Insights into migraine attacks from neuroimaging

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Migraine is one of the most common neurological diseases and it has a huge social and personal impact. Although head pain is the core symptom, individuals with migraine can have a plethora of non-headache symptoms that precede, accompany, or follow the pain. Neuroimaging studies have shown that the involvement of specific brain areas can explain many of the symptoms reported during the different phases of migraine. Recruitment of the hypothalamus, pons, spinal trigeminal nucleus, thalamus, and visual and pain-processing cortical areas starts during the premonitory phase and persists through the headache phase, contributing to the onset of pain and associated symptoms. Once the pain stops, the involvement of most brain areas ends, although the pons, hypothalamus, and visual cortex remain active after acute treatment intake and resolution of migraine symptoms. A better understanding of the correlations between imaging findings and migraine symptomatology can provide new insight into migraine pathophysiology and the mechanisms of novel migraine-specific treatments.

Introduction

Migraine is one of the most frequent neurological diseases with a huge social and personal impact.[1] According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2019, migraine is the leading cause of disability in people younger than 50 years.[2] Migraine is characterised by recurring episodes of headache and non-headache symptoms, commonly interspersed with asymptomatic periods. The migraine attack can progress through different phases that are sequential but overlapping; namely, the premonitory, aura, headache, postdromal, and interictal phases. The core symptom of migraine is headache pain that, by its presence or absence, marks the transition through the headache phase. However, individuals with migraine can also have a plethora of non-headache symptoms, such as nausea, photophobia, and concentration difficulties, which precede, accompany, or follow the pain.[3]

The pathogenesis of migraine is complex, with an interplay between multiple neuronal networks, and increased release and inadequate clearance of neuropeptides. Although the mechanisms that cause a migraine attack are unknown, migraine is recognised to involve the activation and sensitisation of the trigeminovascular system, brainstem, and diencephalic and cortical areas.[4] Many neuroimaging studies have explored the mechanisms underlying migraine pain and the wide range of associated symptoms, and have shown that the involvement of specific brain areas can explain the symptoms reported during the different phases of the disease.[5]

This Review aims to highlight findings since 2014, on the functional and structural brain alterations associated with symptoms that characterise the acute phases of migraine (premonitory, aura, headache, and postdromal phases), and to discuss the association between interictal brain characteristics and acute migraine symptoms. As migraine-specific drugs are now available, insights into the mechanisms underlying migraine symptoms from neuroimaging studies will be crucial to improve understanding of how these novel treatments work.

Premonitory phase

The premonitory phase starts before headache onset and can last for up to 3 days. Premonitory symptoms can be broadly categorised as: fatigue or cognitive changes, including irritability, concentration difficulties, lethargy, mood disturbances, and speech difficulty; homoeostatic alterations, such as yawning, food craving, food aversion, thirst, and frequent urination; sensory hypersensitivities, including photophobia, phonophobia, and neck stiffness; and gastrointestinal symptoms, such as nausea and abdominal pain.[6] The most commonly reported premonitory symptoms are tiredness, photophobia, phonophobia, and mood changes.[7]

Functional imaging techniques, such as SPECT, PET, and functional MRI (fMRI) have been used to examine people with migraine during the premonitory phase. SPECT and PET approaches provide information regarding the metabolism and function of brain areas by use of radiolabelled molecules.[8] The blood oxygenation level-dependent (BOLD) signal is used in fMRI to measure regional changes in blood oxygenation. As a result, fMRI approaches provide information on the location and amount of activation in different brain areas at rest, or when performing a particular task.[9] Studies exploring neural correlates of premonitory symptoms have provided several main findings (table 1).

In a ground-breaking PET study, Maniyar and colleagues[10] reported that eight patients with migraine who had nitroglycerin-triggered premonitory symptoms showed a greater activation of the hypothalamus, periaqueductal grey matter, ventral tegmental area, dorsal pons, and several occipital, temporal, parietal, frontal, and cerebellar brain areas compared to the baseline status of the same patients when they were symptom free. Involvement of the hypothalamus in the premonitory phase was confirmed by two fMRI studies, in which individuals with migraine were studied daily for a month during nociceptive trigeminal stimulation.[16,17] These studies revealed a higher hypothalamic activity and an altered functional interaction between the hypothalamus and the spinal trigeminal nucleus before the headache onset.[16,17] However, in these two studies, the premonitory

	Cohort (n)	Imaging modality	Experimental paradigm (n)	Results*	Study†
Premonitory					
Yawning, fatigue, nausea, neck stiffness, concentration difficulties, photophobia, polyuria, thirst, and mood changes	Patients with episodic migraine without aura (8)	PET	Nitroglycerin-triggered migraine attacks (8)	Baseline *vs* triggered attacks: increased activation of the hypothalamus, periaqueductal grey matter, ventral tegmental area, dorsal pons, and several occipital, temporal, parietal, frontal, and cerebellar brain areas	Maniyar et al (2014)[10]
Yawning, fatigue, nausea, neck stiffness, concentration difficulties, osmophobia, food cravings, and polyuria	Patients with episodic migraine without aura (12) and healthy controls (10)	fMRI in response to oral glucose administration	Nitroglycerin-triggered migraine attacks (12), spontaneous migraine attacks (5), and nitroglycerin-administration in controls (10)	Baseline *vs* triggered or spontaneous attacks in patients: fast and abrupt increase of the hypothalamic BOLD response in both patients with triggered and spontaneous migraine attacks; baseline *vs* attacks in controls: no functional changes	van Oosterhout et al (2021)[11]
Tiredness, photophobia, and concentration difficulties	Patients with migraine with aura (11) and patients with migraine without aura (10)	Resting state fMRI	Nitroglycerin-triggered migraine attacks (21) and placebo administration (21)	Baseline *vs* triggered attacks: decreased functional connectivity between the pons and limbic cortical areas; baseline *vs* triggered attacks and placebo *vs* nitroglycerin: decreased thalamic connectivity with the cuneus and precuneus in the nitroglycerin group	Karsan et al (2020)[12]
Photophobia	Patients with episodic migraine without aura (10)	PET	Nitroglycerin-triggered migraine attacks with photophobia (5) and nitroglycerin-triggered migraine attacks without photophobia (5)	Baseline *vs* triggered attacks, and no photophobia *vs* photophobia: increased activation of the extrastriate visual cortex and precentral gyrus in patients with photophobia compared with patients without photophobia	Maniyar et al (2014)[13]
Nausea	Patients with episodic migraine without aura (10)	PET	Nitroglycerin-triggered migraine attacks with nausea (5) and nitroglycerin-triggered migraine attacks without nausea (5)	Baseline *vs* triggered attacks, and no nausea *vs* nausea: increased activation of the rostral dorsal medullary area and periaqueductal grey matter in patients with nausea compared with patients without nausea	Maniyar et al (2014)[14]
Aura					
Visual scotoma (negative symptoms), and flickering white spots (positive symptoms)	Patients with episodic migraine with aura (5)	fMRI during visual stimulation	Hypoxia-triggered aura attacks (3), aura attacks triggered by sham hypoxia (1), aura attacks triggered by combined exercise and photostimulation (1)	Baseline *vs* aura: increased activation of the V1–V4 visual areas in patients with positive symptoms and decreased activation of the V1–V4 visual areas in patients with negative symptoms	Arngrim et al (2017)[15]

BOLD=blood oxygenation level dependent. fMRI=functional MRI. *During the baseline visit patients were migraine-free. †Only studies published from Jan 1, 2014, to March 14, 2023, are reported, in agreement with our search criteria.

