Recent advances in headache neuroimaging

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Purpose of review
Primary headaches, such as migraine and cluster headache, are one of the most common and disabling neurological diseases worldwide. Neuroimaging studies have changed the way we understand these diseases and have enriched our knowledge of the mechanisms of actions of currently available therapies.

Recent findings
The present review highlights the major findings reported in migraine and cluster headache neuroimaging over the last year. Widespread structural and functional abnormalities in cortical and subcortical areas involved in multisensory, including pain, processing have been shown in migraine and cluster headache patients during different phases of the disease. Beyond the involvement of single brain areas, dysfunctional brain networks contribute to their pathophysiology. New central mechanisms of action of headache preventive treatments have also been explored.

Summary
A better understanding of migraine and cluster headache biology has paved the way for the development of new improved treatments for both these conditions. Although significant advances have been made over the last year, there are still many unsolved questions to address.

Keywords
cluster headache, functional imaging, migraine, morphometric techniques, neuroimaging

INTRODUCTION

Over the last decades, an increasing recognition of the importance of primary headaches, such as migraine and cluster headache, has led to a growing interest in understanding their pathophysiology and developing new treatments. Preclinical and neuroimaging studies have changed the way we understand these conditions. It is now widely accepted that they should be viewed as complex brain network disorders that involve multiple cortical, subcortical, and brainstem regions, instead of purely vascular disorders [1,2]. Conventional and advanced magnetic resonance techniques have been applied extensively to the study of patients with these headaches, both in the course of an acute attack and during the interictal phase. Functional imaging techniques, such as arterial spin labeling, task-related and resting state functional magnetic resonance imaging (fMRI), allow assessment of hemodynamic changes which are coupled to regional neural activity. Functional connectivity fMRI data provide information about the interplay between different brain areas. Their application in studying headache patients has shed light on the mechanisms responsible for initiation and propagation of attacks, and has disclosed the activity of cortical and subcortical regions during the different phases of the attack [3,4]. In association with functional imaging abnormalities, modern morphometric techniques, like voxel-based, surface-based morphometry, and diffusion tensor imaging, which provide insights into the macrostructure and microstructure of brain gray matter and white matter, have shown widespread brain structural abnormalities in patients with headache [5,6]. The present review aims to highlight the most recent advances in headache neuroimaging, focusing the attention on MRI studies that have explored brain function and structure in patients with migraine and cluster headache.

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KEY POINTS

- Neuroimaging studies have changed the way we understand migraine and cluster headache, supporting a key role of the brain in their pathophysiology.
- Widespread brain functional and structural changes have been demonstrated in patients with migraine and cluster headache in different phases of the disease.
- New central mechanisms of action of headache preventive treatments have been explored.
- A better understanding of migraine and cluster headache biology has paved the way for the development of new improved treatments for both these conditions.

Understanding migraine pathophysiology

Over the last 60–70 years, pathophysiological mechanisms of migraine have been widely debated. Although, there is ample evidence supporting the involvement of the trigeminovascular system in the pain phase, there is no proof that vascular changes may *per se* lead to pain [7]. Moreover, a purely vascular theory would not explain the many non-nociceptive symptoms typically experienced by migraineurs during the premonitory (prodromal) and postdrome phase [1,8]. In support of the neuronal theory, neuroimaging findings demonstrated widespread brain functional [4,9] and structural [10,11] alterations in migraineurs both during and outside the migraine attack. The main brain regions described by recent studies as key areas involved in the various migraine phases are summarized in Fig. 1.

Exploring the migraine brain in the ictal phase

Where exactly the migraine attack originates is one of the main pathophysiological questions that is still unresolved, and assumes there is single site. Early positron emission tomography studies [12,13] demonstrated a selective activation of the dorsal pons during spontaneous migraine attacks that persisted after complete pain-resolution because of sumatriptan administration, leading to the conclusion that this brainstem region might be the migraine 'generator'. A significant role of the pons in migraine attack and especially in the headache phase has been lately confirmed in migraine patients with aura. Two recent studies have revealed an increased connectivity between the pons and the ipsilateral primary somatosensory cortex [14], as well as hyperperfusion in a brainstem region corresponding to the 'migraine generator' [15▪], during headache preceded by aura.

An interesting recent study [16▪] has shift attention to the hypothalamus as migraine 'generator'.

