Published in final edited form as:

Curr Opin Neurol. 2015 June ; 28(3): 265–270. doi:10.1097/WCO.0000000000000194.

Functional Imaging and Migraine: New Connections?

Todd J. Schwedt, M.D. and Catherine D. Chong, PhD

Abstract

Purpose of Review—Over the last several years, a growing number of brain functional imaging studies have provided insights into mechanisms underlying migraine. This manuscript reviews the recent migraine functional neuroimaging literature and provides recommendations for future studies that will help fill knowledge gaps.

Recent Findings—Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have identified brain regions that might be responsible for mediating the onset of a migraine attack and those associated with migraine symptoms. Enhanced activation of brain regions that facilitate processing of sensory stimuli suggests a mechanism by which migraineurs are hypersensitive to visual, olfactory, and cutaneous stimuli. Resting state functional connectivity MRI studies have identified numerous brain regions and functional networks with atypical functional connectivity in migraineurs, suggesting that migraine is associated with aberrant brain functional organization.

Summary—fMRI and PET studies that have identified brain regions and brain networks that are atypical in migraine have helped to describe the neurofunctional basis for migraine symptoms. Future studies should compare functional imaging findings in migraine to other headache and pain disorders and should explore the utility of functional imaging data as biomarkers for diagnostic and treatment purposes.

Keywords

migraine; functional magnetic resonance imaging; positron emission tomography; functional connectivity

Introduction

Functional imaging has provided important insights into the brain mechanisms underlying migraine symptoms during and between migraine attacks. The majority of recently published functional neuroimaging studies of migraine have used magnetic resonance imaging (MRI) or positron emission tomography (PET). Most of these studies have investigated stimulus-induced activations or resting state-functional connectivity of the migraine brain between individual migraine attacks (i.e. during the “interictal” period), while a few have investigated stimulus-induced activations and spontaneous activity during a migraine attack (i.e. during the “ictal” period). This manuscript summarizes the recently

Todd J. Schwedt, MD, Associate Professor of Neurology, Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, Arizona 85054, Phone: (480) 301-6574, Fax: (480) 342-3083, Schwedt.todd@mayo.edu

Conflicts of Interest: The authors report no conflicts of interest.

published functional imaging literature, commenting on the current state of the field and on areas in need of further investigation.

Functional Imaging Studies Investigating the Processing of Sensory Stimuli

Functional imaging studies of migraine have contributed substantially to our understanding of how the migraine brain processes external sensory stimuli. Hypersensitivity to sensory stimuli, such as visual, auditory, olfactory and somatosensory stimuli, is a characteristic feature of migraine during and between migraine attacks. Sensory hypersensitivities are most prevalent and most prominent during individual migraine attacks. During the migraine attack, up to 90% of patients report hypersensitivities to visual and auditory stimuli, over 25% report hypersensitivity to olfactory stimuli, and 2/3 of patients have cutaneous allodynia.^{1–8} Between full-blown migraine attacks, less prominent hypersensitivities persist in many patients with migraine.^{9–13} Physiologic tests of the interictal migraineur demonstrate these persistent hypersensitivities in the form of lower visual discomfort thresholds, lower auditory discomfort thresholds, and lower pain thresholds compared to healthy controls.^{9, 11, 12, 14}

Functional imaging studies have investigated the processing of sensory stimuli in interictal migraineurs. The majority of such studies have used exposure to visual stimuli (e.g. flickering checkerboard pattern) or exposure to painful stimuli of the skin (e.g. heat applied to the skin with a contact thermode) to compare stimulus-induced brain activation patterns in interictal migraineurs to those in healthy controls. These studies provide objective evidence that the migraine brain is “hyperresponsive” to sensory stimuli even between migraine attacks. Functional MRI studies investigating thermal pain-induced brain activations have found migraineurs to have differential activation compared to healthy controls in several brain regions including temporal pole, parahippocampal gyrus, anterior cingulate cortex, lentiform nuclei, fusiform gyrus, subthalamic nucleus, hippocampus, middle cingulate cortex, somatosensory cortex, dorsolateral prefrontal cortex, secondary somatosensory cortex, precentral gyrus, superior temporal gyrus, and brainstem.^{15–18} Although most of these regions, including pain-facilitating regions, have stronger activation in migraineurs compared to healthy controls, pain-inhibiting regions are hypoactive in migraineurs, suggesting an imbalance of pain facilitation and pain inhibition within the migraine brain. This imbalance of pain facilitation and pain inhibition could contribute to migraineurs being more sensitive to noxious stimuli and to the development of cutaneous allodynia during a migraine attack. Functional imaging studies utilizing visual stimuli have found migraineurs to have greater activation compared to healthy controls in primary visual cortex, lateral geniculate nucleus, and motion-responsive middle temporal cortex.^{19–25} Differences in visual stimuli-induced activation patterns found in migraineurs compared to healthy controls might be attributable to patients who have migraine with aura as opposed to patients who have migraine without aura.^{20, 25} This finding would be consistent with the theory that migraineurs with aura have visual auras due to an underlying hyperexcitable occipital cortex that predisposes the brain to cortical spreading depression.

