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Advanced Neuroimaging of Migraine

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Abstract

Advanced neuroimaging has led to an evolution in knowledge about migraine pathophysiology. Migraine has transformed from a vascular, to neurovascular, and most recently, to a central nervous system disorder. Functional imaging has confirmed the importance of cortical spreading depression (CSD) as the pathophysiologic mechanism of migraine aura in humans, while novel animal studies are unraveling the mechanistic underpinnings of CSD. Altered cerebral blood flow and neurotransmitter systems have been identified during and between headaches in migraine with and without aura. Advanced neuroimaging has identified mechanisms involved in the transformation of migraine from an episodic disorder to one with near continuous symptomatology. Questions regarding secondary effects of migraine on brain structure and function, possibly related to attack frequency and duration of illness, have been raised. New imaging techniques may lead to novel diagnostic and therapeutic interventions that will help improve the lives of millions of migraine sufferers. In this review, we summarize the most important findings from current imaging studies of migraine.

Introduction

Migraine headaches cause significant individual and societal burden due to pain, environmental sensitivities, resulting disability and lost productivity. Migraine has a point prevalence equal to 12% of the general population, with a cumulative lifetime incidence of 43% in women and 18% in men. ⁽¹⁾ Migraine results in substantial pain, disability, and a decreased overall quality of life. ^(2,3) Direct and indirect medical costs from migraine exceed \$15 billion annually in the United States and €27 billion per year in Europe. ^(4,5) A better understanding of migraine mechanisms will lead to improved treatments and a reduction in the negative impact of migraine.

Neuroimaging has led to advancement in the description of migraine mechanisms and to identification of secondary structural and functional effects from migraine. Imaging during migraine pain has led to a transition from a purely vascular hypothesis of migraine pathophysiology, to a neurovascular hypothesis, and now to a central nervous system theory. Imaging has led us closer to identification of the elusive “migraine generator”, or structure

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that is responsible for initiation of the migraine attack. Investigations have given important insights into the role of central sensitization in the pathophysiology of individual attacks and disease progression, as well as insights into medication overuse headache, and the mechanisms of action of migraine abortive and prophylactic medications. Cortical spreading depression (CSD) has been identified during migraine with, and possibly without aura. Migraineurs have structural and functional brain alterations between migraine attacks that are correlated with disease duration and severity, suggesting that more severe disease may result in abnormalities that persist between migraines.

In this review, we summarize some of the most important imaging investigations that have led to a better understanding of migraine mechanisms.

Search Strategy and Selection Criteria

We searched PubMed for manuscripts published between 1950 and April 2009 using the following search terms: “migraine” and “imaging” or “migraine” and “magnetic resonance imaging” or “migraine” and “diffusion tensor imaging” or “migraine” and “arterial spin labeling” or “migraine” and “positron emission tomography” or “migraine” and “voxel-based morphometry” or “migraine” and “functional magnetic resonance imaging” or “migraine” and “blood oxygen level dependent” or “migraine” and “magnetic resonance spectroscopy” or “migraine” and “single photon emission computed tomography” with limits to English language and human studies. In addition the reference lists of identified manuscripts and the authors’ own files were searched for relevant publications. Publications were selected for inclusion based upon their originality, contribution to migraine pathophysiology, diagnosis or treatment, and relevance to the topics included in this review.

Imaging Migraine

Due to the episodic and generally unpredictable nature of individual migraine attacks, imaging during spontaneous migraine has proven difficult. Some investigators have exposed migraine subjects to attack triggers, such as photic stimulation, physical exertion or nitroglycerin in order to initiate migraine. A few investigators have captured the onset of a migraine headache while others have imaged just after the headache began. The overall number of studies imaging the migraine attack remains small.

