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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Cortical pain processing in migraine

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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

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pain processing in patients who are affected by migraine (Sprenger 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 (Bolay 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 (Uthaikhup 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 (Uglem et al. 2017a, b).

Another way to judge subjective PPI is to verify the threshold of pain perception in response to a painful CO_2 laser or contact heat stimulus and record the resulting cortical response, termed pain-related evoked potentials (PREPs). Using a CO_2 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 extracephalic (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; Stankewitz 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; Kisler 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 postsynaptic 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 symptomology.

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

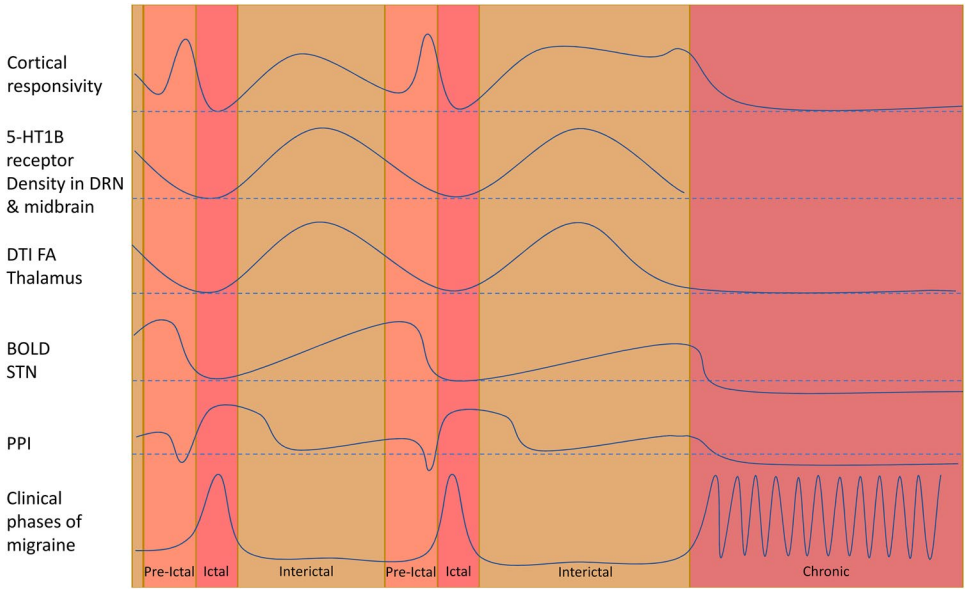

Fig. 1 Schematic representation of the results provided by the studies that found a correlation between different clinical, morphological, or functional variables and the number of days elapsed since the last migraine attack. During the interictal phase, the BOLD activity of the spinal trigeminal nucleus (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 midbrain approach their minimum. During the headache phase, when PPI reaches its maximum increase, STN BOLD activity, as well as thalamic FA and 5-HT1B 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 multisensory 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 orbitofrontal 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 frontoinsular 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).

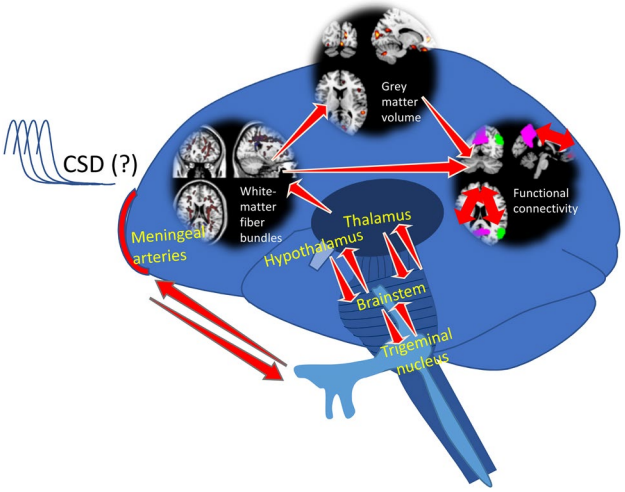

Fig. 2 Schematic representation of the possible pain processing model in migraine. Migraine may involve irritation of meningeal perivascular nociceptive trigeminal nerve endings. It is not known whether this involvement is initiated by cortical spreading depression (CSD), manifested in migraine with 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.

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