Curr Neurol Neurosci Rep (2016) 16: 64
DOI 10.1007/s11910-016-0662-5

Migraine: What Imaging Reveals

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Published online: 16 May 2016

Abstract Although migraine symptomatology is well-defined, our understanding of migraine pathophysiology is incomplete. Structural and functional brain imaging can contribute to a greater understanding of migraine pathophysiology. Recent neuroimaging studies demonstrate that migraine is associated with structural and functional alterations of brain regions commonly implicated in pain processing. This review summarizes recent brain structural and functional imaging findings in migraine and highlights those that are associated with characteristics such as the presence or absence of aura, associated cognitive dysfunction, sex-differences (male vs. female migraineurs), age, and disease burden.

Keywords Migraine · Neuroimaging · Magnetic resonance imaging · MRI · fMRI · Functional magnetic resonance imaging · Resting-state · Functional connectivity

Introduction

Migraine affects over 12 % (38 million) of the people in the USA and is three times more common in women than in men [1, 2]. Population-based data suggest that migraine is more common than diabetes and asthma combined [3–5]. Migraine is characterized by a constellation of symptoms including moderate to severe headache, hypersensitivity to light, sound, touch, and odor [6–9], gastrointestinal (nausea and emesis), mood, cognitive, autonomic, and constitutional (fatigue, lethargy) symptoms. Many migraine sufferers also describe a range of interictal symptoms between attacks [10–13]. While the migraine phenotype is well characterized [6], there are gaps in our understanding of migraine pathophysiology that may be bridged by structural and functional brain imaging findings.

T1-weighted magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) can be used to study regional gray and white matter structural alterations in migraine, respectively. Brain function in migraine can be measured using functional magnetic resonance imaging (fMRI), a technique based on detecting blood-oxygenation-level dependent (BOLD) signal fluctuations. FMRI can be run during either (i) task-based designs, which measure brain responses to a specific stimulus or action or (ii) resting-state designs, which interrogate the functional connectivity of the brain at rest (rs-fMRI).

There is a growing consensus over the past decade that migraine is related to brain structural and functional alterations in regions that participate in the pain experience. In addition, several functional imaging studies have interrogated brain activation patterns in migraineurs in response to exposure to thermal pain and olfactory or visual stimulation. These studies have implicated common regions that show more activation or *hyperactivation* between attacks (interictally) in migraineurs relative to healthy controls during sensory processing. These include prefrontal, parietal (postcentral/primary somatosensory gyrus), temporal (temporal pole, fusiform, hippocampus, parahippocampal gyrus) cortex, and subcortical regions (cingulate, thalamic complex) [14–18]. Regions where migraineurs show less interictal activation or *hypoactivation* relative to healthy controls include areas of the brainstem (pons, medulla) and temporal and parietal (secondary somatosensory) cortex [15, 19–21]. Furthermore, ictal

This article is part of the Topical collection on *Neuroimaging*

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migraineurs show enhanced brain activation during sensory stimulation in temporo-occipital regions (temporal pole, primary visual cortex) as well as subcortical areas (thalamus, insula, amygdala), cerebellum, and brainstem (midbrain, pons, medulla) regions [19, 22, 23]. These regions relate to the cognitive, affective, sensory-discriminative, and modulatory components of pain processing.

Studies that have interrogated resting-state functional connectivity (*rs-fc)* patterns in migraineurs relative to healthy controls have corroborated the findings of task-based fMRI studies and found altered functional connectivity (*fc*) amongst various sensory-processing regions [24–34]. DTI and T1-weighted imaging have demonstrated white and gray matter alterations in cortical and subcortical pain-related areas [28, 35–40, 41•, 42, 43] in migraineurs compared to healthy controls. These data indicate that migraine affects gray and white matter integrity as well as functional activation patterns of sensory-processing regions. In addition, migraine also appears to alter how sensory-processing areas are able to communicate with one another. These findings have clarified that migraine is *not* associated with a dysfunction of a *specific* brain area or a brain circuit but rather that migraine affects an array of integrated networks that are responsible for the diversity of the symptoms that constitute migraine.

