Functional MRI and Diffusion Tensor Imaging in Migraine: A Review of Migraine Functional and White Matter Microstructural Changes

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ABSTRACT

Migraine is a complex and heterogenous disorder whose disease mechanisms remain disputed. This narrative review summarizes functional MRI (fMRI) and diffusion tensor imaging (DTI) findings and interprets their association with migraine symptoms and subtype to support and expand our current understanding of migraine pathophysiology. Our PubMed search evaluated and included fMRI and DTI studies involving comparisons between migraineurs vs healthy controls, migraineurs with vs without aura, and episodic vs chronic migraineurs. Migraineurs demonstrate changes in functional connectivity (FC) and regional activation in numerous pain-related networks depending on migraine phase, presence of aura, and chronicity. Changes to diffusion indices are observed in major cortical white matter tracts extending to the brainstem and cerebellum, more prominent in chronic migraine and associated with FC changes. Reported changes in FC and regional activation likely relate to pain processing and sensory hypersensitivities. Diffuse white matter microstructural changes in dysfunctional cortical pain and sensory pathways complement these functional differences. Interpretations of reported fMRI and DTI measure trends have not achieved a clear consensus due to inconsistencies in the migraine neuroimaging literature. Future fMRI and DTI studies should establish and implement a uniform methodology that reproduces existing results and directly compares migraineurs with different subtypes. Combined fMRI and DTI imaging may provide better pathophysiological explanations for nonspecific FC and white matter microstructural differences.

KEYWORDS: Migraine, functional MRI, diffusion tensor imaging, aura, chronic

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Introduction

Migraine is a highly prevalent, multifactorial primary headache disorder that affects 1 in 10 people worldwide.[1] Headache attacks are recurring and debilitating, with associated neurological symptoms.[2] The migraine cycle is characterized by distinct phases including: interictal, preictal, prodrome, aura, headache or ictal, and postictal.[2,3] The aura phase preceding attacks commonly involves sensory and speech disturbances with possible brainstem or motor symptoms.[3,4] Migraine is further divided across a spectrum of subtypes that include migraine with aura (MA), migraine without aura (MwoA), episodic migraine (EM), and chronic migraine (CM), defined by the *International Classification of Headache Disorders-3*.[4,5] Compared to EM, CM more frequently involves comorbidities of obesity, sleep disturbances, depression, and anxiety.[6,7]

The pathogenesis for migraine remains disputed due to the complexity of the disorder. Large bodies of evidence suggest migraine pathophysiology involves altered excitability of trigeminovascular nociceptive pathways, while the migraine aura has been widely attributed to the phenomenon of cortical spreading depression.[5,8] Persistent interictal alterations in neuronal networks likely explain the sensory, cognitive, emotional, and motor disturbances that migraineurs frequently experience during and outside of headaches, which manifest as visual and auditory hypersensitivity, cognitive impairment, and psychiatric comorbidities.[2,5,8-10]

Although not applied in routine clinical practice towards migraine, neuroimaging has studied these underlying neurological phenomena.[11] Functional MRI (fMRI) enables non-invasive investigation into migraine-related reorganized connectivity of specific brain regions and networks functionally

responsible for sensory processing, as well as the measurement of abnormal brain responses to sensory stimulation observed with migraine sensory hypersensitivities. Diffusion tensor imaging (DTI) allows for noninvasive examination of migraine-related structural alterations to cell and axon integrity to highlight underlying neuronal pathology and plastic changes in migraine. Together, functional and white matter microstructural differences have elucidated disruptions to pain-related networks that likely underlie migraine pathophysiology and may serve as effective imaging biomarkers for predicting disease course and therapy.[12]

In this comprehensive narrative review, we separately detail fMRI and DTI findings, first discussing their respective associations with migraine symptoms and phase. Next, we examine comparison studies between migraine subtypes based on presence of aura and chronicity. Finally, we aim to clarify discrepancies within the migraine literature and propose future research directions for each imaging modality, with an emphasis on combining fMRI and DTI to study the interplay between functional and white matter microstructural changes.