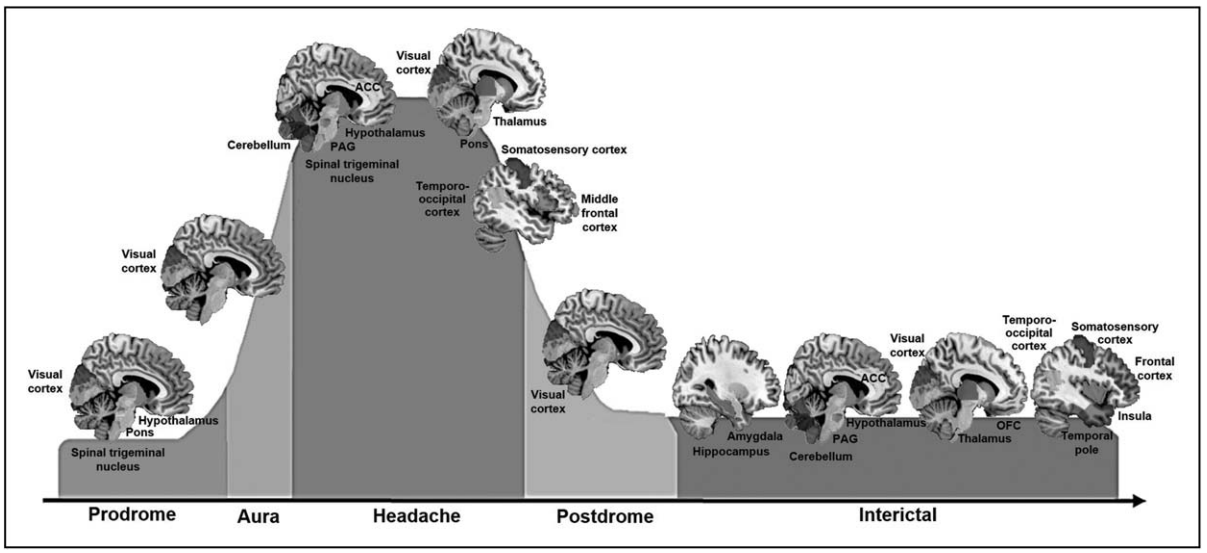

FIGURE 1. A schematic illustration of the main brain regions described by recent studies as key areas involved in the various migraine phases, represented on a high-resolution T1-weighted template. Prodrome: hypothalamus, pons, spinal trigeminal nucleus and visual cortex [16▪]; Aura: visual cortex [23▪▪]; Headache: ACC [44], cerebellum and PAG [19], hypothalamus [16▪,17], pons [14,15▪,16▪], spinal trigeminal nucleus and visual cortex [16▪], middle frontal, somatosensory and temporo-occipital cortex [14], thalamus [18]; Postdrome: visual cortex [16▪]; Interictal: ACC [10,44], amygdala [26,28], cerebellum [10,19,26,27], hippocampus [25,26], hypothalamus [17], insula [27,29], frontal, temporal and somatosensory cortex [10,26,27,30], PAG [19,24], thalamus [27,44], temporo-occipital and visual cortex [26,27,34,46]. Abbreviations: ACC, anterior cingulate cortex; OFC, orbito-frontal cortex; PAG, periaqueductal gray.

It was already known that the region of the hypothalamus was active during the premonitory and pain phase [8]. Schulte *et al.* [16▪], studying a migraine patient without aura for 30 consecutive days, confirmed these findings and revealed altered functional connectivity between the hypothalamus and the spinal trigeminal nuclei and dorsal pons during the preictal and pain phase. The authors postulated that the functional changes of this network might be the real driver of migraine attacks. Interestingly, this study has also showed a persistent altered activation of the visual cortex during the different phases of migraine. In a following study [17], the same authors reported an increased activity of the anterior hypothalamus as a response to pain in chronic migraine patients, regardless the disease phase. However, a higher activity of the posterior hypothalamus was revealed in both patients with episodic and chronic migraine during the ictal phase. These results led the authors to hypothesize that the anterior part of the hypothalamus may play a role in migraine chronification, whereas the posterior part may be involved in the acute pain phase regardless the disease severity.

The thalamus is a sensory relay station that contributes to the development of most of the symptoms usually experienced by migraineurs. In support of this, Amin *et al.* [18] reported an abnormal connectivity between the posterior thalamus, where the ascending pain pathways converge, and pain modulating and encoding cortical areas during spontaneous attacks of migraine without aura.

A cerebellar involvement in migraine pathophysiology has also been recently suggested. Coactivation of the cerebellum and periaqueductal gray has been revealed during trigeminal pain stimulation in patients experiencing a migraine attack [19].

Although single brain regions may have a pivotal role in migraine attack, it seems more likely that migraine originates from dysfunction of brain networks. Connectivity studies reported abnormal functional organization during the ictal phase in networks relevant for mediating cognitive, attentional, and emotional components of pain [4,20].

Another crucial question is whether the blood–brain barrier (BBB) might be affected during migraine attacks. Two recent dynamic contrast-enhanced MRI studies did not find any significant change in the BBB permeability in patients with migraine with [15▪] and without [21▪] aura who were examined between 4 and 24 h after the onset of spontaneous migraine attack, confirming that the BBB is normal in migraine. These results have important implications for the development of new antimigraine treatments.