A study using ammonia gas for nociceptive stimulation of the trigeminal system suggests that brain activation patterns correlate with the timing until the next migraine attack.²⁶ The intensity of stimulus-induced activation in the spinal trigeminal nuclei is greater in interictal migraineurs compared to healthy controls and the extent of activation in the spinal trigeminal nuclei correlates with the number of days until the next migraine attack (i.e. greater activation in patients who were closer to their next migraine attack). These study results suggest that models of functional neuroimaging data might be capable of predicting the timing of impending migraines.

Imaging Studies Investigating Brain Functional Connectivity in Migraine

Functional connectivity studies have begun to identify brain regions and brain resting state networks that have altered connectivity in patients with migraine. Resting state functional connectivity MRI (rs-fcMRI) is based upon the principal that when the brain is at rest (i.e. the study subject is not being stimulated, is not performing a task, and is lying quietly in the scanner), there are continuous low-frequency fluctuations in blood oxygenation level dependent (BOLD) signal. Brain regions that have temporal correlations in their BOLD signal fluctuations are thought to be brain regions that are “functionally connected”. Functional connectivity analyses have identified several resting state functional networks including the default mode network, salience network, sensorimotor network, visual processing network, executive control network, dorsal attention network, and auditory network.²⁷ The strength of functional connectivity amongst regions within networks and between regions of different networks can change within individuals in response to brain usage patterns (e.g. regions that frequently co-activate develop stronger functional connectivity) and due to the effects of disease.

Rs-fcMRI studies have demonstrated migraine to be associated with atypical connectivity of regions including somatosensory cortex, anterior and posterior insula, anterior cingulate cortex, hippocampus, amygdala, parahippocampal gyrus, periaqueductal gray, nucleus cuneiformis, and hypothalamus.^{28–47} Atypical rs-fc in migraine involves several resting-state networks including the default mode network, salience network, frontoparietal network, executive network, and sensorimotor network.^{28, 29, 31, 32, 38, 39, 41–45} In many studies, the extent of rs-fc abnormalities positively correlate with markers of migraine burden such as headache frequency and number of years with migraine. These correlations are highly suggestive of a true relationship between the imaging findings and migraine. However, the correlations do not clarify if recurrent migraines result in progressively abnormal functional connectivity or if worse baseline functional connectivity predisposes the migraine patient to more severe migraine patterns. A single longitudinal study of 19 migraine patients who had increasing headache activity over a 6 week period showed the extent of regional homogeneity (a measure of functional connectivity) changes in the putamen, orbitofrontal cortex, secondary somatosensory cortex, brainstem and thalamus (regions for which regional homogeneity in the migraine patients differed from healthy controls) tracked the worsening clinical pattern, suggesting that the imaging findings were secondary to the recurrent migraines as opposed to being a baseline brain trait.⁴⁸

Functional Imaging Studies During a Migraine Attack

Identification of brain regions that first activate during a migraine attack would provide a better understanding of how a migraine attack is initiated and might provide important targets for migraine therapies. However, the unpredictable timing of individual migraine attacks makes studying spontaneous migraines a substantial logistical challenge. Thus, functional imaging studies of the migraine attack have typically triggered migraines, using substances such as nitroglycerin.

A H_2^{15}O PET study of nitroglycerin-induced migraine attacks studied 8 patients during the premonitory phase of a migraine attack.⁴⁹ During this pre-headache premonitory phase, many migraineurs experience symptoms such as fatigue, irritability, difficulty concentrating, yawning, and neck stiffness.⁵⁰ PET imaging of migraineurs with premonitory symptoms showed activations within the posterior hypothalamus, periaqueductal gray, midbrain tegmental area, dorsal pons and several cortical areas during the premonitory phase. Involvement of the hypothalamus during the premonitory phase could help to explain the generation of common premonitory symptoms and why migraines are commonly triggered by changes in hypothalamic-driven functions such as sleep and eating patterns. Imaging during the headache phase of migraine attacks has shown increased activity within cingulate, insula, precentral gyrus, postcentral gyrus, cerebellum, putamen, precuneus, thalamus, prefrontal cortex, temporal lobes, and in the brainstem (dorsal pons, substantia nigra, red nucleus).^{49, 51–55} Brainstem activation persists after resolution of migraine symptoms, suggesting an important role of brainstem structures in mediating the onset of a migraine attack (as opposed to the activation being responsible for the migraine symptoms or the activation occurring in response to migraine symptoms).^{52, 55} Brain activation patterns during the premonitory phase of a migraine attack, the headache phase of a migraine attack, and after symptom resolution are shown in Figure 1.