Table 1: **Studies exploring neural correlates of symptoms during the premonitory and aura phases of migraine**

phase was defined as the last 48 h preceding the headache onset, and not according to the presence of premonitory symptoms. A 2021 fMRI study[11] explored hypothalamic activity in response to oral glucose ingestion during the premonitory phase of spontaneous (five patients) and nitroglycerin-triggered (12 patients) migraine attacks. In both patients with migraine and people in the control group, at baseline, the hypothalamic BOLD response to glucose showed a steep decrease followed by a slow recovery, which was characterised by an increase in BOLD response back to baseline. During the premonitory phase of both triggered and spontaneous migraine attacks, the hypothalamic BOLD response after glucose administration presented a faster recovery compared with people in the control group with no migraine. These results suggest that hypothalamic activity is altered during the premonitory phase of nitroglycerin-provoked and spontaneous migraine attacks.

The hypothalamus is highly connected to distinct cortical and subcortical brain areas, and plays an important role in body homoeostasis, including control of feeding, thirst, and the sleep–wake cycle, and in autonomic and endocrine regulation.[18] Hypothalamic activation could be responsible for premonitory symptoms such as thirst, food craving, and yawning, and might explain why the brain is vulnerable to homoeostatic changes during the premonitory period.[6,10] Hypothalamic neurotransmitters possibly implicated in such symptoms are dopamine, orexin, somatostatin, and vasopressin.[3]

Evidence from animal models of migraine suggests that premonitory fatigue could be mediated by the hypothalamic orexinergic system and the noradrenergic pathway of the locus coeruleus located in the pons.[19,20] Mood changes and cognitive and sensory symptoms in the premonitory phase might be mediated by functional reorganisation of subcortical–cortical networks, including

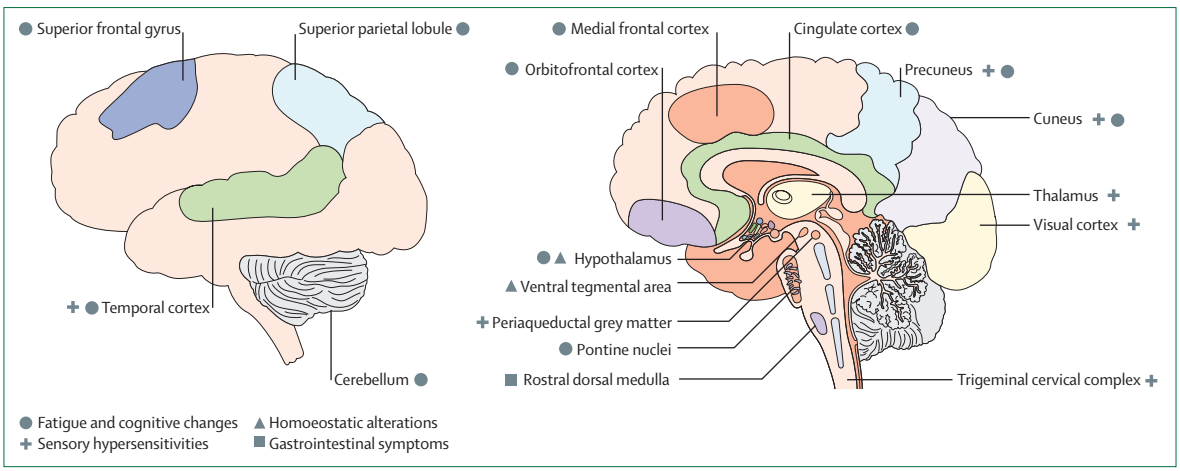

Figure 1: **Brain areas implicated in symptoms during the premonitory phase of migraine**
Fatigue or cognitive changes are thought to involve the hypothalamus, pons, and frontal, parietal, temporal, and cerebellar regions. Homoeostatic alterations are thought to involve the hypothalamus and ventral tegmental area. Sensory hypersensitivities are thought to involve the thalamus, periaqueductal grey, trigeminal cervical complex, and visual, parietal, and temporal areas. Gastrointestinal symptoms are thought to involve the rostral dorsal medulla. Figure created with BioRender.com.

diencephalic, brainstem, and cortical areas. In a 2020 fMRI study, Karsan and colleagues[12] explored the resting state functional connectivity of brain areas implicated in migraine pathogenesis during the nitroglycerin-triggered premonitory phase in 21 patients. The study showed a decreased functional interplay between the pons and limbic cortical areas (ie, the medial frontal gyrus and anterior cingulate cortex), and reduced functional thalamic connectivity with the cuneus and precuneus.[12] Functional reorganisation of cortical frontal and parietal areas implicated in cognitive processing might be responsible for the cognitive symptoms, including concentration difficulties, reported by patients during the triggered premonitory phase.[12]

Although nausea, photophobia, and phonophobia are characterise the headache phase of migraine, many patients can have such symptoms during the premonitory phase.[21] A PET study compared patients with nitroglycerin-triggered premonitory photophobia with those without, revealing an association between photophobia and increased activity of extrastriate cortical visual areas.[13] Higher activity of the rostral dorsal medullary area and periaqueductal grey matter in patients with nausea has also been shown to occur during the premonitory phase compared with patients without nausea.[14] These findings suggest that central sites mediate the onset of nausea and photophobia before pain onset. The brain regions mediating migraine premonitory symptoms are shown in figure 1.

