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Recent Neuroimaging Advances in the Study of Primary Headaches

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Abstract Neuroimaging techniques can be used to investigate both functional and structural features of the brain in patients who have primary headache disorders such as migraine or cluster headache. Improved treatments are needed for both, and this goal will likely be facilitated by a better understanding of the underlying biology. Functional imaging studies have identified regions active during attacks, as well as abnormalities that are present during the interictal period. Volumetric, surface-based morphometric, and tractography studies have revealed structural changes, although whether these represent a cause or effect of the condition remains to be determined. The development of new techniques and modalities promises to yield additional insights in the future. This article aims to review the major findings and most recent advances in neuroimaging of migraine and cluster headache.

Keywords Imaging · MRI · fMRI · PET · Functional · Structural

Introduction

Migraine is a primary headache disorder featuring attacks accompanied by an array of non-pain symptoms including sensory sensitivity, nausea, and cognitive and emotional dysfunction. With the collection of symptoms including higher-order functions, migraine must affect the brain, and a complete understanding of the central nervous system dysfunction has yet to be elucidated. Migraine pathophysiology can be studied on many levels, ranging from animal models to cellular and neurotransmitter basic science to electrophysiological systems. Neuroimaging methods complement the laboratory by probing pathophysiology on a macroscopic or network level, thereby providing a different perspective. As an example, imaging studies played a pivotal role in debunking the vascular theory of migraine.

Neuroimaging techniques fall broadly into two categories, examining either structure (anatomy) or function. Multiple methods can be employed in either approach and are described in the corresponding sections below. In addition, new functional techniques are being developed that will likely provide additional insights.

As the most common and most disabling of all neurological disorders worldwide [1•], the need for a better understanding of migraine pathophysiology, with subsequent improvement in the development of therapeutics, is clear. This review aims to provide an overview of the most recent neuroimaging advances in the study of primary headache disorders, focusing on the most prevalent and therefore most frequently studied disorder of migraine.

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Migraine

Structural

White Matter

White matter has primarily been examined for the presence of changes, often described as "infarct-like" in the absence of

neuropathological correlation, or white matter hyperintensities (WMH). Characterization of white matter tracts using diffusion tensor imaging (DTI) is becoming increasingly common, although its application in migraine is currently limited to research.

Multiple population-based imaging studies have found that migraine with aura is associated with an increased risk of subclinical, infarct-like changes in women [2–5]. While two studies found this increased risk was for specifically for changes in the cerebellum [2, 5], in another study, they were primarily supratentorial [4]. These studies were conducted in Caucasian populations ranging from mid- to late life, and a similar association was recently reported in a largely Hispanic population over the age of 55, though stratification by aura status was not possible in this study due to the low number of infarct-like changes [6]. These imaging findings are consistent with epidemiologic studies showing a higher incidence of clinical stroke in women who have migraine and in those with aura [7–11], although it has never been shown that these changes are due to infarction as such.

Migraine is also associated with deep WMH [3, 4, 12], with some studies finding an association only in women regardless of aura status [3], and others only when aura is present and not affected by sex [4]. A small, uncontrolled study found that migraine with aura was associated with progression of WMH, with the number of new white matter foci correlating with aura duration and the number of aura attacks [13]. Another study recently reported that chronic migraine is associated with a higher WMH load when compared to both controls and to chronic migraineurs with medication overuse [14]. The overused medications in this study were primarily nonsteroidal anti-inflammatories, which the authors suggest may have a protective effect against white matter changes. A number of studies have recently reported WMH in pediatric populations presenting with headache, with an incidence ranging from 4 to17% [15–18]. Similar to adults, the white matter changes are generally punctate, small, supratentorial, and can be single or multiple.

The underlying pathophysiology of these white matter changes is not known, nor is their clinical significance, such as whether these changes represent an increased risk for stroke in otherwise healthy migraineurs. Of note, the presence of white matter hyperintensities has not been associated with cognitive impairment in migraineurs [4, 19•]. A multi-modal magnetic resonance imaging (MRI) study of WMH in migraineurs found that the physical characteristics of these changes are similar to those seen in ischemic lesions [20], but without histopathological analysis, hypotheses about the underlying mechanism remain speculative.

In terms of whether these white matter changes represent reversible, permanent, or progressive changes, longitudinal data is limited and conflicting. One study found no association between migraine and progression of WMH [21] and another found an association in women with progression of supratentorial hyperintensities in the deep white matter but not infarct-like lesions or WMH in other locations [19•].

Most recently, DTI studies in migraineurs have reported changes in fractional anisotropy (FA), a measure of water movement restriction with higher values representing greater restriction or directionality, as seen along white matter tracts. Decreased FA has been reported in the corpus callosum, internal capsule, and thalamus in migraineurs without aura [22, 23], suggesting widespread microstructural alterations in the major cerebral tracts. Interestingly, one study found increased FA of the entire thalamus in interictal but not peri-ictal (within 12 h of attack onset) migraineurs when compared to controls [24], which seems to echo electrophysiologic abnormalities in the thalamus, namely reduction of high-frequency oscillations, that normalize with attack onset [25].