During more recent years, the neuroimaging literature has focused on attaining a better understanding of how alterations in regions that process sensory stimuli and mediate cognitive function relate to specific characteristics of the migraine sufferer (e.g., the sex of the patient) and the nature of the migraine attack (e.g., aura vs. no aura). Several recent neuroimaging studies have compared patients with aura to those without aura, men vs. women, and have interrogated correlations between imaging findings with migraine-associated cognitive dysfunction. Finally, imaging findings in pediatric cases and from longitudinal studies have yielded evidence that migraine can be associated with baseline brain alterations or might change the structure and function of the brain over time.

Here, we review recent neuroimaging findings that have specifically interrogated structural and functional changes associated with (a) aura, (b) sex-specific differences in migraine, (c) cognitive function, and (d) longitudinal brain changes. A PubMed database search was limited to migraine neuroimaging studies published between January 2012 and January 2016, although, due to the scarcity of studies investigating cognitive function deficits, one study published in 2008 was included. The search was limited to group data of migraineurs and healthy control; single-case studies were not included in this review. In order to provide a more focused review, we limited our search to studies using MRI-based techniques, including DTI, T1- and T2-weighted imaging, task-based fMRI, and *rs-fc* fMRI.

Migraine and Aura

Approximately 30 % of migraine patients have aura and these are visual in the vast majority [1, 44]. In a landmark study, Hadjikhani at al. (2001) showed a wave of heightened visual cortex activation followed by a wave of attenuated visual cortex activation in patients during migraine aura [45], thus suggesting a cortical spreading depression-like event in the visual cortex of humans.

Although a number of studies have compared brain structure and function in migraineurs with aura (MwA) to healthy controls or have included mixed cohorts of MwA and migraineurs without aura (MwoA) compared to healthy controls, these studies are not ideal for isolating the effect of aura on brain integrity as group differences are co-mingled with aura symptoms. Over recent years, several studies have specifically interrogated brain changes associated with aura symptomatology by contrasting groups of MwA, MwoA, and healthy controls (Table 1).

Tedeschi and colleagues (2015) interrogated the functional connectivity of visual cortex and found that interictal MwA had heightened functional connectivity of occipital regions relative to healthy controls and to migraineurs without aura (MwoA) [46]. *Rs-fc* results by Niddam et al. [47•] showed weaker *fc* between the anterior insula and extrastriate regions in MwA compared to MwoA and healthy controls. In contrast, Datta et al. (2013) [17] and Tessitore et al. (2015) [30] failed to demonstrate *rs-fc* differences between MwA and MwoA. As differences in study design and patient characteristics might be a factor in the disparity of findings, future studies using larger sample sizes will be needed to further interrogate brain changes associated with aura.

Several studies using visual stimulation BOLD fMRI paradigms have detected hyper-responsiveness in striate areas during visual stimulation in interictal MwA [17, 48] as well as more brain activation in the visual functional network including the inferior frontal gyrus and the inferior and superior parietal lobule, all regions involved with attention orienting and oculomotor control (Hougaard and colleagues 2014) [18]. Although results of a smaller study by Bridge et al. (2015) [49•] did not find differences in striate cortex activation between MwA and MwoA, the authors demonstrated decreased GABA levels in the occipital cortex and a positive relationship between BOLD-signal change and occipital glutamate/creatine ratios using magnetic resonance spectroscopy (MRS). The combined use of fMRI and MRS is new to the field, and the results are intriguing and support the notion of disordered brain excitatory and inhibitory mechanisms, which might explain the biological susceptibility to spontaneous and/or triggered cortical spreading depression (CSD) events [45].