Aura phase

Headache pain in 20–30% of people with migraine can be preceded by migraine aura.[22,23] Migraine aura is characterised by fully reversible, focal neurological symptoms that spread gradually, lasting between 5 min and 60 min.[24] More than 90% of people with migraine experiencing aura have a visual aura, which usually starts with zigzag lines or scintillations (ie, positive visual disturbances) propagating from the centre of the visual field to the periphery, or from the periphery to the centre. Sometimes, positive visual disturbances are followed by a central scotoma (ie, negative visual disturbances).[23,25,26] Sensory aura consist of unilateral paraesthesia or numbness that begins in the hand and spreads to the entire upper limb, sometimes involving the ipsilateral face and tongue; and dysphasic aura consists of transient speech or language problems. Both sensory and dysphasic aura are less common than visual aura. Non-visual aura symptoms can occur concurrently with visual disturbances or, less frequently, independently.[27]

There is ample evidence suggesting that cortical spreading depression (CSD), a wave of neuronal depolarisation followed by depression of cortical activity, is the physiological mechanism underpinning migraine aura.[25,28,29] Neurophysiological studies have shown that CSD propagates with a speed of 3 mm/min and lasts for several minutes.[30] In conjunction with CSD, an initial increased blood flow followed by sustained oligaemia is observed in animal models.[3] The similarities between CSD and patient descriptions of their visual aura, as a propagating wave of visual disturbances that spread across the visual field at a rate of 3–6 mm/min, have strengthened the hypothesis that CSD could be the pathogenic substrate of migraine with aura.[26,31]

Neuroimaging studies have further corroborated the association between CSD and migraine aura by showing a wave of oligaemia that originated in the occipital cortex and progressively moved to the anterior brain regions during the aura phase.[5] Using fMRI during checkerboard visual stimulation, Hadjikhani and colleagues[32] investigated the brain activity of three patients with spontaneous or exercise-induced visual aura. They found

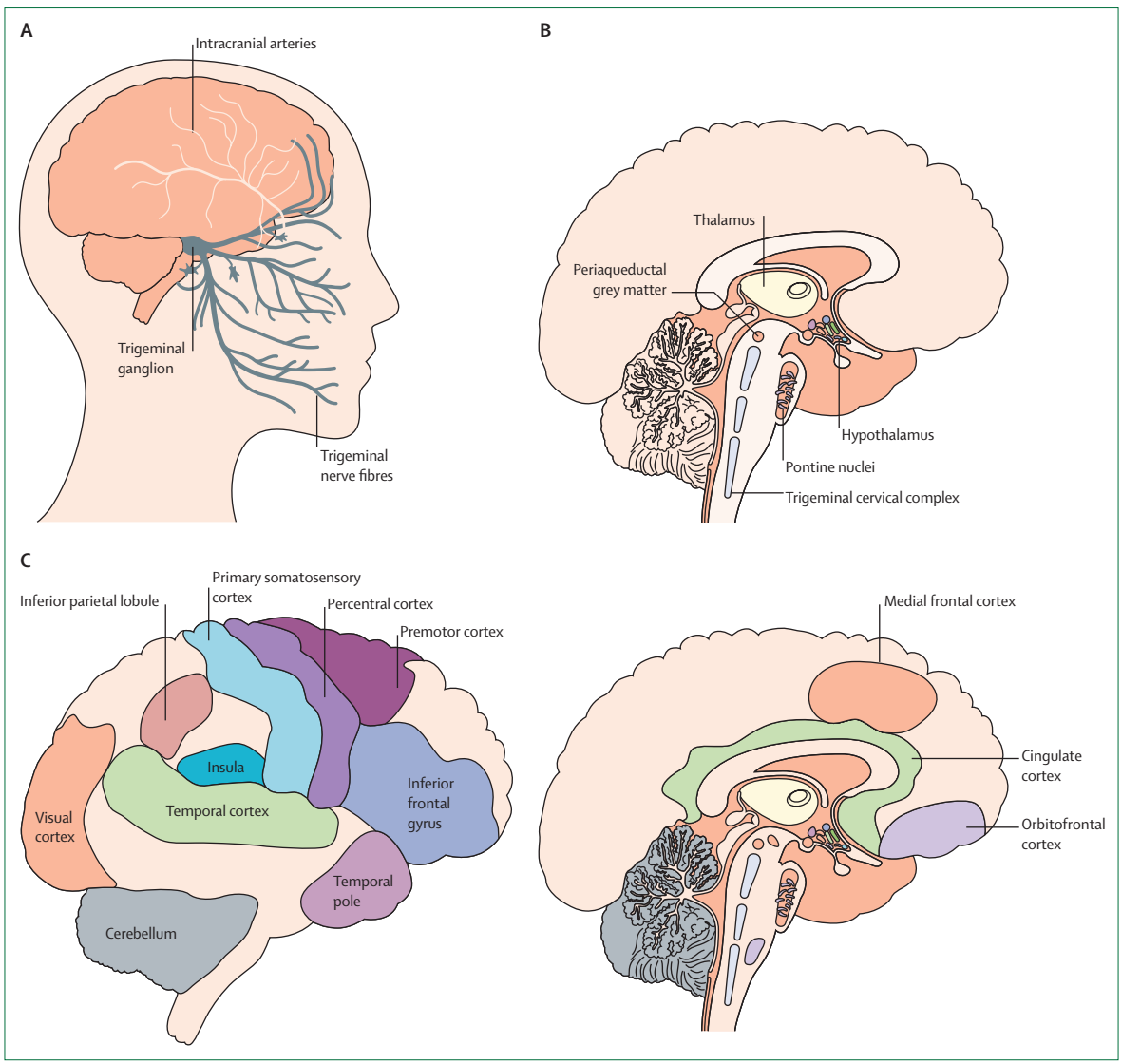

Figure 2: **Structures implicated in pain during the headache phase of migraine**
(A) Nociceptive trigeminal nerve fibres originating from first-order trigeminovascular neurons located in the trigeminal ganglion peripherally innervate extracranial and intracranial arteries, and centrally project to second-order trigeminovascular neurons of the trigeminocervical complex in the brainstem and the upper cervical spinal cord. (B) Second-order trigeminovascular neurons are connected to other brainstem and subcortical regions, including the pons, periaqueductal grey matter, hypothalamus, and thalamus. (C) Subcortical structures relay the nociceptive transmission to the cerebellum and cortical areas involved in the processing of nociceptive stimuli, leading to the perception of pain. Figure created with BioRender.com.

an increased BOLD response of the extrastriate visual areas MT and V3A, which progressed over the contiguous cortex, to occur concomitantly with the onset of scintillations.[32] A decreased BOLD response followed, and was associated with patient perceptions of visual scotoma.[32] These findings were confirmed in an fMRI study with visual stimulation that investigated five patients during migraine aura induced by hypoxia or physical exercise.[15] During the aura, three patients reported visual scotoma, which was associated with a decreased BOLD response in the visual cortex, and two patients had visual flickering that was associated with an increased BOLD response in the visual cortex.[15] Overall, these results suggest an association between positive aura symptoms and visual cortex hyperexcitability, and between negative aura symptoms and reduced neural activity.

Headache phase

Pain

Migraine pain is a unilateral or bilateral throbbing pain of moderate or severe intensity, which can last 4–72 h and can be exacerbated by physical activity.[24] The trigeminovascular system plays a pivotal role in migraine pain. Nociceptive trigeminal nerve fibres, originating from first-order trigeminovascular neurons in the trigeminal ganglion, peripherally innervate the meninges, extracranial arteries,

and intracranial arteries. The nerve fibres also centrally project to second-order trigeminovascular neurons of the trigeminal cervical complex, located in the brainstem and the upper cervical spinal cord.[33] Second-order trigeminovascular neurons are connected to other brainstem regions, including the pons, periaqueductal grey matter, hypothalamus, thalamus, and cortical areas involved in the processing of nociceptive stimuli, thus leading to the perception of pain (figure 2).[34] The main findings of studies exploring neural correlates of symptoms during the headache phase are summarised in table 2.