Gray Matter

Gray matter changes can be characterized in a number of ways. Perhaps the most commonly employed technique is voxel-based morphometry (VBM), an automated process that allows voxel-wise quantification of the density or volume of a particular tissue type (e.g., gray or white) and can be applied to overall brain volume or specific regions. Surface-based morphometric methods examine cortical thickness and surface area. Cortical thickness studies examine the cortical mantle with vertex-wise measurements of the shortest distance between the pial surface and the gray-white junction. Surface area as a measurement roughly reflects the degree of folding.

VBM studies have consistently reported gray matter reductions in migraineurs in regions recognized to be involved in pain processing such as the anterior cingulate cortex, insula, and limbic system [26–30]. The extent of gray matter reductions in some of these regions has been correlated with clinical variables such as frequency of migraine attacks or disease duration. Recent studies have extended these findings, reporting reduced volume in migraineurs of the left dorsal anterior cingulate cortex [31], caudate, and nucleus accumbens [32], all correlating with disease duration. A large, population-based study found a reduction in total gray and white matter volume in migraineurs with depression, with no differences seen in either condition alone [33].

Other studies have reported gray matter increases in migraineurs, including increased density in the PAG [27] and increased cortical thickness in the somatosensory cortex [34, 35] and visual motion processing areas [36]. These findings have not always been replicated, however, with one study finding no differences in cortical thickness of these specific areas or by whole-brain analysis [37]. Finally, increased hippocampal volume was noted in migraineurs with two or less attacks per month but not with more frequent attacks (8 to 14 per month) [38].

A recent study reported a combination of increased and decreased cortical thickness in migraineurs, with the regional distribution of these changes affected by the presence of aura [39]. Interestingly, this same study reported increased surface area of the left lingual gyrus, an area implicated in visual aura [40], in migraineurs with aura compared to those without aura or healthy controls. Taken together, this study's findings suggest that aura may have an influence on brain structure that is distinct from that of migraine. In line with this, a multiparametric MRI study found microstructural changes of multiple thalamic nuclei in migraineurs with visual aura compared to those without aura or healthy controls [41].

A study examining structural-functional relationships found that controls exhibited a negative correlation between cortical thickness of the left superior temporal and inferior parietal region and pain threshold to heat, whereas migraineurs lacked a correlation. This area is implicated in attentional orienting, and the authors postulate that direction of attention may modulate pain, with migraineurs lacking the normal relationship between the two [42].

The mechanisms underlying gray matter changes are not known, although gray matter reductions have frequently been interpreted as evidence of damage resulting from repeated migraine attacks. Gray matter increases have generally been regarded as resulting from increased afferent input associated with migraine attacks. Such changes may simply reflect alterations in function and should not be regarded as permanent or progressive without appropriate longitudinal data. Supporting this notion are studies demonstrating normalization of gray matter changes, both increases and decreases, after cessation of repetitive painful stimulation [43] or after hip replacement in patients with hip osteoarthritis [44, 45]. Finally, in theory gray matter changes could predispose to migraine attacks rather than resulting from them. A recent study found gray matter decreases in migraineurs within the first year after diagnosis, demonstrating that changes occur early [46]. The question of whether gray matter changes may precede the onset of attacks, however, remains unanswered.

Functional

Functional imaging can be divided into task-based or task-free (connectivity) techniques. Traditionally, modalities such as MRI or positron emission tomography (PET) have been used to investigate brain activation patterns during a given task or state, e.g., in response to painful heat stimulation or during a migraine attack. More recently, MRI has been used in a task-free setting to identify regions with correlated low-frequency blood oxygen level-dependent (BOLD) signal fluctuations. Regions that are correlated at rest also activate together, and these ensembles are termed intrinsic connectivity networks, also referred to as resting-state networks.

Task-Based

Functional imaging studies have demonstrated widespread activations during migraine attacks, most consistently in the dorsal pons and midbrain, anterior cingulate cortex, insula, and prefrontal cortex [47–49]. Activation of the hypothalamus during migraine attacks was described in 2007 [48] and was recently described during the premonitory phase of migraine [50].

Other studies have compared functional activations in response to noxious heat stimulation in migraineurs versus controls. One study found that interictally migraineurs exhibited greater activations in the middle cingulate cortex and hippocampus, where activation correlated with headache frequency [51]. Greater deactivation in the hippocampus was previously described in low-frequency versus high-frequency episodic migraineurs [38]. Other work has shown attack frequency-dependent alterations in activations to noxious heat that correlate with volumetric gray matter differences in the postcentral gyrus, middle cingulate cortex, and insula [35].