Several imaging findings have reported no structural changes in MwA. For example, Hougaard et al. (2015) indicated normal cortical thickness and gray matter density

Table 1 Studies interrogating brain changes associated with aura symptomatology

Aura

Authors	Subjects	Imaging modality	Results	Clinical parameters
Bridge et al. (2015) [49•]	13 MwA 13 MwoA	fMRI Task-based: Visual stimulation	MwA vs MwoA: •No differences in V1 activation patterns. •female MwA (but not female MwoA) showed a positive relationship between BOLD-signal change and occipital glutamate/creatine ratios.	
Cucchiara et al. (2015)* [48] * expanded population of Datta at al. study	51 MwA 45 MwoA	fMRI Task-based: Visual stimulation	MwA vs MwoA: •Hyper-responsiveness in primary visual regions (V1).	No correlation between V1 BOLD activation and headache frequency and years lived with migraine.
Datta et al. (2013) [17]	25 MwA 25 MwoA 25 HC	fMRI rs-fMRI Task-based: Visual stimulation	MwA vs MwoA vs HC: •hyper-responsiveness in primary visual regions (V1). Greater activation of LGN in MwA vs MwoA. •No difference in rs-fMRI patterns between groups.	
Dinia et al. (2013) [47•]	41 MwA Longitudinal study: follow-up: 33.2 months	T2 FLAIR	63.4 % had WML at baseline. At follow-up: 19.5 % had new WML.	•Positive correlation between aura duration and number of new WML. •Positive correlation between new WML and number of migraine attacks with aura •No correlation between number of new WML and disease duration.
Hougaard et al. (2014) [18]	20 MwA* *10 subjects with left-sided and 10 subjects with right-sided aura	fMRI Task-based: Visual stimulation	•More activation in hemisphere lateralized to aura symptoms in regions including inferior and superior parietal lobule, and inferior frontal gyrus.	
Hougaard et al. (2015) [50]	20 MWA* *10 subjects with left-sided and 10 subjects with right-sided aura	VBM SBM	•Absence of lateralized structural changes associated with right or left-sided aura symptoms.	
Messina et al. (2013) [39]	32 MwA 31 MwoA 18 HC	SBM Cortical thickness Cortical surface area	MwA vs. MwoA: •MwA had more cortical surface area in lingual gyrus and pericallosal sulcus and less cortical surface area in the inferior temporal gyrus. •MwA had more cortical thickness in supramarginal gyrus in central sulcus and insula regions.	
Niddam et al. (2015) [47•]	26 MwA 26 MwoA 26 HC	Rs-fc	MwA vs MwoA vs HC: •Weaker fc MwA between anterior insula and extrastriate visual regions.	•Negative correlation between headache intensity and fc between anterior insula and occipital regions.
Tedeschi et al. (2016) [46]	20 MwA 20 MwoA 20 HC	rs-fMRI DTI VBM	•MwA have stronger fc in visual network (extrastriate cortex/lingual gyrus) compared to HC and MwoA: •No brain structural gray or white matter abnormalities were detected in MwA in striate regions.	No correlation between disease severity and fc in right lingual region.
Tessitore et al. (2015) [30]	20 MwA 20 MwoA 20 HC	Rs-fc DTI VBM	•No differences between MwA and MwoA in the executive control network MwA and MwoA vs HC: •Migraineurs had reduced executive control network connectivity in the middle frontal gyrus and anterior cingulate cortex. •No group differences in underlying brain (gray and white matter) structure	•No executive function deficits in MwA and MwoA. •Negative correlation between the executive control network and pain intensity during migraine attacks in MwoA but not MwA.