The Brain

Studies that have captured the onset of migraine suggest the migraine generator resides in the brainstem. Cao and colleagues performed a set of blood oxygen dependent (BOLD) functional magnetic resonance imaging (fMRI) studies of spontaneous migraine following recurrent checkerboard visual stimulation. ⁽⁶⁾ Consistent with prior studies implicating midbrain structures in migraine and pain processing, the majority of subjects who developed migraine had signal intensity increases in the region of the red nucleus and substantia nigra. ⁽⁷⁾ This was followed by occipital cortex signal increase and then onset of visually triggered symptoms. Less consistently, subjects were found to have signal increases in other regions of the brainstem including the cerebral peduncle, locus ceruleus, periaqueductal gray, medial longitudinal fasciculus, basilar pons, medial lemniscus, pontine tegmentum, and central midbrain.

Spontaneous attacks were also investigated by Afridi and colleagues in positron emission tomography (PET) studies of 3 migraineurs without aura and 2 migraineurs with aura. ⁽⁸⁾ Comparison of images during migraine (studied within 24 hours of migraine onset) to interictal scans (greater than 72 hours after last migraine) revealed significant activation in the dorsal pons during migraine. Activations were also detected in the anterior and posterior

cingulate, cerebellum, thalamus, insula, prefrontal cortex, and temporal lobes. These studies by Cao and Afridi identified activation of brainstem structures during migraine. However, one of the main challenges in interpreting these results is to differentiate findings consistent with the general pain response from those which may be specific to migraine. One approach is to compare areas of activation/deactivation during a migraine to activations/deactivations following effective abortive therapy. It is anticipated that regions responsible for the pain of migraine would change following effective therapy, while regions responsible for the generation of the migraine attack may remain active. This approach was employed in a PET study of 24 subjects with glyceryl trinitrate induced migraines.⁽⁹⁾ Significant brainstem activation was noted during migraine in the dorsal pons and rostral medulla. Other areas of activation included the anterior cingulate, insula, cerebellar hemispheres, prefrontal cortex, and putamen. Following treatment of the migraine with sumatriptan, the dorsal pons remained activated.^(9–11) Eight chronic migraine patients treated with occipital nerve stimulation underwent PET study in an investigation by Matharu and colleagues.⁽¹²⁾ PET was performed with stimulators active and the subjects pain free with paresthesias, with stimulators deactivated and the subjects with migraine but no paresthesias, and with the stimulators partially activated and patients with intermediate levels of pain and paresthesias. Significant changes in regional cerebral blood flow correlating with migraine pain were found in the region of the dorsal rostral pons, anterior cingulate cortex, and cuneus while changes in the anterior cingulate cortex and pulvinar correlated with paresthesias. Increased activity in the dorsal rostral pons during migraine and when pain free compared to the intermediate state suggests a persistent dysfunction of this structure in these chronic migraine subjects. These studies suggest that a migraine generator exists in the brainstem, likely the dorsal rostral pons. Persistent activation of the dorsal rostral pons after sumatriptan therapy and suboccipital stimulator therapy implies this region being specific to migraine.

Functional brain events during migraine identified via modern imaging techniques are summarized in Table 1.

The Cerebrovasculature

The vascular and neurovascular theories of migraine had assumed that dilation of cerebral and meningeal arteries is essential for the production of migraine pain. A multitude of studies using mostly indirect measurements of vascular diameter have provided conflicting results.^(13–17) A recent 3-Tesla magnetic resonance angiography study has questioned the importance of the cerebral vasculature in the pathophysiology of migraine.⁽¹⁸⁾ Investigations of twenty migraine without aura attacks provoked by nitroglycerin identified no significant changes in cerebral artery diameters or cerebral blood flow during migraine. Findings suggest that changes in vascular diameter may not occur, or at least may not be necessary during migraine, and further support that migraine should be considered a central nervous system disorder. Additional studies are needed to confirm these early findings. Subjects were not imaged at the onset of migraine and thus a transient change in vascular diameter and blood flow could have been missed.

Central Sensitization

Development of central sensitization in the migraineur results in additional pain during a migraine (cutaneous allodynia) and may contribute to the transformation from episodic migraine to chronic migraine.⁽¹⁹⁾ Cutaneous allodynia develops in about 65% of migraineurs during individual headaches.^(20–22) Allodynic patients report painful sensitivity of the skin to normally innocuous stimuli such as light touch. Methods of blocking the development of or reversing central sensitization may reduce the pain of migraine and reduce the rate of transformation to chronic migraine.

