesis: migraine, a central biochemical dys-nociception. *Headache* 16:145–159
- Siniatchkin M, Gerber WD, Kropp P et al (2000) Are the periodic changes of neurophysiological parameters during the pain-free interval in migraine related to abnormal orienting activity? *Cephalalgia* 20:20–29
- Soheili-Nezhad S, Sedghi A, Schweser F et al (2019) Structural and functional reorganization of the brain in migraine without aura. *Front Neurol*. <https://doi.org/10.3389/fneur.2019.00442>
- Sprenger T, Borssook D (2012) Migraine changes the brain: neuroimaging makes its mark. *Curr Opin Neurol* 25:252–262
- Stankewitz A, May A (2011) Increased limbic and brainstem activity during migraine attacks following olfactory stimulation. *Neurology* 77:476–482
- Stankewitz A, Aderjan D, Eippert F, May A (2011) Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *J Neurosci* 31:1937–1943
- Stankewitz A, Schulz E, May A (2013) Neuronal correlates of impaired habituation in response to repeated trigemino-nociceptive but not to olfactory input in migraineurs: an fMRI study. *Cephalalgia* 33:256–265
- Szabó N, Kincses ZT, Párdutz A et al (2012) White matter microstructural alterations in migraine: a diffusion-weighted MRI study. *Pain* 153:651–656
- Szabó N, Faragó P, Király A et al (2018) Evidence for plastic processes in migraine with aura: a diffusion weighted MRI study. *Front Neuroanat* 11:138. <https://doi.org/10.3389/fnana.2017.00138>
- Tedeschi G, Russo A, Conte F et al (2016) Increased interictal visual network connectivity in patients with migraine with aura. *Cephalalgia* 36:139–147. <https://doi.org/10.1177/0333102415584360>
- Teepker M, Peters M, Kundermann B et al (2011) The effects of oral contraceptives on detection and pain thresholds as well as headache intensity during menstrual cycle in migraine. *Headache* 51:92–104. <https://doi.org/10.1111/j.1526-4610.2010.01775.x>
- Teepker M, Kunz M, Peters M et al (2014) Endogenous pain inhibition during menstrual cycle in migraine. *Eur J Pain* 18:989–998
- Tessitore A, Russo A, Giordano A et al (2013) Disrupted default mode network connectivity in migraine without aura. *J Headache Pain* 14:89
- Tessitore A, Russo A, Conte F et al (2015) Abnormal connectivity within executive resting-state network in migraine with aura. *Headache J Head Face Pain* 55:794–805. <https://doi.org/10.1111/head.12587>
- Uglem M, Omland PM, Nilsen KB et al (2017a) Does pain sensitivity change by migraine phase? A blinded longitudinal study. *Cephalalgia* 37:1337–1349. <https://doi.org/10.1177/0333102416679955>
- Uglem M, Omland PM, Stjern M et al (2017b) Habituation of laser-evoked potentials by migraine phase: a blinded longitudinal study. *J Headache Pain* 18:100. <https://doi.org/10.1186/s10194-017-0810-6>
- Uthakhpur S, Sterling M, Jull G (2009) Widespread sensory hypersensitivity is not a feature of chronic headache in elders. *Clin J Pain* 25:699–704. <https://doi.org/10.1097/AJP.0b013e3181a38f88>
- Valeriani M, Tommaso D, Restuccia D et al (2003) Reduced habituation to experimental pain in migraine patients: a CO₂ laser evoked potential study. *Pain* 105:57–64
- Valfrè W, Rainero I, Bergui M, Pinessi L (2008) Voxel-based morphometry reveals gray matter abnormalities in migraine. *Headache* 48:109–117
- Vecchio E, Ricci K, Montemurno A et al (2016) Effects of left primary motor and dorsolateral prefrontal cortex transcranial direct current stimulation on laser-evoked potentials in migraine patients and normal subjects. *Neurosci Lett* 626:149–157. <https://doi.org/10.1016/j.neulet.2016.05.034>
- Vecchio E, Bassez I, Ricci K et al (2018a) Effect of non-invasive vagus nerve stimulation on resting-state electroencephalography and laser-evoked potentials in migraine patients: mechanistic insights. *Front Hum Neurosci* 12:366. <https://doi.org/10.3389/fnhum.2018.00366>
- Vecchio E, Gentile E, Franco G et al (2018b) Effects of external trigeminal nerve stimulation (eTNS) on laser evoked cortical potentials (LEP): a pilot study in migraine patients and controls. *Cephalalgia* 38:1245–1256. <https://doi.org/10.1177/0333102417728748>