MwA migraineurs with aura, *MwoA* migraineurs without aura, *HC* healthy controls, *DTI* diffusion tensor imaging, *fMRI* functional magnetic resonance imaging, *rs-fc* resting-state functional connectivity, *LGN* lateral geniculate nucleus; *SBM* surface-based morphometry, *VBM* voxel-based morphometry, *fc* functional connectivity, *V1* primary visual cortex

despite lateralized aura [50]. Similarly, two other studies demonstrated an absence of gray or white matter changes in striate areas (Tedeschi et al. 2016) and in structural regions underlying the executive function networks (Tessitore et al. 2015) in MwA compared to MwoA [30, 46]. Contrary to these findings, Messina and colleagues (2013) found more cortical

surface area (left lingual gyrus and the left pericallosal sulcus) and thicker cortex (bilateral supermarginal gyrus, right insula, right central sulcus) in MwA, along with reduced cortical surface area in the inferior temporal gyrus [39]. A small longitudinal study by Dinia et al. (2013) [47•] detected progression of white matter lesions over a period of 33 months in MwA. Furthermore, results showed there was a positive correlation between aura duration and the number of new white matter lesions that developed, as well as a positive correlation between the number of migraine attacks and new white matter lesions. Although this study lacked a healthy comparison group, this longitudinally designed study by Dinia and colleagues provide important results that suggest a link between the progression of white matter changes and specific migraine characteristics.

In summary, the majority of functional studies indicate that MwA is associated with functional alterations in striate and extrastriate visual processing regions. Two studies in MwA showed a lack of correlation of *rs* brain connectivity or visually induced brain activation to either headache frequency or to years lived with migraine. This potentially indicates that brain functional activity in the primary visual cortex of MwA is an intrinsic biomarker of susceptibility to aura as opposed to the result of recurrent attacks [46, 48]. Finally, as brain structural data are still limited, it remains inconclusive whether symptoms of aura are related to or cause changes in brain structure.

Sex-Specific Differences in Migraine

Epidemiological studies indicate that migraine typically begins in late childhood or early adulthood and is approximately three times as common in women than it is in men [51, 52]. Whereas the prevalence of migraine is relatively equal between sexes before the onset of puberty, migraine prevalence sharply rises in females after puberty relative to males [2]. In addition, women report more migraine-related symptoms and greater impairment compared to male migraineurs [51]. These data have led some researchers to suggest a putative role of female sex hormones in prevalence and clinical expression of migraine [53]. These sex-specific differences in prevalence and symptomatology are still poorly understood and have driven neuroimaging research to investigate changes in brain structure and function between male and female migraine patients—possibly indicating a sex-specific phenotype (Table 2).

Faria and colleagues (2015) have shown that female pediatric migraine patients who are in mid-puberty have greater gray matter volume relative to age-matched male migraineurs and healthy controls in regions of the thalamus and the putamen [54]. In addition, female pediatric migraineurs had stronger *rs-fc* between the right precuneus and the left putamen, right caudate, left thalamus, and the left amygdala. Maleki and colleagues (2012) showed thicker posterior insula and precuneus regions in

Table 2 Changes in brain structure and function between male and female migraine patients

Sex-specific differences

Authors	Subjects	Imaging	Results
*Dai et al. (2015) [57•] *meta-analysis of 9 VBM studies	222 M 52 males 170 females 230 HC 52 males 178 females	VBM	•*Female* sex associates with decreased GM in r. DLPFC.
Faria et al. (2015) [54]	28 M 14 males 14 females 28 HC 14 males 14 females	SBM VBM rs-fc	*Female pediatric* M vs *male pediatric* M vs HC. •Older (age 14–16) female *pediatric* M had more GM in the thalamus and putamen. •Female *pediatric* M had stronger fc between the r. precuneus and the l. putamen, r. caudate, l. thalamus and l. amygdala.
Maleki et al. (2012) [55]	22 M 11 male 11 female 22 HC 11 male 11 female	SBM rs-fc	*Female* M vs *male* M: •Stronger negative fc between post insula and S1, post. cingulate, precuneus and temporal pole. •Stronger fc between precuneus and amygdala and S1. •Thicker post. Insula and precuneus in *female* M vs *male* M and HC.