Migraine throbbing pain was initially assumed to be caused by the dilation of extracranial and intracranial vessels that activate trigeminal nociceptors. This theory was supported by the finding that ergotamine, a vasoconstrictor, blocked migraine attacks. On this basis, many studies have investigated haemodynamic changes of cerebral and meningeal vessels in patients with migraine.[48] Early SPECT studies revealed an increase in regional cerebral blood flow during the headache phase of spontaneous migraine attacks in patients with migraine with aura, which followed the oligaemia observed during the aura. However, no changes in the regional cerebral blood flow were found in the headache phase of patients with migraine without aura.[49] Using magnetic resonance angiography, Amin and colleagues[50] investigated 19 patients with migraine without aura during spontaneous migraine attacks, and showed that migraine pain is associated with only modest intracranial dilation of the middle cerebral and internal carotid arteries (vessel diameter increased by around 10%) but not with extracranial arterial dilation. A later magnetic resonance angiography study[35] showed dilation of the middle meningeal artery on the pain side during cilostazol-induced unilateral migraine attacks without aura. The middle meningeal artery dilated further in the following 24 h on both the pain and non-pain sides, implying that early unilateral activation of perivascular nociceptors could be followed by bilateral activation and sensitisation of trigeminal perivascular nociceptors. In both studies,[35,50] administration of effective acute treatments, such as triptans, did not change the dilation of cerebral arteries. Taken together, these results suggest that small intracranial arterial dilation, but not extracranial vascular changes, can occur in patients with migraine, although they are not sufficient to cause the migraine pain simply through mechanical distention, and are unrelated to the ameliorating effect of therapies. CSD has been hypothesised to activate and sensitise perivascular trigeminal afferents in patients with migraine with and without aura, thus resulting in the onset of migraine pain.[51,52]

Although the mechanisms that lead to the onset of migraine pain remain unclear, imaging advances have shifted our understanding of migraine pain from a vascular to a neuro-vascular process, during which neuronal alterations trigger the vascular changes and sensitisation of the trigeminovascular pathway. During the headache phase of spontaneous migraine attacks, early PET studies found higher activity of the dorsal pons, hypothalamus, and cingulate, frontal, visual, and auditory cortices compared with the interictal phase.[53,54] The dorsal pons and hypothalamus are key areas implicated in migraine pain. Pontine nuclei, such as the locus coeruleus, rostral ventromedial medulla, and nucleus raphe magnus are part of the endogenous pain modulatory pathway.[55] Hypothalamic descending projections connecting the hypothalamus to the trigeminal cervical complex, periaqueductal grey matter, and pontine nuclei modulate the trigeminovascular nociceptive processing.[3] Schulte and colleagues[36] used fMRI during painful intranasal ammonia stimulation and showed that the most posterior part of the hypothalamus was specifically involved in the acute pain phase of the migraine attack. Several imaging studies evaluating patients with migraine during spontaneous[37,38,56] and triggered[10,12,57] attacks have reinforced the importance of the pons in the headache phase of migraine. A resting state fMRI study[37] of the headache phase of 16 patients with migraine following aura revealed a higher functional coupling between the pons and the ipsilateral primary somatosensory cortex, including the face and head areas compared with the interictal phase or symptom-free phase. The pons also showed increased resting state functional connectivity with pain processing brain areas, including the cerebellum, spinal trigeminal nucleus, cingulate, and frontal cortex, in patients with migraine, both with and without aura, during nitroglycerin-triggered attacks[12] compared with the interictal phase or symptom-free phase. Higher resting state functional connectivity between the pons and hypothalamus has also been shown during the pain phase in patients with migraine studied in the interictal phase and during trigeminal nociceptive stimulation.[16,39]

Using fMRI and cutaneous thermal stimulation, Maleki and colleagues[38] assessed the brain activity of 19 patients with migraine reporting extracephalic cutaneous allodynia, which is pain caused by the application of non-noxious stimuli to healthy skin[58] during the headache phase. The presence of extracephalic cutaneous allodynia during the ictal phase of migraine was associated with a higher activity of the pons, spinal trigeminal nucleus, thalamus, and insula. These findings suggest that cutaneous allodynia might be mediated by a greater activity of the trigeminothalamic circuit.

The thalamus is a sensory relay area that processes and integrates nociceptive stimuli.[59] Two resting state fMRI studies[40,41] showed an altered functional interaction between the thalamus and the pain-processing cortical and subcortical regions in patients with migraine during spontaneous and triggered migraine attacks compared with interictal or asymptomatic phases, supporting the hypothesis of thalamic involvement in the manifestation of migraine pain.