One of the difficulties in the neuroimaging of central sensitization is to differentiate changes resulting from the increased pain experience of cutaneous allodynia from those structures which may specifically mediate the production and maintenance of central sensitization. Recent fMRI studies have made advancements in this regard. Using the heat/capsaicin model of sensitization, fMRI studies have identified activation in the region of the midbrain reticular formation that seems specific to central sensitization.^(23, 24) Investigators theorize that activation occurred at the location of the nucleus cuneiformis and rostral superior colliculi/periaqueductal gray.

Further fMRI studies examined the modulating effect of gabapentin on brain activations following painful mechanical stimulation of normal skin compared to skin with capsaicin-induced secondary hyperalgesia.⁽²⁵⁾ In both conditions, gabapentin reduced activations in the operculoinular cortex. However, only in the presence of central sensitization did gabapentin reduce activations in the brainstem and suppress stimulus-induced deactivations, indicating that gabapentin more effectively reduces painful transmission in the presence of central sensitization. These findings set the stage for additional investigations focused on identifying the site at which gabapentin exerts its effect on central sensitization. This could provide important information for the development of future therapies aimed at inhibiting central sensitization.

Migraine Medications

Advanced neuroimaging will hopefully lead to identification of mechanisms responsible for the transformation from infrequent to frequent headache patterns. A risk factor for this transformation is the excessive use of migraine abortive medications, a condition termed medication-overuse headache. 18-FDG-PET was used to study subjects while suffering from analgesic overuse headache and again 3 weeks following withdrawal of the overused medication.⁽²⁶⁾ Despite similar pain levels at the time of testing, multiple areas of abnormal metabolic activity while suffering from medication overuse headache (hypometabolism at thalamus, orbitofrontal cortex, anterior cingulate cortex, insula, inferior parietal lobule; hypermetabolism at cerebellar vermis) normalized after medication withdrawal. The exception was a further reduction in metabolic activity of the orbitofrontal cortex, suggesting a role for this structure in the predisposition to analgesic overuse. Of note, orbitofrontal cortex dysfunction has also been identified in numerous other disorders including substance-dependence and in those with gaming addictions.^(27, 28)

Exemplifying how advanced neuroimaging may lend explanation to mechanisms by which migraine medications exert their effects, the rate of serotonin synthesis during migraine and following treatment with sumatriptan was recently studied using PET.⁽²⁹⁾ Six patients were scanned within 6 hours of onset of a spontaneous migraine, 2 hours following treatment with sumatriptan, and when migraine-free for at least 3 days. During the pain-free state, migraineurs had significantly lower serotonin synthesis compared to controls. Serotonin synthetic rate increased during a migraine attack and was reduced to levels lower than the pain-free state by administration of sumatriptan. Reductions in serotonin synthetic rate were independent of changes in pain intensity, suggesting that sumatriptan exerts its effect on serotonin synthesis at a different site than its pain relieving effects. Although further work is needed to identify these sites of action, it is theorized that action at 5-HT_{1B} receptors of the raphe nucleus is responsible for the reduction of serotonin synthesis, while action at 5-HT_{1D/1F} receptors in the trigeminal nucleus caudalis or 5-HT_{1B/1D} receptors of the periaqueductal gray is responsible for the pain relieving effect.⁽³⁰⁾

Imaging Cortical Spreading Depression/Migraine Aura

CSD has long been considered the physiologic substrate of migraine aura. During CSD there is an initial neuronal depolarization, followed by hyperpolarization and relative neuronal silence that spreads contiguously from the occipital lobe forward. This spreading wave of neuronal depression travels slowly, at 3–5 mm/minute, which coincides with the progressive visual symptoms typical of migraine aura. As the neuronal events occur, there are changes in cortical blood flow. A brief decrease in blood flow is followed by hyperperfusion lasting a couple of minutes and then a prolonged hypoperfusion. ^(31–34)