M migraine patients, *GM* gray matter, *HC* healthy controls, *rs-fc* resting-state functional connectivity, *S1* primary somatosensory area, *SBM* surface-based morphometry, *VBM* voxel-based morphometry, *DLPFC* dorsolateral prefrontal cortex, *r* right, *l* left

adult female migraineurs compared to adult male migraineurs and healthy controls.

Female migraineurs had stronger *rs-fc* between the posterior insula and the primary somatosensory cortex, posterior cingulate, precuneus, amygdala, and temporal pole. They also had stronger *fc* between the precuneus and the amygdala and the primary somatosensory cortex [55]. Another study by the same group (2015) showed that, while thinning of the insula occurred with advancing age in healthy female controls, this was not seen in female migraineurs [56]. A recent meta-analysis by Dai et al. (2015) of nine voxel-based morphological studies (total of 222 migraineurs and 230 healthy controls) indicated that in migraineurs, female sex was associated with less gray matter in the right dorsolateral prefrontal cortex [57•]. Important results provided by this meta-analysis as well as by other smaller studies suggest that there might be sex-specific brain biomarkers for migraine. Furthermore, the regularity with which alterations in brain structure or function have been found for the dorsolateral prefrontal cortex, the precuneus, and the insula suggest a sex-specific role of cognitive-affective pain processing in female migraine patients.

Attention/Cognition Deficits in Migraine: An Ongoing Debate

Migraineurs often self-report attention-related impairment as well as difficulties with processing speed during a migraine attack [58, 59]. These findings are corroborated by neuropsychological studies that show decreased performance on measures of attention, verbal learning, and memory during the attack [60, 61] as well as between attacks [62, 63]. However, other studies have failed to identify neuropsychological function deficits in migraineurs [30, 64, 65].

Many imaging studies to date have demonstrated altered brain structure and function in prefrontal areas of migraine patients [25, 31, 36, 66, 67] in regions associated with cognitive aspects of pain processing. Similarly, a number of recent *rs-fc* MRI studies have indicated abnormal *fc* within the salience network, a core resting-state network that includes paralimbic-limbic regions believed to play a role in the detection of stimuli and the allocation of attentional resources. *Rs-fc* results indicate heightened connectivity within the salience network in migraineurs without aura [68] and reduced functional connectivity between the salience and the visual networks in migraine patients with aura [69].

Recently, several studies have simultaneously interrogated cognitive function and brain structural and functional alterations in cognitive-processing regions in order to better understand whether alterations in brain structure are linked to deficits in cognitive performance in migraine patients (Table 3). In an earlier study, Schmitz and colleagues (2008) [64] found that less frontal and parietal gray matter density in migraine patients negatively correlated with slower response times during an attention-shifting task, thus indicating a potential relationship between cognitive function and gray matter deficits in migraine patients. Using a novel study design, Mathur et al. (2015) investigated brain activation patterns during the performance of a cognitive task while undergoing concurrent thermal-pain stimulation [70•]. Performance of the attention task was no different between healthy controls and migraineurs as reflected by measures of reaction time and error rates. Although both healthy controls and migraineurs had task-related deactivation in regions involved in pain modulation such as the dorsolateral prefrontal cortex, the middle cingulate, and the cerebellum—migraineurs showed significantly less deactivation in these regions. Whereas there was a relationship between deactivation and task-difficulty in healthy controls, this was absent for migraineurs. Results of this study are intriguing and indicate a potential abnormal modulation of pain-cognition circuits in patients with migraine [70•].

Mickleborough et al. (2015) [71] used an fMRI visual attention-orienting task to interrogate brain activation patterns in interictal migraineurs and healthy controls. Interestingly, although migraineurs performed as well as healthy controls on the attention task, migraineurs showed less activation of the ventral fronto-parietal attention network including the right temporal parietal junction, a region relevant for re-orienting attention to salient stimuli [71]. Results by Tessitore et al. (2015) have indicated that, although migraineurs show weaker connectivity in their executive control network relative to healthy controls, there is an absence of performance deficits on a variety of neurocognitive measures [30].