Methods

Our literature search was conducted by 3 authors who independently assessed the eligibility criteria for our included studies. This search was conducted on the PubMed database in January 2023. The breakdown and results of our search strategy are presented in Figure 1.

In our fMRI search, we identified studies that used conventional resting state fMRI (rs-fMRI) analysis and task-based fMRI using sensory stimulation to compare functional connectivity (FC) and blood oxygen level-dependent (BOLD) activation between migraineurs against healthy controls and across migraine subgroups. The search terms we used included "resting state fMRI and migraine," "functional connectivity and migraine," and "sensory stimulation and fMRI and migraine." We filtered articles with dates ranging from January 2010 to January 2023. Our inclusion criteria evaluated studies based on relevance, original results, findings supporting or contradicting previous studies, and direct comparisons based on presence of aura and chronicity. The reference lists of our included studies and 6 previous review articles were also evaluated for additional relevant studies. We excluded reviews, clinical trials, in vitro or ex vivo studies, animal studies, non-migraine diagnoses, non-conventional rs-fMRI analysis, and studies with inadequate methods or interpretation of results.

In our DTI search, we identified studies that used tract-based or region of interest analysis to compare diffusion indices between migraineurs and healthy controls and across migraine subgroups. The search terms we used included "diffusion tensor imaging and migraine" and "white matter microstructure and migraine." Due to fewer search results available compared to fMRI, we did not filter articles based on date. Akin to our fMRI search, we evaluated studies based on relevance, original results, findings supporting or contradicting previous studies, and direct comparisons based on presence of aura and chronicity. The reference lists of our included studies and 2 previous review articles were also evaluated for additional relevant studies. We excluded reviews, clinical trials, in vitro or ex vivo studies, animal studies, non-migraine diagnoses, nonconventional DTI analysis, and studies with inadequate methods or interpretation of results.