Recently, the first imaging study of visual snow, a phenomenon distinct from but influenced by migraine and aura, demonstrated hypermetabolism in the lingual gyrus when compared to controls [52•].

Task-free/Resting-state

The number of resting-state studies in migraine has increased dramatically in recent years. Two major approaches for examining functional connectivity exist. Independent component analysis is a "data-driven" approach where group differences can be sought without specific anatomical hypotheses, although networks of interest must be identified. Region-of-interest (ROI) analysis is a "hypothesis-driven" approach where connectivity of specific areas is examined based on anatomical knowledge.

Migraineurs exhibit widespread changes in intrinsic connectivity, with alterations reported in the executive, default mode, and salience networks, although the direction of changes differed between studies [53–55]. Using ROI-based analyses, studies have found increased connectivity in migraineurs of pain-related regions such as the periaqueductal gray, nucleus cuneiformis, anterior insula, and anterior cingulate cortex with other regions [31, 56–59]. In addition, migraineurs have altered connectivity of the amygdala, hippocampus, hypothalamus, thalamus, basal ganglia, and precuneus, generally with increased connectivity compared to controls [60, 61, 38, 62, 63, 58, 32].

Regional homogeneity is another method for examining resting-state, low-frequency BOLD fluctuations. It is a "data-driven" method that allows voxel-wise comparison of these fluctuations to characterize the similarity between neighboring voxels. A few studies have reported altered regional

homogeneity in migraineurs correlating (either positively or negatively) with disease duration in areas including the thalamus, anterior cingulate cortex, and insula [64, 65]. A study using regional homogeneity results to seed a connectivity analysis found altered connectivity of the putamen correlating (either positively or negatively) with attack frequency [66].

New Techniques

PET and fMRI are indirect measures of neuronal activation, relying on changes in metabolism or the accompanying blood flow, and thereby have limited temporal and spatial resolution. Spin-lock fMRI is a new technique that is being developed for direct measurement of tissue changes related to neuronal activity [67]. In a rat model of provoked cortical spreading depression, spin-lock fMRI signal was shown to be generated by parenchymal mechanisms and not associated with hemodynamic or cellular edema factors; the specific mechanism that gives rise to spin-lock signal changes is not known but may be related to a change in phosphate concentration as a result of increased energy consumption [68]. A direct imaging measure of neuronal activity represents an exciting paradigm shift in functional imaging. In addition, a ^{11}C PET tracer for the CGRP receptor was recently reported [69], which may provide new insights into migraine pathophysiology, particularly in the context of the emerging small-molecule and biologic CGRP mechanism antagonists for both acute and preventive treatment.

Cluster Headache

Structural

Gray

Three studies have reported volumetric gray matter changes in cluster headache with differing results. One study found increased volume of the area that is active during cluster headache attacks, slightly inferior and posterior to the hypothalamus [70]. The other two studies found gray matter reductions in differing locations [71, 72]. One study examining cortical thickness found reduction in the angular and precentral gyri contralateral to pain [73].

White

Studies of white matter changes in cluster headache have also yielded inconsistent findings. One study found no white matter changes [71], another found scattered, focal areas of reduced FA [74], and another found widespread reduction in FA in most major cerebral tracts, primarily contralateral to pain [75]. Most recently, multiple alterations were reported when examining all measures of diffusivity (radial, axial, and mean diffusivity in addition to the standard measure of FA), with all abnormalities displaying structural connectivity with the hypothalamus using probabilistic tractography [76].

Functional

Functional imaging studies of triggered and spontaneous cluster headache attacks, using both PET and fMRI, have consistently shown activation in a location in the midbrain slightly posterior and inferior to the hypothalamus [77–80]. Furthermore, interictal cluster headache patients show decreased metabolism in the prefrontal cortex compared to controls [81]. Most recently, two studies have reported altered functional connectivity of the "hypothalamus," one using a spherical ROI centered on the previously reported coordinates of activation during attacks, just outside the hypothalamus [82], and one using an unusually large ROI incorporating the entire hypothalamus [83]. The former found increased connectivity with the insula and temporal lobes [82].

Conclusions

Much has been learned through neuroimaging about the structural and functional changes that occur in primary headache disorders. Advances in technology and computing capabilities will likely generate ever increasing quantities of imaging data. This will need to be balanced with thoughtful and judicious application of these techniques so that the results have clinical relevance, informing us about pathophysiology or generating new hypotheses. Currently, with no reliable biomarkers for primary headache disorders, diagnoses are made on the basis of overlapping clinical features. Perhaps one day imaging markers will allow us to define groups based on similar pathophysiological features or achieve the lofty goal of identifying which patients are most likely to respond to a given treatment.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Amy R. Tso and Dr. Peter J. Goadsby declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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