Although the existence of attention deficits in migraine remains controversial, these results could indicate that neurocognitive measures are not as sensitive as fMRI for detecting subtle changes in attention in migraine patients. Furthermore, results show that neurocognitive measures and brain activation patterns do not track each other well and could potentially indicate that fMRI might have better sensitivity than neurocognitive tests for detecting sub-clinical processing deficits in migraine.

Longitudinally Designed Studies and Pediatric Studies in Migraine

Although cross-sectional studies can draw inferences between migraine characteristics and alterations in brain structure and function, these inferences have to be interpreted with caution and have limited prognostic value for predicting disease

Table 3 Studies interrogating cognitive function and brain structural and functional alterations in cognitive-processing regions

Attention

Authors	Subjects	Imaging	Results	Clinical parameters
Mathur et al. (2015) [70•]	14 M 14 HC	fMRI Task-based Attentional network test performance during concurrent heat stimulation.	M vs HC: • Less task-related deactivation in M in DLPFC, middle cingulate and cerebellum.	• No difference in task performance (reaction time/error rates) between M and HC.
Mickleborough et al. (2015) [71]	16 M 16 HC	fMRI Task-based Visual orienting task	M vs HC: • M had less activation in the fronto-parietal attention network including the right temporo-parietal junction.	• No difference in task performance between M and HC.
Schmitz et al. (2008) [64]	25 M 25 HC	VBM	M vs HC: • M had less frontal and parietal gray matter density.	• Negative correlation between frontal gray matter density and response times on executive task.
Tessitore et al. (2015) [30]	20 MwA, 20 MwoA, 20 HC	rs-fc DTI VBM	MwA and MwoA vs HC: • migraineurs had weaker executive control network connectivity in the middle frontal gyrus and anterior cingulate cortex. • no group differences in underlying brain (gray and white matter) structure.	• No executive function deficits • Negative correlation between the executive control network and pain intensity during migraine attacks in MwoA but not MwA.

M migraine patients *GM* gray matter, *HC* healthy controls, *TBSS* tract-based spatial statistics, *SBM* surface-based morphometry, *DLPFC* dorsolateral prefrontal cortex

progression. Repeated imaging of subjects at multiple time-points allows the evaluation of brain changes in individual patients over time. These studies have profound value and enable the actual "tracking" of migraine progression (Table 4).

A recent longitudinal imaging study by Liu et al (2015) [72] in adult patients who were newly diagnosed with migraine demonstrated brain gray matter, but not white matter structural volume loss over a period of one year. Dinia and colleagues (2014) [47•] detected a progression of white matter hyperintensities in migraineurs with aura (33-month follow-up). Neither study showed a correlation between headache characteristics and structural changes. A 3-year follow-up study by Erdélyi-Botor et al. [73] has also showed progression of white matter hyperintensities in migraine patients. These hyperintensities were more common in high-frequency than in low-frequency migraineurs. Lastly, a 9-year follow-up study by Palm-Meinders et al. 2012 [74•] investigated longitudinal MRI-based brain changes in 203 migraineurs and 83 healthy controls. This important large-scale cohort study showed that female migraineurs had more white matter lesions relative to female controls and that female migraineurs showed a higher progression of these white matter lesions over time. However, the authors again showed no association between headache frequency and the progression of white matter lesions. Zhao et al. (2014) [75] found progressive *fc* changes in pain-processing networks and abnormal regional homogeneity changes in the putamen, thalamus, orbitofrontal cortex, secondary somatosensory cortex, and the brainstem over a period of 6 weeks in migraineurs who were experiencing increasing migraine frequency.