Migraine aura

Around 30% of patients with migraine experience aura symptoms during their migraine attack. Cortical spreading depression (CSD), a wave of cortical depolarization followed by neuronal suppression, is widely accepted as the underlying mechanism of aura [1]. Neuroimaging studies reported a different pattern of cerebral hemodynamic changes during aura symptoms [3,22]. A recent fMRI study [23▪▪] investigated whether the blood oxygenation level dependent (BOLD) response to checkerboard visual pattern may change during visual aura symptoms induced by hypoxia, sham hypoxia, or physical exercise. The authors reported different changes in BOLD response across the visual cortex in relation to various aura symptoms: reduced BOLD response in patients reporting negative symptoms (e.g. scotoma) and increased response in patients who only experienced positive symptoms (e.g. flickering). These findings suggest that the heterogenous aura symptomatology may result from different CSD effects on neuronal activity or neurovascular coupling.

Exploring the migraine brain in the interictal phase

Numerous interictal neuroimaging studies have provided evidence of widespread structural and functional reorganization of regions involved in pain and multisensory processing, such as the PAG [19,24], hippocampus [25,26], cerebellum [10,19,26,27], somatosensory, and cingulate cortex [10,27], in patients with episodic and chronic migraine. Connectivity studies have disclosed broad alterations in limbic [28,29], sensory-motor [30], and cognitive [31] networks that might influence multisensory integration and pain experience in migraineurs, and contribute to migraine chronification.

Using a data-driven classification approach, Schwedt *et al.* [32▪] have been able to distinguish patients with migraine with different disease severity based upon their brain structures. However, the model could not clearly distinguish migraine patients from healthy controls. Although, as suggested by the authors, this might be the results of only subtle structural alterations experienced by migraineurs; the difficulty in finding controls who do not harbor a migraine biology should also be considered given the lifetime prevalence data [33].

Another recent morphometric study [34] has investigated a large sample of patients with and without aura recruited from the general population. The authors found a significant decreased gray matter volume in visual processing areas regardless of the presence of migraine aura or disease activity,

thus indicating that these changes might have been present throughout life and migraine with and without aura might share common pathophysiologic mechanisms. Whether structural abnormalities might either predispose to migraine or be a consequence of the disease is still unclear. In a well planned study Gaist *et al.* [35▪] compared a group of female migraine twins with aura to their migraine-free co-twins and unrelated migraine-free twins, that served as controls. The authors found a significant thicker cortex in V2 and V3A visual areas that were not associated to the frequency of headache or aura attacks. These findings strengthen the hypothesis that thicker visual cortex may be an inherent trait associated with migraine with aura, thus predisposing to the initiation of visual aura symptoms.

A further unanswered question is whether morphometric changes are migraine specific or are common to other headache and chronic pain disorders. Two latest studies revealed distinct gray matter volume patterns that distinguish migraineurs from patients with tension-type [36] or persistent posttraumatic headache [37], thus suggesting that different pathophysiologic mechanisms might occur in different type of headaches.

Neuroimaging data on the association of white matter hyperintensities and migraine has been conflicting. Some studies reported a higher prevalence of subcortical, deep, and cerebellar ischemic hyperintensities in migraineurs compared to controls [38–40], whereas other studies did not confirm such results [41,42]. Discordant findings have also been found regarding the influence of potential risk factors, such as the pain side [39], aura symptoms, disease activity [42], or reduced cerebral blood flow [40,41].

Magnetic resonance spectroscopy allows investigation of neuronal and glial integrity and metabolism *in vivo*. Previous findings demonstrated an abnormal energy metabolism and excitatory–inhibitory balance in migraineurs [43]. Niddam *et al.* [44] have found reduced N-acetyl-aspartate levels in thalamus and anterior cingulate cortex (ACC) in chronic migraine patients compared to episodic patients and healthy controls. These changes were strictly correlated with each other and such relation was significantly different from that found in healthy controls. These findings lend support to the role of a dysfunctional thalamo-cortical networks in migraine chronification.

Although the role of the visual cortex is well established in migraine with aura, data [16▪,34] support its involvement also in the pathophysiology of migraine without aura. Various studies reported a hyper-responsivity of the visual cortex in migraine patients, which is more pronounced in those experiencing aura symptoms [4,45]. Interestingly, Zielman *et al.* [46] have recently found significant increased levels of glutamate, one of the main excitatory neurotransmitters, in the visual cortex in patients with migraine without aura but not in those with aura. To clarify the meaning of such visual abnormalities, further studies including patients without aura and with no visual hypersensitivity are needed.