Recent neuroimaging has allowed for detection of CSD in humans and has raised new questions about its possible role in migraine without aura. Hadjikhani and colleagues studied three migraine with aura subjects using fMRI (BOLD) during spontaneous attacks. ⁽³⁵⁾ All subjects were studied within 20 minutes of attack onset and one subject who could trigger migraine by exercise was studied at the onset of the episode. Investigators found evidence for CSD: 1) Initial focal increase in BOLD signal in the extrastriate cortex; 2) BOLD changes were time-locked to onset of migraine aura; 3) BOLD changes progressed contiguously over the occipital cortex at approximately 3.5 mm/minute; 4) BOLD signal then diminished following the increase; 5) BOLD signal followed the retinotopic progression of the visual precept. Cerebral hypoperfusion with migraine aura has also been seen using MRI perfusion-weighted imaging. ⁽³⁶⁾ Five migraine with aura attacks were imaged within 45 minutes of aura onset. Decreases in cerebral blood flow (16–53%) and blood volume (6–33%) and increases in mean transit time (10–54%) were seen in the occipital lobe.

Although CSD was initially assumed to be a process isolated to migraine with aura, a few investigations have now documented evidence of CSD-like changes in cerebral blood flow during migraine without aura. In the classic case of Woods and colleagues, PET imaging detected bilateral hypoperfusion of the occipital lobes spreading anterior to the temporal and parietal lobes in a patient with spontaneous migraine without aura. ⁽³⁷⁾ Investigators had the fortuitous opportunity of imaging the onset of the migraine attack when their study subject developed one of her typical migraines while serving as a volunteer for a PET study for another purpose. Since it was one of the first demonstrations of what appeared to be CSD during migraine without aura, there was substantial discussion about the subject's symptoms. Although by definition she suffered a migraine without aura attack, the significance of her report of mild inability to focus her vision during the headache has raised questions about this diagnosis. However, recent PET studies in migraineurs without aura may provide additional evidence for CSD in migraine without aura. Denuelle and colleagues performed PET studies on 7 subjects during spontaneous attacks of migraine without aura. ⁽³⁸⁾ Mean time from attack onset to imaging was just over 3 hours. Investigators found a relative decrease in perfusion in the bilateral occipital, parietal, and temporal cortices during the migraine compared to the headache-free state. Regional cerebral blood flow was reduced by just over 10%. It is not clear if this reduction in cerebral perfusion was associated with the presence of pain or was a manifestation of CSD. ⁽³⁹⁾ Demonstration of what appears to be CSD in migraine without aura suggests a common pathophysiologic link between migraine with and without aura. It is possible that CSD is symptomatic in some patients and during some attacks (migraine with aura) while it is silent in others (migraine without aura). However, caution must be exercised when interpreting these results given several conflicting reports of cerebral perfusion during migraine without aura. Several studies have detected no change in cerebral perfusion during migraine without aura. ^(40, 41) Furthermore, demonstration of a progressive wave of hypoperfusion would be more indicative of CSD than single measurements of perfusion.

Functional brain events identified in humans during migraine aura using modern imaging techniques are summarized in Table 2.

Optical intrinsic signal (OIS) imaging and electrophysiology have recently been used to simultaneously study the vascular and brain parenchyma changes during CSD in a rodent model.⁽⁴²⁾ It had previously been assumed that vascular changes occur concurrently or following the CSD wave and may be a product of CSD. OIS imaging allows for simultaneous investigation of CSD (parenchymal reflectance) and cortical surface arteriole diameter. Investigators found that arteriolar vasodilation propagates with a greater velocity than CSD and thus precedes CSD in its spread across the brain cortex. Furthermore, there was dissociation of vascular changes and CSD in areas distant to the CSD propagation and with frequent repetitive CSD events. Repetitive CSD was associated with a reduced or absent vascular response. These findings imply that vascular changes associated with CSD have a mechanism of propagation independent from the CSD wave itself. Investigators also used OIS to compare CSD in male vs. female mice.⁽⁴³⁾ Female mice were found to have a lower threshold for triggering of CSD than male mice, perhaps contributing to the explanation for higher prevalence of migraine among women compared to men.