These studies all reveal longitudinal brain structural changes in migraineurs over time though there was variable correlation of headache frequency with the progression of structural alterations. However, as only two studies included a control group, future studies are needed to confirm if structural changes are specific to migraine as opposed to being attributable to aging.

Pediatric Cohorts

The neuroimaging literature has mostly focused on studying adult migraine populations, leaving brain structure and function in children with migraine largely under-investigated. Longitudinal studies that begin during childhood will be especially useful since they offer the unique opportunity to study the migraine disease process at its earliest stage.

Two studies using voxel-based morphometry analysis (VBM) and tract-based spatial statistics (TBSS) found reduced volume of and altered white matter connectivity between regions associated with pain processing in pediatric migraineurs. Rocca and colleagues (2014) [41•] investigated brain volumetric changes in pediatric migraine patients. Results indicate that pediatric migraineurs have greater putamen but reduced gray matter brain volume in fronto-temporal areas including the middle temporal, orbitofrontal, inferior frontal gyrus, and the cingulum relative to age-matched non-migraine controls. Volume in the putamen correlated with

Table 4 Changes in brain structure in pediatric migraineurs and longitudinally designed studies in migraine

Authors	Subjects	Imaging	Results	Clinical parameters
Pediatric migraineurs				
Messina et al. (2015) [76]	15 M mean age: 14.1 years 15 HC mean age: 13.8 years	DTI TBSS	M vs HC: •Alterations in diffusion parameters in widespread white matter tracts	•No correlation between headache frequency, years lived with migraine and diffusion parameters.
Rocca et al. (2014) [41•]	12 M mean age: 14.2 years 15 HC mean age: 13.3 years	VBM	M vs HC: •Less gray matter volume in frontal-temporal areas. •More gray matter volume in putamen. •No white matter volume changes	•No correlation between fronto-temporal brain structural changes and headache frequency and years lived with migraine. •Positive. correlation between years lived with migraine and putamen volume.
Longitudinal studies				
Dinia et al. (2014) [47•]	41 MwA Longitudinal study: *33.2 month follow-up	T2 FLAIR	63.4 % had WML at baseline. At follow-up: 19.5 % had new WML	•No correlation between number of new WML and disease duration. •Positive correlation between aura duration and number of new WML. •Positive correlation between new WML and number of migraine attacks with aura.
Erdélyi-Botor et al. [73] (2014)	17 M Longitudinal study: *3-year follow-up	T2	•Progression of WMH over a period of 3 years	•Progression of deep WMH was more common in high-frequency vs low-frequency migraineurs.
Liu et al. (2013) [72]	36 M Longitudinal study: *1-year follow-up	T1 VBM TBSS	•M had less gray matter in DLPFC, superior frontal cortex, orbitofrontal cortex, hippocampus, precuneus, S1 and S2. •No changes in white matter diffusion parameters	•No correlation between headache frequency and pain intensity and structural measures.
Palm-Meinders et al. (2012) [74•]	203 M 83 HC Longitudinal study: *9-year follow-up	T2	•female M had a higher incidence and a higher progression of WML compared to female healthy controls	•No association between headache frequency and WML progression.
Zhao et al. (2014) [75]	19 M 20 HC Longitudinal study: *6-week follow-up of M whose HF increased over this time period	rs-fc	M vs HC: •M had alterations in pain-processing networks and abnormal ReHo changes in the putamen, thalamus, orbitofrontal cortex, S2, and the brainstem •Functional changes in these regions were exacerbated after 6 weeks.	•M patients with increasing HF have progressive brain changes.

HC healthy controls, *M* migraine patients, *MwA* migraineurs with aura, *TBSS* tract-based spatial statistics, *MP* migraine patients, *HC* healthy controls, *rs-fc* resting-state functional connectivity, *ReHO* regional homogeneity, *VBM* voxel-based morphometry, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *WMH* white matter hyperintensities, *TBSS* tract-based spatial statistics

years lived with migraine. No changes in white matter brain volume were identified.