- Veréb D, Szabó N, Tuka B et al (2018) Correlation of neurochemical and imaging markers in migraine. *Neurology* 91:e1166–e1174. <https://doi.org/10.1212/WNL.0000000000006201>
- Wang W, Timsit-Berthier M, Schoenen J (1996) Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? *Neurology* 46:1404–1409
- Wang T, Zhan W, Chen Q et al (2016) Altered resting-state ascending/descending pathways associated with the posterior thalamus in migraine without aura. *Neuroreport* 27:257–263. <https://doi.org/10.1097/WNR.0000000000000529>
- Weiller C, May A, Limmroth V et al (1995) Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1:658–660
- Weissman-Fogel I (2003) Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. *Pain* 104:693–700. [https://doi.org/10.1016/S0304-3959\(03\)00159-3](https://doi.org/10.1016/S0304-3959(03)00159-3)
- Welch KMA, Nagesh V, Aurora SK, Gelman N (2001) Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? *Headache* 41:629–637. <https://doi.org/10.1046/j.1526-4610.2001.041007629.x>
- Williams AE, Miller MM, Bartley EJ et al (2019) Impairment of inhibition of trigeminal nociception via conditioned pain modulation in persons with migraine headaches. *Pain Med*. <https://doi.org/10.1093/pm/pny305>
- Woolf CJ (2011) Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 152:S2–S15
- Wutzler A, Winter C, Kitzrow W et al (2008) Loudness dependence of auditory evoked potentials as indicator of central serotonergic neurotransmission: simultaneous electrophysiological recordings and in vivo microdialysis in the rat primary auditory cortex. *Neuropsychopharmacology* 33:3176–3181
- Xue T, Yuan K, Zhao L et al (2012) Intrinsic brain network abnormalities in migraines without aura revealed in resting-state fMRI. *PLoS One* 7:10
- Yang F-C, Chou K-H, Hsu A-L et al (2018) Altered brain functional connectome in migraine with and without restless legs syndrome: a resting-state functional MRI study. *Front Neurol* 9:25. <https://doi.org/10.3389/fneur.2018.00025>
- Yu D, Yuan K, Zhao L et al (2012) Regional homogeneity abnormalities in patients with interictal migraine without aura: a resting-state study. *NMR Biomed* 25:806–812
- Yu D, Yuan K, Zhao L et al (2013) White matter integrity affected by depressive symptoms in migraine without aura: a tract-based spatial statistics study. *NMR Biomed* 26:1103–1112
- Yu D, Yuan K, Luo L et al (2017a) Abnormal functional integration across core brain networks in migraine without aura. *Mol Pain* 13:174480691773746. <https://doi.org/10.1177/1744806917737461>
- Yu Z, Lv Y, Song L et al (2017b) Functional connectivity differences in the insular sub-regions in migraine without aura: a resting-state functional magnetic resonance imaging study. *Front Behav Neurosci* 11:124. <https://doi.org/10.3389/fnbeh.2017.00124>

- Yuan K, Qin W, Liu P et al (2012) Reduced fractional anisotropy of corpus callosum modulates inter-hemispheric resting state functional connectivity in migraine patients without aura. *PLoS One* 7:10
- Yuan K, Zhao L, Cheng P et al (2013) Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. *J Pain* 14:836–844
- Zambreanu L, Wise RG, Brooks JC et al (2005) A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. *Pain* 114:397–407
- Zappaterra M, Guerzoni S, Cainazzo MM et al (2011) Basal cutaneous pain threshold in headache patients. *J Headache Pain* 12:303–310. <https://doi.org/10.1007/s10194-011-0313-9>
- Zhao L, Liu J, Dong X et al (2013) Alterations in regional homogeneity assessed by fMRI in patients with migraine without aura stratified by disease duration. *J Headache Pain* 14:85
- Zohsel K, Hohmeister J, Oelkers-Ax R et al (2006) Quantitative sensory testing in children with migraine: preliminary evidence for enhanced sensitivity to painful stimuli especially in girls. *Pain* 123:10–18

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.