	Imaging modality	Experimental paradigm (n)	Results*	Study†
Patients with episodic migraine without aura (8)	PET	Nitroglycerin-triggered migraine attacks (8)	Baseline *vs* triggered attacks: increased activation of the pons, insula, cerebellum, claustrum, frontal and parietal brain areas	Maniyar et al (2014)[10]
Patient with episodic migraine without aura (1)	fMRI during painful intranasal ammonia stimulation	Spontaneous headache (1)	Baseline *vs* spontaneous attacks: increased activation of the pons and decreased activation of the visual cortex; increased functional connectivity between the hypothalamus and pons	Schulte and May (2016)[16]
Patients with migraine with aura (11) and patients with migraine without aura (10)	Resting state fMRI	Nitroglycerin-triggered migraine attacks (21), and placebo administration (21)	Baseline *vs* triggered attacks: increased functional connectivity between the pons and the cerebellar tonsils, and the pons and medulla, decreased functional connectivity between the pons and limbic cortical areas; baseline *vs* triggered attacks and nitroglycerin *vs* placebo: no functional changes	Karsan et al 2020[12]
Patients with migraine without aura (26)	Magnetic resonance angiography	Cilostazol-triggered migraine attacks (26)	Baseline *vs* triggered attacks: increased diameter of the middle meningeal artery on the pain side compared with non-pain side, which persisted during the late phase of the attack; untreated migraine attacks *vs* sumatriptan: decreased diameter of extracranial arteries after sumatriptan	Khan et al (2019)[35]
Patients with episodic migraine (18), patients with chronic migraine (17), and healthy controls (19)	fMRI during painful intranasal ammonia stimulation	Spontaneous headache (7 patients with episodic and 12 with chronic migraine) and patients without headache (11 patients with episodic and five patients with chronic migraine)	Patients with migraine without headache and controls *vs* patients with migraine with headache: increased activation of the posterior hypothalamus in patients with headache	Schulte et al (2017)[36]
Patients with migraine with aura (16)	Resting state fMRI	Spontaneous headache (16)	Baseline *vs* spontaneous attacks: increased functional connectivity between the pons and the primary somatosensory cortex and superior parietal lobule; increased functional connectivity between visual area V5 and the middle frontal gyrus	Hougaard et al (2017)[37]
Patients with episodic migraine without aura (14) and patients with episodic migraine with aura (5)	fMRI during painful heat stimulation of the hand	Patients with spontaneous headache (19 patients: seven with no allodynia, four with localised allodynia, and eight with extracephalic allodynia)	Baseline *vs* spontaneous attacks: increased activation of the pons, spinal trigeminal nucleus, insula, cerebellum, supramarginal gyrus, cingulum, frontal, temporal, and occipital brain areas; baseline *vs* spontaneous attacks and no allodynia *vs* extracephalic allodynia: increased activation of the pons, spinal trigeminal nucleus, insula, and thalamus in patients with extracephalic allodynia	Maleki et al (2021)[38]
Patients with episodic migraine without aura (7), and patient with episodic migraine with aura (1)	Resting state fMRI	Spontaneous headache (8)	Baseline *vs* spontaneous attacks: increased functional connectivity between the pons and the hypothalamus, and the pons and nucleus accumbens	Schulte et al (2020)[39]
Patients with episodic migraine without aura (17)	Resting state fMRI	Spontaneous headache (17)	Baseline *vs* spontaneous attacks: increased thalamic functional connectivity with the insula, parietal brain areas, primary motor and orbitofrontal cortex; decreased thalamic functional connectivity with the primary somatosensory and premotor cortex	Amin et al (2017)[40]
Patients with episodic migraine without aura (5)	Resting state fMRI	Nitroglycerin-triggered migraine attacks (5)	Baseline *vs* triggered attacks: decreased functional connectivity between the thalamus and the pons, cerebellum, and medial orbital gyrus; loss of functional synchronisation between the thalamus and the salience network	Martinelli et al (2021)[41]
Patients with episodic migraine without aura (13) and healthy controls (19)	Resting state fMRI	Spontaneous headache (13)	Controls *vs* patients: increased functional connectivity between the medial prefrontal and posterior cingulate cortex, and between the medial prefrontal cortex and insula within the default mode network in patients	Coppola et al (2017)[42]
Patients with migraine without aura (44) and healthy controls (32)	Resting state fMRI, and voxel-based morphometry	Spontaneous headache (10) and interictal phase (34)	Controls *vs* interictal patients: decreased functional connectivity between the middle frontal gyrus and the precuneus, cingulum, and superior frontal gyrus in patients; controls *vs* patients with headache: increased functional connectivity between the middle frontal gyrus and the cerebellum in patients; interictal *vs* patients with migraine with headache: decreased functional connectivity between the middle frontal gyrus and superior frontal gyrus in interictal patients; controls *vs* patients: decreased grey matter volume in the middle frontal gyrus in patients	Cao et al (2022)[43]
Patients with episodic migraine without aura (13) and healthy controls (19)	Resting state fMRI, DTI	Spontaneous headache (13)	Controls *vs* patients with migraine during untreated headache: decreased functional connectivity between the dorsoventral attention system and executive control network in patients; negative correlation between thalamic fractional anisotropy and the functional connectivity strength of the dorsoventral attention system in controls but not in patients	Coppola et al (2016)[44]

(Table 2 continues on next page)

	Imaging modality	Experimental paradigm (n)	Results*	Study†
(Continued from previous page)				
Patients with migraine without aura (24)	Resting state fMRI	PACAP38-triggered migraine attacks (16) and VIP-triggered migraine attacks (15)	Baseline *vs* PACAP38-triggered attacks: increased functional connectivity of the inferior frontal gyrus within the salience network; increased functional connectivity of the premotor cortex and decreased functional connectivity of the visual cortex within the somatosensory network; increased functional connectivity of the auditory, visual, somatosensory, and premotor cortices and decreased functional connectivity of the frontal lobe and cerebellum within the default mode network; baseline *vs* VIP-triggered attacks: no functional changes	Amin et al (2016)[45]
Patients with episodic migraine without aura (15)	Surface-based morphometry	Spontaneous headache (15)	Baseline *vs* spontaneous attacks: decreased cortical thickness and volume of precentral and pericalcarine cortex during attacks; decreased cortical thickness of the temporal pole and increased volume of the hippocampus	Amin et al (2021)[46]
Patients with episodic migraine without aura (15) and healthy controls (20)	DTI, and resting state fMRI	Spontaneous headache (15)	Controls *vs* patients: increased mean, axial, and radial diffusivity, and decreased fractional anisotropy of the whole hypothalamus and its most posterior part in patients compared with controls; in patients, negative correlation between pain severity and the hypothalamic axial diffusivity; positive correlation between the anterior hypothalamic mean, axial, and radial diffusivity and mean duration of the attacks; increased efficiency demand of the salience network in patients compared with controls	Porcaro et al (2022)[47]

DTI=diffusion tensor imaging. fMRI=functional magnetic resonance imaging. PACAP-38=pituitary adenylate cyclase-activating polypeptide-38. VIP=vasoactive intestinal polypeptide. *During the baseline visit patients were migraine-free. †Only studies published from Jan 1, 2014, to March 14, 2023, in agreement with our search criteria, were reported.

Table 2: **Studies exploring neural correlates of pain during the headache phase of migraine**

The cortical network implicated in pain perception involves sensory-discriminative areas, such as the somatosensory cortices, and brain regions mediating the affective and cognitive aspects of pain, such as the anterior cingulate cortex.[60] Patients with migraine studied during a spontaneous migraine attack showed altered resting state functional connectivity of frontal brain areas with the insula and posterior cingulate cortex, which was strongly associated with the pain intensity reported during that attack. This association suggests that frontal and parietal brain regions might encode the pain severity perceived by patients with migraine during their attacks.[42,43] Functional alterations of cortical brain networks known to be involved in the attentional, cognitive, and emotional aspects of pain have also been shown in patients with migraine studied during spontaneous and induced migraine attacks.[42,44,45]

By use of modern morphometric techniques, it is possible to study in vivo brain morphometry, quantify macroscopic and microscopic structural alterations, and evaluate their changes over time.[61,62] Volume-based morphometric approaches, such as voxel-based morphometry, provide a voxel-by-voxel comparison of the regional grey matter and white matter volume of the brain between different groups of people. Surface-based approaches allow for investigation of the laminar organisation of the cerebral cortex and its division into columns, providing information about morphometric measures, such as cortical thickness, cortical surface area, and the gyrification index, on a vertex-by-vertex basis.[63]