It has been hypothesized that CSD activates trigeminal sensory afferents which then cause the pain of migraine headache.⁽⁴⁴⁾ If so, inhibiting CSD would be useful for migraine prevention. Moskowitz and colleagues have demonstrated that common migraine prophylactic medications do suppress CSD in rats.⁽⁴⁵⁾ Rats pre-treated with topiramate, valproate, propranolol, amitriptyline, or methysergide had less frequent CSD and higher CSD electrical stimulation thresholds. CSD frequency was reduced by 40% to 80% in rats pre-treated over weeks and months with longer treatment durations producing a greater degree of CSD suppression. However, it is not clear that CSD is a prerequisite for migraine headaches nor that suppression of CSD is the mechanism by which prophylactic medications reduce headache frequency.⁽⁴⁶⁾ For example, tonabersat (a benzoylamino benzopyran with anticonvulsant properties) has been shown to inhibit CSD in animals but did not clearly demonstrate benefit in preventing migraine headaches in a randomized clinical trial.^(47–49) Further work is needed to investigate the relationship between CSD, production of migraine pain, and the effects of CSD suppression on migraine headaches.

Interictal Imaging of the Migraineur

Interictal imaging has identified brain structural and functional alterations in migraineurs. Studies showing an association of these alterations with increased migraine frequency and duration suggest that these alterations are a result of migraine. However, we are often left with a “chicken and the egg” question, with inability to determine if the identified alterations may predispose the subject to migraine or if they are the secondary effect of having migraine headaches. Longitudinal studies would most adequately answer cause-and-effect questions.

Structural alterations in the migraine brain identified by modern imaging are summarized in Table 3.

Conventional MRI

Conventional MRI studies have identified migraineurs to be at increased risk for brain deep white matter lesions and strokes. The risk of ischemic stroke is elevated in migraineurs with and without aura.⁽⁵⁰⁾ Overall, migraine is associated with an approximate doubling in the relative risk for stroke.^(50–53) However, the relative risk is higher among migraineurs with aura, younger patients, smokers, oral contraceptive pill users, and those with more frequent migraines.^(50, 53–56) Smoking at least triples this risk and using oral contraceptive pills quadruples the risk.^(53–55) The increased risk of stroke in migraineurs may be confined to

small cerebellar watershed zone strokes. ^(56, 57) The adjusted odds ratio for such strokes is 7.1 (95% confidence interval 0.9 to 55) compared to non-migraine controls. ⁽⁵⁶⁾ The risk is increased further in migraine with aura subjects and with an increasing frequency of migraine headaches (odds ratio of 15.8, 95% confidence interval 1.8 to 140). ⁽⁵⁶⁾ Approximately 10% of subjects who have migraine with aura and at least 1 migraine per month have been found to have a posterior circulation stroke. ⁽⁵⁶⁾ Of note, the great majority of these strokes are asymptomatic and their clinical significance is undetermined. Migraine also increases the risk of brain deep white matter lesions compared to controls (odds ratio 2.1, 95% confidence interval 1.0 to 4.1). ⁽⁵⁶⁾ More frequent migraines (at least 1 per month) further elevates this risk (odds ratio 2.6, 95% confidence interval 1.2 to 5.7). No difference in risk among those with and those without aura has been detected. Although the clinical significance of these white matter lesions is yet to be determined definitively, to date there is no evidence that they are associated with functional consequences.