A study by Messina and colleagues (2015) [76] that interrogated white matter tract structure in a pediatric migraine cohort showed white matter alterations reflected by lower mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in widespread cortical (fronto-temporal-occipital), subcortical (thalamic), and brainstem regions as well as increased fractional anisotropy (FA) in the optic radiations. Both studies showed no association between clinical factors (such has headache frequency and years lived with migraine) and cortical volume loss or fiber tract alterations leading the authors to hypothesize that fronto-temporal gray matter volume and white matter structural alterations found in pediatric migraineurs could potentially be trait biomarkers of the disease.

Although white matter lesions identified by high-signal intensities shown on T2-weighted imaging are common in adult migraineurs, recent evidence shows that white matter lesions are also present in 4.4 to 17 % of children and adolescents with migraine [77–80]. Longitudinal data by Bayram and colleagues (2013) detected white matter hyperintensities in pediatric *headache* patients on baseline MRIs (time-point I), yet, no new white matter lesions in pediatric patients with headache on follow-up imaging after an average of 16 months (time-point II) [79]. This is an interesting finding that will have to be replicated using longitudinally designed studies with longer follow-up intervals in pediatric migraine populations.

An important goal for migraine research is the identification of brain imaging biomarkers that could help identify whether certain characteristics of brain structure or

function might differentiate migraine patients from healthy controls and from other headache types. Although results of some longitudinal studies suggest that brain changes are driven by disease factors, other longitudinal data as well as structural findings in pediatric migraine populations suggest that imaging changes reflect a trait biomarker rather than the consequence of repeated attacks. As such, whether migraine-related brain changes exist "from the very beginning" or whether they are modified by the disease is an unresolved issue. Of course, these possibilities are not mutually exclusive. One could hypothesize for example that certain brain alterations are present in migraineurs at the earliest stages and that these regions are further modified as a function of disease burden (e.g., frequency of attacks). Although past cross-sectional studies and current longitudinal studies yield some evidence of a relationship between progressive brain changes and migraine characteristics (such as headache frequency), the literature does not yet provide evidence as to whether these brain changes are reversible with improvements or resolution of migraine attacks.

Conclusion

Neuroimaging research has demonstrated brain structural and functional alterations in migraineurs in a variety of regions associated with sensory and pain processing. More recent findings indicate that these regional alterations might relate to migraine factors such as patient demographics (sex, age), migraine characteristics (presence or absence of aura) or migraine-associated cognitive dysfunctions. Lastly, imaging results from pediatric migraine patients and results of longitudinal studies yield evidence of baseline brain alterations as well as evidence that migraine burden such as migraine frequency might modify brain structure and function over time.

Compliance with Ethical Standards

Conflict of Interest Catherine D. Chong declares that she has no conflict of interest.

Todd J. Schwedt has received consulting fees from Allergan, Amgen, Dr. Reddy's, GBS, Supernus, Teva, and Zogenix. He receives royalties from Cambridge University Press and UpToDate .

David W. Dodick, MD, in the past 12 months, has served on advisory boards and has consulted for Allergan, Amgen, Alder, CoLucid, Dr Reddy's, Merck, ENeura, Eli Lilly & Company, Autonomic Technologies, Teva, Xenen, Tonix, Trigemina, Supernus, ScionNeurostim, and Boston Scientific. He has options in Xalan, Epien, and Second Opinion. He is on the board of directors of the King Devick Test. Within the past 12 months, Dr. Dodick has received royalties, funding for travel, speaking, or editorial activities from the following: Healthlogix, Haymarket Media Group, Ltd., SAGE Publishing, Lippincott Williams & Wilkins, Oxford University Press, and Cambridge University Press. He receives publishing royalties for Wolff's Headache, 8th edition (Oxford University Press, 2009) and Handbook of Headache (Cambridge University Press, 2010).

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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