Along with functional imaging alterations, transient reduction of volume and thickness of pain-related cortical areas have been shown during the pain phase of spontaneous migraine attacks.[46] Specifically, 15 patients with migraine without aura developed decreased thickness and volume of the precentral and calcarine cortices, as well as decreased cortical thickness of the temporal pole, during spontaneous and untreated migraine attacks compared with the interictal phase. The mean time between the interictal and ictal scans was 30 days, with the shortest interval of 12 days, suggesting the presence of rapid and short-lasting morphometric changes that might be a consequence of hypoperfusion or cell shrinking.[46]

Diffusion-weighted MRI is a quantitative technique based on water diffusion in biological tissues. An accurate quantification of this diffusion can be assessed in terms of a tensor by use of diffusion tensor imaging (DTI). The extent of water diffusion can be expressed with the mean diffusivity, radial diffusivity, and axial diffusivity, and the degree of anisotropy, which reflects the underlying tissue organisation, can be calculated with the fractional anisotropy.[64] By use of DTI, 15 patients with episodic migraine without aura were studied during spontaneous migraine attacks, and showed higher hypothalamic mean diffusivity, radial diffusivity, and axial diffusivity compared with the healthy control group.[47] No statistically significant differences between the patient and control groups were observed in the most anterior part of the hypothalamus, but the higher the diffusivity parameters of the anterior hypothalamus, the longer the mean duration of migraine attacks. These findings could suggest that a typically functioning anterior hypothalamus might contribute to determining the end of a migraine attack, supporting a hypothalamic

involvement not only in migraine attack initiation, but also in regulating attack duration and termination.[64]

Symptoms accompanying migraine pain

According to the third edition of the International Classification of Headache Disorders,[24] to confirm a diagnosis of migraine during an attack, the migraine pain must be associated with at least one of three symptoms: nausea or vomiting, or both; phonophobia; and photophobia.

Although it is widely accepted that the migraine brain is hypersensitive to sensory stimuli, particularly visual, auditory, and olfactory stimuli, only a few imaging studies have explored the neural basis of sensory hypersensitivity during a migraine attack. In a PET study, Denuelle and colleagues[65] explored the brain activity of eight patients with migraine without aura during spontaneous migraine attacks in which photophobia was provoked. The exposure to a low, continuous, luminous stimulation increased the activity of visual cortical areas, including the lingual gyrus and cuneus, during the headache phase and after headache relief by triptans, but not during attack-free intervals. These results suggest that ictal photophobia is linked with visual cortex hyperexcitability. To our knowledge, no imaging studies have explored the neural correlates of ictal phonophobia, nausea, and vomiting, or less common ictal symptoms, such as osmophobia.

Postdromal phase

The postdromal phase starts when the migraine pain ends and can persist for up to 48 h after the resolution of headache pain. Various symptoms, including fatigue, sensory hypersensitivity, concentration difficulties, mood changes, and neck stiffness, have been described by patients during this migraine phase.[66,67]

Studying the postdromal phase of migraine is difficult because migraine attack duration is unpredictable and acute migraine treatments can influence imaging findings. Using fMRI during trigeminal nociceptive stimulation, two studies assessed the brain activity of patients with migraine during the postdromal phase.[16,17] In these studies, the postdromal phase was defined as the 24 h following headache resolution, and was not based on the presence of postdromal symptoms.[16,17] The first study assessed one patient with migraine without aura, and showed a higher activity of the visual cortex during the postdromal phase, compared with the headache phase or interictal phase. The second study[17] assessed seven patients with migraine and investigated only hypothalamic activity during the different phases of migraine, revealing no hypothalamic functional changes in the postdromal phase compared with the interictal phase. Two other resting state fMRI studies, which defined the postdromal phase as the 72 h period following the end of headache pain, confirmed that no hypothalamic functional alterations occurred, along with no alterations in the activity of the pons and spinal trigeminal nucleus.[68,69] Future studies are needed to explore the neural correlates of symptoms during the postdromal phase.

Links between the interictal migraine brain and acute migraine symptoms

Migraine is a cyclic disorder with dynamic functional and structural brain changes that influence patients' susceptibility to the onset of a migraine attack. In a study of 20 patients with migraine, Stankewitz and colleagues[70] showed gradient-like activity in the spinal trigeminal nucleus after nociceptive stimulation: spinal trigeminal nucleus activation decreased during the interictal phase, but then increased over the pain-free migraine period.[70] The amplitude of the spinal trigeminal nucleus signal could predict the time interval between headache attacks, suggesting an association between the oscillating behaviour of the spinal trigeminal nucleus during the interictal phase and the onset of the headache phase.[70]

A 2021 resting state fMRI study[71] explored hypothalamic activity fluctuations over the entire migraine cycle, revealing that the hypothalamic functional connectivity with the cerebellum, basal ganglia, frontal, and limbic brain areas increased linearly over the interictal phase, reached its peak shortly before the headache initiation, and dropped when the headache started. A later study[72] reported similar results and showed that resting state functional connectivity of cortical networks, including the primary visual, auditory, somatosensory, executive, salience, and default mode networks, followed a linear increase over the interictal phase that peaked just before the headache onset and dropped to baseline during the headache phase. The increasing resting state functional connectivity over the interictal phase towards the headache onset could reflect a higher susceptibility to internal and external migraine triggers that ultimately lead to migraine attacks.

Evidence shows an altered functional interplay of cortical–brainstem pain-modulating networks, including the pons, spinal trigeminal nucleus, rostral ventromedial medulla, nucleus accumbens, and frontal cortical areas, immediately before a migraine attack.[39,68,69,73,74] This alteration supports the presence of preictal functional changes in descending pain control networks that might facilitate onset of the headache phase.

The application of DTI has highlighted the presence of dynamic thalamic structural changes in patients with migraine across the interictal and ictal phases. Compared with the control group without migraine, patients with migraine had higher fractional anisotropy values and lower mean diffusivity values in the thalami during the interictal phase, but values became similar to those of controls during the pain phase.[75] The greater the number of days elapsed since the previous attack, the higher the fractional anisotropy of the right thalamus.

The interictal migraine brain can experience longitudinal functional and structural changes that influence patients' disease activity over time. Patients with migraine