In addition to increasing the risk for stroke and deep white matter lesions, migraine has been associated with multiple other structural brain changes. High-resolution MRI mapping of transverse relaxation rates was used to study the paramagnetic properties of iron in the regions of the periaqueductal gray, red nucleus, and substantia nigra of episodic migraineurs and subjects with medication overuse headache (who had transformed from episodic migraine without aura). ⁽⁵⁸⁾ Episodic migraine and medication overuse headache subjects both had evidence for increased iron deposition in the regions of the periaqueductal gray compared to non-migraine controls. Furthermore, a longer duration of illness was correlated with abnormal iron deposition. These findings were replicated in a more recent population-based study involving 138 migraineurs. ⁽⁵⁹⁾ Investigators found increased iron concentrations in the regions of the putamen, globus pallidus, and red nucleus of migraine subjects less than 50 years of age as compared to matched non-migraine controls. In this group, iron deposition in the regions of the putamen, caudate, and red nucleus was positively associated with longer disease duration. These studies give further support for the importance of several deep brain nuclei in migraine pathophysiology. Furthermore, the positive association of iron deposition and longer migraine duration suggest that migraine may have cumulative effects on the brain.

Voxel-Based Morphometry (VBM)

Voxel-based morphometry (VBM) is a newer technique that yields detailed information about structural differences in the brains of migraineurs compared to non-migraine controls. VBM is an automated method that allows for the structural comparison of white and gray matter between subjects and controls. VBM allows for comparison of whole brain and regional volumes on a voxel-by-voxel basis.

Although an initial VBM study of migraineurs with and without aura found no differences in global or regional grey or white matter between migraineurs and controls and between migraine with and without aura, more recent studies have found differences. ⁽⁶⁰⁾ A study of 28 adult migraineurs (8 with aura, 20 without aura) identified reductions in the density of frontal, parietal, and occipital white matter and frontal gray matter as compared to non-migraine controls. ⁽⁶¹⁾ Migraineurs with a high attack frequency (>3 migraines per month) and with a longer duration of disease (>15 years of migraine) had differences in grey and white matter density compared to those with lower attack frequency (<3 migraines per month) and with a shorter disease duration (<15 years of migraine). Investigators showed that brain regions likely to be affected in migraineurs include the frontal lobes, limbic system, parietal lobes, basal ganglia, brainstem, and the cerebellum. A separate VBM study confirmed that structural differences in migraineurs are associated with headache frequency. ⁽⁶²⁾ Subjects with episodic (n=16) and chronic migraine (n=11) had reductions in gray matter in the superior and inferior temporal gyri and precentral gyrus as compared to

controls. Compared to those with episodic migraine, those with chronic migraine had decreased gray matter in the anterior cingulate cortex, insula, amygdala, parietal operculum, and middle and inferior frontal gyrus. Rocca and colleagues used VBM to study whether migraineurs with white matter damage detected on conventional MRI have changes in gray matter density as compared to non-migraine controls.⁽⁶³⁾ Migraineurs had regions of reduced gray matter density in the bilateral frontal and temporal lobes and cingulum and increased density of the periaqueductal gray. Reduced gray matter density was correlated with age, disease duration, and white matter lesion load. Kim and colleagues studied grey matter volume in 20 migraine subjects with normal conventional MRIs.⁽⁶⁴⁾ Compared to controls, migraine subjects had reduced volumes in the insula, motor/premotor cortex, prefrontal cortex, cingulate cortex, posterior parietal cortex, and orbitofrontal cortex. Grey matter volume was negatively correlated with disease duration and lifetime headache frequency. These studies confirm that migraineurs have alterations in grey and white matter, beyond that which can be detected using conventional MRI, and that these alterations are positively associated with duration of migraine and headache frequency. However, given that similar structural alterations have been found in many chronic pain disorders, it is likely that some or all of these findings are not specific to migraine.⁽⁶⁵⁾ Furthermore, longitudinal studies are needed to determine if structural changes are permanent or if they may normalize with effective treatment or resolution of pain.

Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is a MRI technique that allows for visualization of the orientation and anisotropy of white and grey matter. The technique is based upon the measurement of water diffusion (Brownian motion) within brain tissue. Diffusion is affected by the magnitude of myelination, density, and orientation of axons. DTI has proven useful for the identification of structural brain damage that modifies the tissue microstructure and thus affects water diffusivity through tissues. Since DTI can detect microstructural changes, it is considered to be more sensitive than conventional MRI techniques in identifying brain structural damage.