PET studies utilizing [(11)C]carfentanil have investigated mu-opioid receptor availability during migraine.^{56–58} Indicating that there is endogenous opioid release during a migraine attack, these studies have shown reduced mu-opioid non-displaceable binding potential in the cingulate cortex, nucleus accumbens, thalamus, periaqueductal gray, and medial prefrontal cortex.^{56, 57}

Other studies have investigated how the migraine brain processes external sensory stimuli during a migraine attack. Suggesting a role for the thalamus in production of extracephalic allodynia, a study of somatosensory stimulation-induced brain activations in patients having a migraine attack with allodynia showed greater activation in the posterior thalamus compared to their migraine and allodynia-free state.⁵⁹ A study utilizing painful heat stimulation of the skin found greater activation of the temporal pole and parahippocampal gyrus during migraine attacks compared to the interictal period.¹⁵ Enhanced activation of the temporal pole during a migraine attack could contribute to the production of hypersensitivities to sensory stimuli and atypical multisensory integration of such stimuli that occur during a migraine attack.⁶⁰ Compared to healthy control subjects, migraineurs during a migraine attack have greater odor-induced activations of the amygdala, insula, temporal pole, superior temporal gyrus, cerebellum, and of a region in the rostral pons.⁶¹

Greater activation of these regions during a migraine attack likely associates with the olfactory hypersensitivity that is commonly present during a migraine. Odor-induced activation of a region in the rostral pons, a region that might be a “migraine generator”, could suggest a mechanism by which exposure to odors could trigger a migraine attack and exacerbate the pain of a migraine headache.

Avenues for Future Functional Neuroimaging Studies of Migraine

The current functional imaging literature does not clarify whether abnormalities detected in migraine are a brain state (i.e. changing with changes in migraine patterns) or if they are a brain trait (i.e. stable regardless of changes in migraine pattern). One possibility is that the imaging abnormalities are a stable brain trait that predisposes an individual to the development of migraine. The extent of the imaging abnormalities might correlate with migraine severity, with more “severe” brain dysfunction predisposing a patient to more severe migraine. Alternatively, imaging abnormalities detected in migraine could be a result of recurrent migraine attacks and thus could fluctuate with changes in migraine frequency and severity. As discussed above, a single longitudinal study of rs-fc that showed worsening functional connectivity patterns to be correlated with worsening migraine clinical patterns supports this hypothesis.⁴⁸ A third possibility is that abnormalities within some regions could predispose a person to migraine while abnormalities in other regions are a result of the migraine attacks themselves. Several functional imaging studies have found positive correlations between the extent of imaging abnormalities and headache frequency or number of years with migraine. Although these correlations firmly support that the imaging findings are associated with having migraine, the direction of that association is still not clarified. Additional longitudinal studies in which individual patients with migraine undergo repetitive neuroimaging over many years would allow for calculating associations between changing migraine patterns (including onset and offset of migraine) and changing imaging findings, thus helping to clarify the direction of the relationship.

Future studies should compare imaging findings in patients with migraine to those in patients with other headache and pain disorders. The vast majority of migraine neuroimaging research has compared people with migraine to healthy people without headaches, people who have migraine with aura to people who have migraine without aura, and people with migraine during an attack to themselves when between migraine attacks. Although such studies have provided useful insights into brain regions that associate with migraine features, these studies cannot determine if imaging findings are migraine-specific or if the imaging findings would be shared by other headache types and other types of pain. Identifying brain alterations that are specific to migraine could advance the field in several ways: 1) *Better description of migraine-specific mechanisms*. Currently, it is largely unknown which migraine functional imaging findings are specific to migraine and which are shared by headache disorders like tension-type headache or cluster. Phenotypically, migraine stands out from other primary headache disorders due to prominent hypersensitivities to sensory stimuli and worsening of pain by physical movement and thus a desire to avoid movement during a migraine attack. However, primary headache disorders have phenotypic overlap. For example, cluster patients often have hypersensitivities to visual and auditory stimuli.⁶² Thus, although hypotheses can be made regarding specific