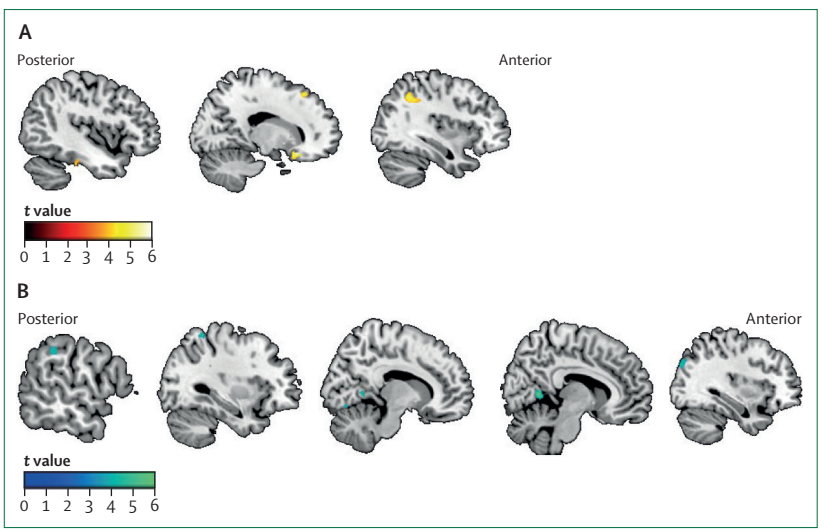

Figure 3: **Longitudinal structural changes of the interictal migraine brain after 4 years, represented on a high resolution T1-weighted template**
(A) Increased grey matter volume of frontotemporal nociceptive brain areas in 24 patients with migraine compared with 25 people without migraine in the control group. (B) Decreased grey matter volume of visual and parietal areas in the same population of patients with migraine compared with the control group. Areas of increased grey matter volume are shown in warm colours (colour-coded for their *t* values), and areas of decreased grey matter volume are represented in cold colours (colour-coded for their *t* values). Only brain sections showing between-group differences are shown. Reproduced with permission from Messina et al.[76]

studied over 4 years developed increased volume of frontotemporal nociceptive regions, which was more prominent in patients with longer disease duration and a higher attack frequency. The volume of visual areas decreased, which was related to higher pain severity (figure 3).[76] A longitudinal fMRI study revealed hypothalamic functional changes in patients with migraine after 4 years, characterised by an increased hypothalamic resting state functional connectivity with the orbitofrontal gyrus, and decreased resting state functional connectivity with the lingual gyrus. The higher the resting state functional connectivity between the hypothalamus and orbitofrontal gyrus, the lower the migraine attack frequency.[77] PET studies[65,77,78] investigating patients with migraine during spontaneous migraine attacks revealed increased activity in visual, hypothalamic, and pontine areas during the headache phase that persisted after complete resolution of pain and associated symptoms induced by triptans, suggesting a key role of these regions as putative drivers of the migraine attack.

Most imaging studies have investigated asymptomatic patients during the interictal phase of migraine, showing alterations in the function and structure of cortical and subcortical brain areas implicated in pain and visual processing in patients with migraine compared with healthy controls.[79–81] However, the current literature does not provide a clear picture regarding the increase or decrease in number of these functional and structural alterations, and their clinical implications.[5] Some of these studies revealed an association between interictal brain alterations and clinical symptoms during the ictal phases. Evidence shows that during the interictal phase, nociceptive brain areas, such as the insula, cerebellum, anterior cingulate cortex, cuneus, and precuneus, interact with each other to form a complex brain network.[82] Communication between these brain areas was more efficient in patients with migraine compared with the control groups, and could affect the severity of pain perceived by patients.[83] Interictal alterations in the activity and structure of pain-inhibitory and pain-modulatory areas, including the spinal trigeminal nucleus, thalamus, periaqueductal grey matter, insula, hippocampus, somatosensory cortex, and anterior cingulate cortex, could lead to an imbalance in the inhibition and facilitation of pain signalling, and explain the development of cutaneous allodynia during the ictal phases.[84–87]

In addition to modulating pain perception, the interictal activity of the periaqueductal grey matter has been suggested to affect the presence of sensory and autonomic symptoms during the ictal phase of migraine.[88] Using a machine-learning approach, activity of the periaqueductal grey matter was the most discriminative MRI feature in distinguishing patients with migraine from the people without migraine in the control groups. This activity was shown to be statistically significantly related to cranial autonomic symptoms and migraine-specific symptoms, including movement sensitivity, phonophobia, nausea, or vomiting, during migraine attacks.[88] A 2021 surface-based morphometry study[89] of 72 interictal paediatric and adolescent patients with migraine reported a statistically significant association between nausea or vomiting during the headache phase, and cortical thickness of the pars opercularis of the left inferior frontal gyrus, an area implicated in the perception and integration of gustatory stimuli.

Evidence suggests that the presence of somatosensory and dysphasic symptoms in association with visual disturbances during episodes of aura could be influenced by interictal microstructural thalamic alterations and altered resting state functional connectivity of visual and somatosensory networks in patients with complex auras compared with patients with only visual aura symptoms or without aura.[90,91] Individuals with migraine with and without aura are more sensitive to visual stimuli than people without migraine, not only during the acute phases of migraine, but also during the interictal phase. Interictal photophobia can be explained by the presence of higher functional activity and thicker primary and extrastriate visual cortices in patients with migraine studied during the interictal phase compared with people without migraine.[92,93]

Conclusion and future directions

Over the past few years, the application of MRI techniques has revealed functional and structural changes of the migraine brain across the phases of a