Rocca and colleagues used DTI to study normal appearing brain tissue in 34 migraineurs.⁽⁶⁶⁾ Supporting the notion that migraine is associated with brain damage that cannot be detected by conventional MRI, investigators found reduced mean diffusivity peaks in the normal appearing brain tissue of migraineurs with and without aura as compared to controls. Using DTI, DaSilva and colleagues found areas of greatest difference in the migraine brain compared to control brain in the ventroposterior medial thalamus and the corona radiata near the lateral ventricular horn along the trigeminothalamic tract.⁽⁶⁷⁾ In addition, lower fractional anisotropy was found in the periaqueductal grey in migraineurs without aura. Each of these structures has been previously implicated in the pathophysiology of migraine.

Imaging Findings with Functional Correlates

Interictal imaging has identified structural differences in the migraine brain. Association of these changes with higher headache frequency and longer disease duration suggests that these changes are secondary to migraine. However, we are just beginning to learn whether these changes have clinical effects on the patient with migraine. Schmitz and colleagues measured grey matter density using VBM and performed tests of executive function in 25 migraine subjects.⁽⁶⁸⁾ Investigators found that migraineurs had reductions in frontal and parietal lobe density and inferior executive function with time to task-shifting. Reduced gray matter density in the frontal lobes correlated with slow response times in the migraine subjects, suggesting that the anatomical alterations leads to impaired executive function.

Based upon the observation that migraine patients have abnormal visual motion perception during and between migraines, cortical thickness measurements and DTI of the visual motion processing network has been performed. ⁽⁶⁹⁾ Migraineurs with and without aura had anatomical abnormalities in the visual processing network including increased cortical thickness and DTI abnormalities in the superior colliculus and the lateral geniculate nucleus. The optic radiations were further studied using diffusion tensor tractography in migraineurs with and without aura. ⁽⁷⁰⁾ Although the volume of the optic radiations did not differ among groups, migraineurs with aura had decreased fractional anisotropy and increased mean diffusivity. Investigators theorize that these findings suggest axonal damage followed by proliferation and hypertrophy of astrocytes. In addition to these structural changes, functional alterations have also been identified in the visual cortex. After visual stimulation, migraineurs are found to have an enhanced interictal reactivity of the visual cortex detected by fMRI. ⁽⁷¹⁾ Magnetic resonance spectroscopy (MRS) has also been used to compare the visual cortex response to photic stimulation in migraineurs vs. controls. ⁽⁷²⁾ MRS allows for measurements of metabolic activity following neuronal activation. Migraineurs with aura have a more consistent decrease in N-acetylaspartate signal and a slight increase in lactate peak compared to those without aura and non-migraineurs. These findings may represent decreased efficiency of mitochondrial function in the occipital cortex of migraineurs with aura. Similar studies have supported this conclusion. ⁽⁷³⁾

Functional changes have been identified in other regions of the migraine brain as well. Functional MRI was used to investigate brain activation patterns in 15 migraine subjects with white matter abnormalities detected with conventional MRI and matched controls following a simple motor task. ⁽⁷⁴⁾ Migraineurs had greater activation of the primary sensorimotor cortex and a rostral displacement of the supplementary motor area compared to controls. There was evidence that the extent of supplementary motor area displacement was correlated with the degree of subcortical brain damage detected by DTI. Response of the brainstem descending modulatory pathway was studied following heat stimulation during the interictal state in 12 episodic migraine patients using fMRI. ⁽⁷⁵⁾ Migraine subjects had hypofunctional response at the nucleus cuneiformis compared to non-migraine controls. Investigators hypothesize that nucleus cuneiformis dysfunction may result in decreased nociceptive inhibition and may contribute to the development of central sensitization.

Alterations in the migraine brain identified with modern imaging and with presumed functional correlates are summarized in Table 4.

Additional investigations are needed to determine if brain structural changes found in migraineurs result in measurable losses of function on clinical tests. If structural alterations result in clinical deficits, and if the risk of structural alterations increases with increasing headache frequency and duration, more aggressive treatment of migraine may be indicated.