Understanding cluster headache pathophysiology

Although there is large body of evidence supporting a key role of the hypothalamic region, and trigeminovascular and parasympathetic systems in cluster headache, how these structures interact with each other and with other cortical areas, how the attacks originate, and the mechanisms responsible for shifting from the 'out-of-bout' to 'in-bout' period, and vice versa, are still unclear [2].

Early neuroimaging studies [47] have shown a specific activation of the posterior inferior hypothalamus during the pain phase in patients with 'in-bout' cluster headache. A following voxel-based morphometry (VBM) study [48] revealed concurrent gray matter volume increase of this hypothalamic region. However, other morphometric studies did not reproduce the same result. Interestingly, Arkink *et al.* [49] have recently found bilateral enlargement of the hypothalamus in patients with cluster headache compared to patients with controls and migraine, which was mainly driven by the anterior hypothalamus. An increased hypothalamic volume was also found when patients with trigeminal autonomic cephalalgias (cluster headache and chronic paroxysmal hemicrania) were compared to migraineurs and controls. Conversely to previous findings [16▪,17], the authors excluded a hypothalamic involvement in migraine. Both the anterior and posterior hypothalamus may be involved in cluster headache pathophysiology: the anterior hypothalamus with its suprachiasmatic nucleus might contribute to the circadian rhythm of cluster headache attacks [2], whereas the posterior hypothalamus might generate the restlessness commonly experienced by cluster headache patients during the attack [50]. Owing to its small size, the hypothalamus is a brain area that is difficult to measure *in vivo*. The use of different methods to process the images along with different study designs and cohort of patients may explain the inconsistency between VBM studies.

It is also noteworthy that patients with cluster headache experience dynamic structural [51] and

functional [52] changes in cortical and subcortical areas involved in nociception that are related to the disease phase ('in-bout' or 'out-of-bout') and disease activity.

Understanding headache treatments mechanisms of action

In conjunction with progress in theories of migraine and cluster headache pathophysiology, understanding of the mechanisms of action of preventive treatments for headache has evolved.

Migraine

Over the last year neuroimaging studies have explored the therapeutic effects of pharmacological and nonpharmacological treatments commonly used in migraine prevention. Hebestreit and May [53] investigated whether beta blockers, such as metoprolol, might exert a central effect in migraineurs after a 2-month treatment period. Curiously, the authors did not find any significant effect of metoprolol on central pain processing regions. Although, further exploratory analysis demonstrated an increased hypothalamic activity under metoprolol that was correlated to a decrease of headache days.

A potential central effect of a single dose of topiramate in attenuating the pain-related activity of the thalamo-cortical network has been recently demonstrated in healthy controls [54]. Further investigations in migraineurs are needed.

A cortical modulatory effect of external trigeminal nerve stimulation (eTNS) on areas belonging to the descending pain network has been reported in two recent studies [55,56]. After 3 months of eTNS therapy, an overall clinical improvement was associated with a normalization of the pretreatment hypometabolism of the ACC and orbitofrontal cortex [56]. Moreover, the increased ACC activation observed in migraineurs during trigeminal heat stimulation was reduced by the daily use of eTNS [55].

Cluster headache

The promising preventive effect obtained by hypothalamic region deep-brain stimulation (DBS) [57] supports a key role for the region in cluster headache. The site of the optimal stimulation: within the hypothalamus or in the ventral tegmental area (VTA) in the midbrain, is still a matter of debate. Akram *et al.* [58] demonstrated that in patients with medically refractory chronic cluster headache who responded to DBS, the DBS contacts induced a local activation of the VTA. This area was located in the trigeminohypothalamic tract and was connected to the hypothalamus, prefrontal, and mesial temporal areas, as well as the trigeminal system and other brainstem nuclei involved in the descending inhibitory pain pathway. These results suggest that the DBS may exert its therapeutic effect modulating the top-down antinociceptive and trigeminal parasympathetic system, although given its significant morbidity and potential mortality [59], there is no role for this approach in clinical practice at this time.

CONCLUSION

Significant advances in on our understanding of migraine and cluster headache pathophysiology have been made over the last year. New central mechanisms of action of headache preventive treatments have been explored. However, there are still many unsolved questions to address. In the future, more effort should be made in limiting the number of caveats that commonly applied to neuroimaging studies, such as heterogeneous sample of patients and data analyses, small sample size, recruitment of non 'pure' controls. Moreover, longitudinal studies, studies comparing headache patients to patients with other chronic pain disorders and investigating unexplored type of headaches, such as hemicrania continua or short-lasting unilateral neuralgiform headache, are needed.

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Conflicts of interest

R.M. (roberta.messina@kcl.ac.uk), *M.F.* (filippi.massimo@hsr.it) *and P.J.G. had no financial interest in this work.*

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