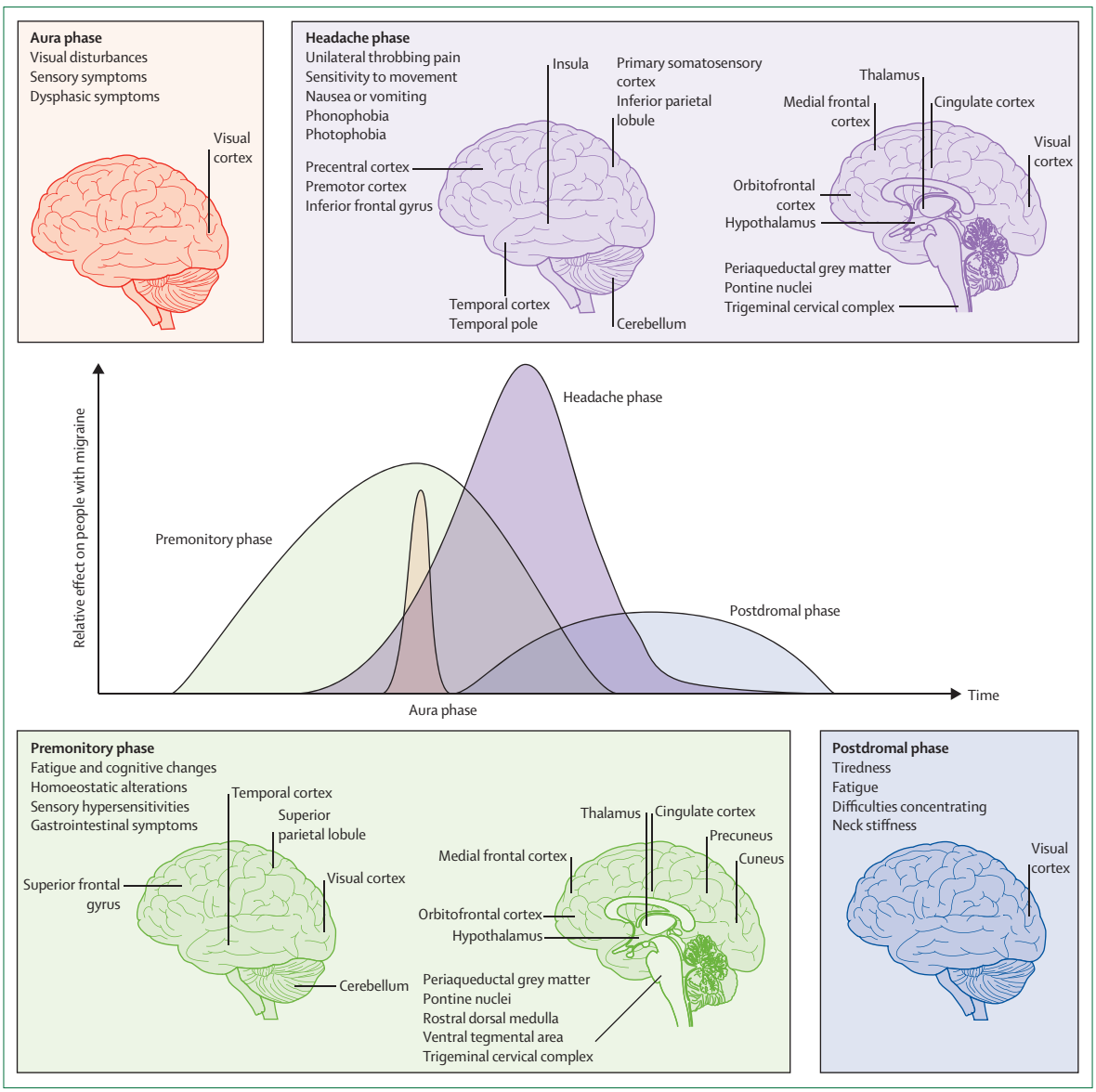

Figure 4: **Phases of the acute migraine attack and implicated brain regions**
The migraine attack can progress through phases that are sequential but overlapping: the premonitory, aura, headache, and postdromal phases. Premonitory symptoms can be broadly categorised into fatigue or cognitive changes, homoeostatic alterations, sensory hypersensitivities, and gastrointestinal symptoms. During the aura phase patients can report transient visual, sensory, and speech disturbances. The headache phase is characterised by a unilateral, throbbing pain of moderate or severe intensity, which can be exacerbated by physical activity and associated with, nausea, vomiting, both nausea and vomiting, phonophobia, and photophobia. Symptoms during the postdromal phase can include fatigue, sensory hypersensitivity, concentration difficulties, mood changes, and neck stiffness. When present, migraine aura symptoms are associated with altered visual cortex excitability, but no data rgarding brain areas involved in other symptoms are available. Only the visual cortex has been shown to be active during the postdromal phase. The relative heights of the curves suggest the extent to which functioning of the affected person is impaired. Figure created with BioRender.com.

migraine attack. These studies have explored the neurobiology underlying headache and non-headache symptoms experienced by patients during the different phases of migraine, revealing an association between clinical features of migraine and the activation of specific brain areas.

The recruitment of the hypothalamus, pons, spinal trigeminal nucleus, thalamus, visual cortex, and pain-processing cortical areas has been proposed to start during the premonitory phase and persist through the headache phase, contributing to the onset of the pain and associated symptoms. When the pain stops, the involvement of most brain areas comes to an end (figure 4). Only the pons, hypothalamus, and visual cortex remain active after acute treatment and resolution of migraine symptoms. Although functional and structural dynamic changes of the interictal migraine brain can contribute to the onset of the acute migraine

Search strategy and selection criteria

Using MEDLINE and PubMed, we searched for the term "migraine" in combination with "imaging", "magnetic resonance imaging", "functional magnetic resonance imaging", "structural magnetic resonance imaging", "symptoms", "nausea", "photophobia", "phonophobia" "sensory hypersensitivities", "vomiting", "pain", "prodromal", "postdromal", "interictal", "ictal", "fatigue", "cognitive deficits", "homeostatic alterations", "yawning", and "aura". Articles identified by this search strategy and judged relevant for the topic of the Review were selected. Our search strategy included studies published in any language from Jan 1, 2014, to March 14, 2023, and other commonly cited and highly regarded papers.

attack, the internal or external factors triggering such changes are still unclear.

Most imaging studies have focused on migraine pain. Whether findings during the headache phase are migraine specific or are common to other headache and chronic pain conditions is still unknown. Some studies[88,94,95] revealed resting state functional connectivity and volumetric differences during the interictal phase in brain networks engaged in pain processing between patients with migraine and patients with other chronic pain conditions. However, no studies have explored whether cerebral mechanisms of acute pain differ between patients with migraine and patients with other pain disorders.

Regarding the premonitory and postdromal phases, many studies have defined these phases using a time criterion rather than the presence of premonitory or postdromal symptoms. No studies to date have investigated the association between brain changes and postdromal symptoms, and only a few studies have assessed patients with migraine during ongoing premonitory symptoms. Migraine dissection into different phases is mainly based on clinical presentations, and whether a time criterion is as good as a symptom-based approach to identify the premonitory and postdromal phases should be assessed. More studies investigating the aura phase are also needed. A better understanding of the correlations between imaging results and the clinical features of migraine has the potential to shed light on migraine pathophysiology and provide new insights into the mechanisms of action of new acute and preventive treatments.

Contributors

RM, MAR, and MF contributed to the conception of the review and revising of the work. RM drafted the review. PJG critically reviewed and edited the manuscript.

Declaration of interests

RM reports personal fees from Eli Lilly, Lunbeck, and Bromatech for participation on advisory boards and for speaker activities. MAR received consulting fees from Biogen, Bristol-Myers Squibb, Eli Lilly, Janssen, and Roche; speaker honoraria from AstraZeneca, Biogen, Bristol-Myers Squibb, Bromatech, Celgene, Genzyme, Horizon Therapeutics Italy, Merck-Serono, Novartis, Roche, Sanofi, and Teva Pharmaceuticals; and research support from the Multiple Sclerosis Society of Canada, the Italian Ministry of Health, and Fondazione Italiana Sclerosi Multipla. PJG reports grants and personal fees from Eli Lilly; a grant from Celgene; personal fees from Aeon Biopharma, Allergan/AbbVie, Biohaven Pharmaceuticals, CoolTech, Dr Reddys, Epalex, Impel Neuropharma, Lundbeck, Novartis, Praxis, Sanofi, Satsuma, and Teva Pharmaceuticals; personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, and Vector Metric; fees for educational materials from CME Outfitters, Omnia Education, and WebMD; publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate, and Wolters Kluwer; payment for medicolegal advice in headache; and a patent on magnetic stimulation for headache (number WO2016090333 A1) assigned to eNeura without fee. MF reports compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, and Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and Teva; participation in advisory boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, and Takeda; scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Eli Lilly, Novartis, and Sanofi-Genzyme; and research support from Biogen Idec, Merck-Serono, Novartis, Roche, Italian Ministry of Health, and Fondazione Italiana Sclerosi Multipla.

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