Conclusions

Advanced neuroimaging has led to an evolution in theory of migraine pathophysiology. No longer can migraine be considered a vascular or neurovascular disorder, but should be considered a disease mediated by the central nervous system. The identification of CSD in migraine with, and possibly without aura, suggests that CSD may be a common physiologic process occurring at the onset of both migraine subtypes. Equally plausible is that altered activity of brainstem nuclei which project diffusely to the cortex results in changes in glial activity, cortical neuronal activity, and cerebral blood flow in all migraineurs, but CSD is triggered only in genetically predisposed migraineurs with aura. Advanced neuroimaging studies have detected altered brain structure and function in some patients with migraine. Since these alterations are positively associated with longer migraine duration and increased

migraine frequency, migraine may have cumulative effects on brain structure and function. Structural alterations have been associated with interictal clinical deficits, showing that although migraine is typically an episodic disorder, there may be persistent clinical manifestations. Further studies are needed to determine if effective migraine therapy can prevent and reverse these structural and functional alterations. Advanced neuroimaging has and will allow us to better define the processes involved in migraine pathophysiology, to define the secondary effects of migraine, and to identify new targets for improved migraine therapy.

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Table 1

Functional brain events during migraine headache identified by modern imaging techniques

	Findings	Refs
Functional MRI	Activation in dorsal rostral pons, periaqueductal grey, red nucleus, substantia nigra, anterior cingulate, posterior cingulate, cerebellum, thalamus, insula, prefrontal cortex, temporal lobes cerebral peduncle, locus ceruleus.	6,7
PET	Activation in dorsal pons, rostral medulla, anterior cingulate, insula, cerebellar hemispheres, prefrontal cortex, putamen, cuneus.	8–12

Table 2

Functional brain events during migraine aura identified by modern imaging techniques

	Findings	Refs
Functional MRI	Increase in BOLD signal in extrastriate cortex, which progressed contiguously over the occipital cortex at 3.5 mm/min.	35
Perfusion-weighted MRI	Decreased cerebral blood flow and blood volume and increased mean transit time in occipital lobe.	36
PET	Bilateral hypoperfusion in occipital, temporal, and parietal lobes.	37,38

BOLD=Blood oxygen level dependent.

Table 3

Structural alterations in the migrainous brain identified by modern imaging techniques

	Findings	Refs
MRI		
Deep white-matter lesions	OR 2.6 if ≥ 1 migraine per month.	50
Cerebellar strokes	OR 7.1; or 15.8 if migraine with aura and ≥ 1 migraine per month.	50,51
Increased iron deposition	Periaqueductal grey, putamen, globus pallidus. Positively associated with longer disease duration.	52,53
Voxel-based morphometry		
Reduced white-matter and grey-matter density	Multiple brain regions. Positively associated with longer disease duration and more frequent headaches.	54–57
Diffusion tensor imaging		
Reduced mean diffusivity peaks and fractional anisotropy	Thalamus, corona radiata, periaqueductal grey.	58,59

Odds ratios (ORs) are in comparison to non-migraine controls.

Table 4

Imaging of identified alterations in the migraine brain with presumed functional correlates

	Findings	Refs
Executive function		
Voxel-based morphometry	Inferior executive function associated with reduced frontal lobe grey-matter density.	68
Visual processing		
Diffusion tensor imaging	Abnormalities in superior colliculus and lateral geniculate nucleus.	69
Diffusion tensor tractography	Decreased fractional anisotropy and increased mean diffusivity in optic radiations of migraineurs with aura.	70
fMRI	Enhanced reactivity to visual stimulation.	71
Magnetic resonance spectroscopy	Decreased N-acetyl aspartate and increased lactate peak in visual cortex of migraineurs with aura compared to migraineurs without aura and controls.	72
Motor task		
fMRI	Greater activation of primary sensorimotor cortex. Rostral displacement of supplementary motor area.	74
Heat sensation		
fMRI	Hypofunctional responses at nucleus cuneiformis.	75

fMRI=Functional MRI.