brain regions that might differentiate migraine from other headache disorders based upon differences in phenotypic expression, phenotypic overlap necessitates direct imaging comparisons of patients with these different disorders. 2) *Imaging biomarkers for migraine activity*. The intensity of atypical function within brain regions that function abnormally in migraine might serve as an indicator of future migraine patterns. For example, the severity of dysfunction within a region might predict migraine transformation (i.e. moving from less frequent to more frequent migraines) and migraine reversion (i.e. moving from more frequent to less frequent migraines). 3) *Imaging biomarkers for treatment responses*. Early normalization of function within brain regions that function abnormally in migraine might be useful as biomarkers of later treatment response when developing new migraine-specific therapies. 4) *Targets for migraine therapy*. The pattern of cortical dysfunction (and perhaps even subcortical dysfunction) in the migraine brain could be used to select targets for neurostimulation therapies.

Future studies should move beyond group-level comparisons, attempting to use imaging data at the level of the individual migraine patient. To date, functional imaging has identified brain functional differences between groups of migraine patients and groups of healthy control subjects and between subgroups of patients with migraine. However, such imaging data are not currently useful at the level of the individual patient with migraine. Future studies that include large numbers of subjects will employ advanced statistical techniques, such as machine-learning based multivariate pattern analyses, to determine the set of functional imaging measures that most accurately differentiates the individual migraine brain from the brains of healthy controls and from the brains of patients with other headache types. These statistical models, or classifiers, might eventually be useful as a diagnostic “gold-standard” for the individual migraine patient. Such a gold-standard will allow for testing the specificity and sensitivity of components of migraine diagnostic criteria and could even assist in diagnosing migraine in the individual patient when that diagnosis is otherwise difficult to make on clinical grounds. Future studies should also explore the development of classifiers that could predict an individual migraine patient’s response to specific migraine therapies and that could predict clinical patterns such as migraine transformation and reversion.

Future studies need to further explore whether imaging abnormalities are normalized by effective migraine therapy. Early “normalization” of atypical functional imaging findings could serve as a useful biomarker for predicting response to migraine therapies. Such a biomarker would be particularly useful during development of new migraine therapies and for studies that aim to identify predictors of treatment response within individual patients.

Summary

Recent functional neuroimaging studies of migraine have enhanced the description of brain regions and networks that are atypical in patients with migraine when they are between migraine attacks, have identified brain regions that activate during the premonitory and headache phases of migraine, and have provided objective evidence for the migraine brain being hypersensitive to sensory stimuli. These studies have helped to identify the neuroanatomical basis for migraine symptomatology. Future studies should aim to identify

brain imaging findings that are specific to migraine as opposed to being shared by other headache and pain disorders, to investigate whether the imaging abnormalities can be normalized by effective migraine therapy, and should move beyond group-level analyses to the level of the individual patient. Optimally, future neuroimaging studies will lead to the development of biomarkers for classifying migraine, for predicting migraine transformation and reversion, and for detecting early treatment responses to migraine-specific therapies.

Acknowledgements

Financial Support and Sponsorship: This work was supported by NIH K23NS070891.

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Key Points

- Migraine is associated with enhanced stimulus-induced activation of brain regions that are responsible for processing visual and olfactory stimuli.
- A combination of enhanced pain-induced activation of pain-facilitating brain regions and less pain-induced activation of pain-inhibiting brain regions might contribute to migraine-associated allodynia.
- Migraine is associated with altered resting state functional connectivity of multiple brain regions and several functional networks.
- Investigation of brain activation patterns at different stages of a migraine attack suggest that a region in the upper brainstem might be responsible for mediating the onset of a migraine attack while the hypothalamus might be responsible for premonitory symptoms.

Figure 1. Brain Activation Patterns During the Premonitory Phase of a Migraine Attack, the Headache Phase of a Migraine Attack, and After Symptom Resolution

The approximate locations of brain regions that have been shown to activate during the premonitory and headache phases of a migraine attack and after symptom resolution are shown on the lateral and medial surfaces of the brain. Existing data suggest that hypothalamic activation might be unique to the premonitory phase while precentral gyrus, postcentral gyrus, and insula activation might be unique to the headache phase (these regions are colored green). Persistent activation of a region in the midbrain and dorsal pons after treatment-induced symptom resolution suggests that this region might be responsible for mediating the onset of a migraine attack as opposed to being associated with the presence of migraine symptoms.