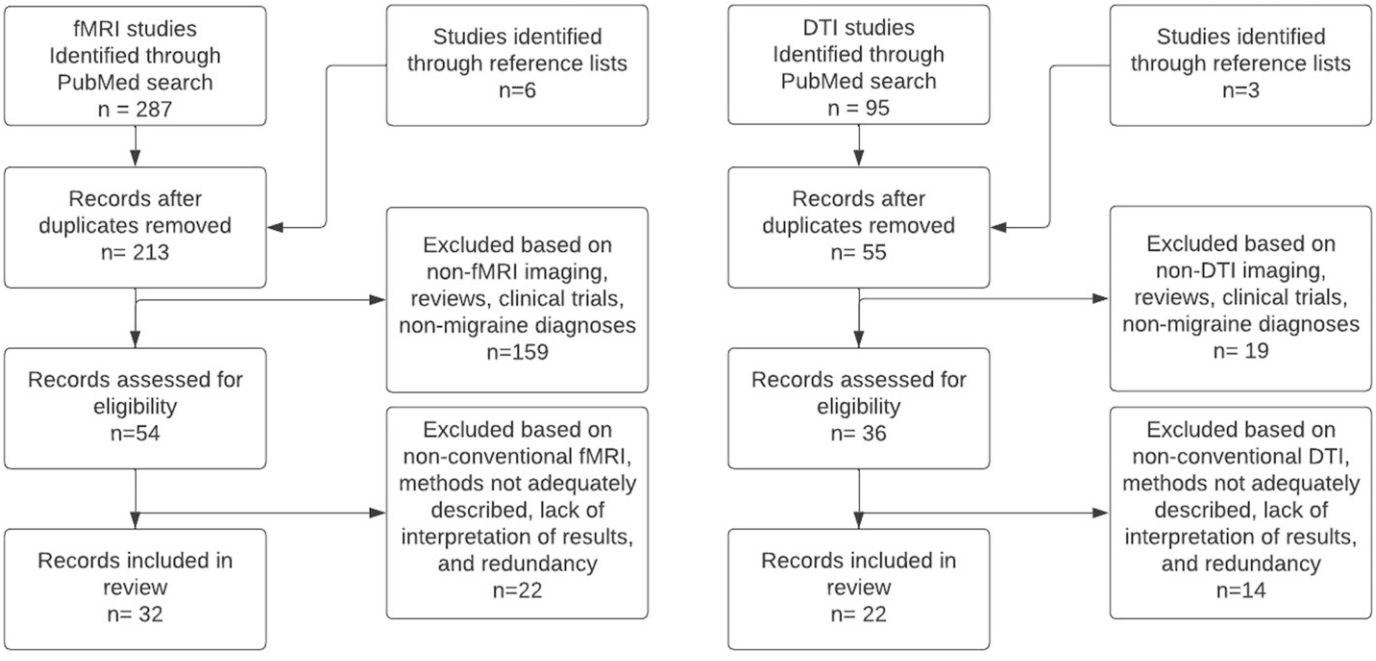

Figure 1. Flow chart of literature search performed for functional MRI and diffusion tensor imaging studies in migraine.

Literature Search Results

Our fMRI search selected 32 studies, all of which included age and sex-matched healthy controls. Of these studies, 22 performed rs-fMRI, and 10 performed task-based fMRI with sensory stimulation. 6 studies directly compared MA to MwoA, and 4 directly compared CM to EM. Among our listed studies, 1 case report and 2 case series were included due to the usage of longitudinal imaging to track migraine phase-specific findings.

Our DTI search selected 22 studies, all of which included age and sex-matched healthy controls. Of these studies, 6 directly compared MA to MwoA, and 4 directly compared CM to EM. 7 studies combined imaging with fMRI.

Functional Connectivity and BOLD Response Changes in Migraine

fMRI is an imaging method that indirectly measures neural activity in specific areas of the brain based on changes in regional blood flow. rs-fMRI measures the spontaneous fluctuations in BOLD signals between different brain regions when the subject is lying still, with no task being performed.[5,13] The recorded BOLD signals detect the degree of synchronization in signal frequencies between different voxels on brain images.[5,13] A high degree of synchronization reflects a strong connectivity in neural activity between the two correlating brain regions.[5,13] Many functional imaging studies have also investigated sensory processing in migraineurs by exposing participants to noxious or visual stimuli to compare differences in BOLD signals and changes in regional activation against healthy controls.[14] Both rs-fMRI and task-based fMRI over the past decade have demonstrated many changes in FC and BOLD responses in migraineurs.

Functional Connectivity Changes in Migraine Compared to Healthy Controls

Alterations to over 20 FC networks have been reported in the interictal phase of migraine, with differences compared against healthy controls listed in Table 1.[15] Some intrinsic connectivity differences have been observed in pain-related networks, which include the default mode network, central executive network, salience network, dorsal attention network, and sensorimotor network (Figure 2).[16-19] Such large-scale changes indicate disruptions in multiple sensory processing and integrative pathways that impact pain processing and modulation.[11,17,20,21] More specifically, some of the most discriminatory differences in pain processing regions have been found in the middle temporal, temporal pole, insula, precuneus, cingulate cortex, prefrontal, primary somatosensory cortex, amygdala, thalamus, pulvinar nucleus, and periaqueductal gray.[18,20-27] These regions contribute to the sensory-discriminative, cognitive, integrative, and emotional components of pain processing, all of which are reflected by the symptoms of multidimensional pain seen in migraineurs.[21,22]

rs-fMRI studies emphasize that abnormal changes to FC in migraineurs contribute to increased regional hyperexcitability and decreased pain inhibition, which may explain the pathophysiology behind hypersensitivities to sensory stimuli in migraine.[14,20,26] For instance, abnormal FC is visible in the ascending trigeminal spinal-thalamo-cortical pathways and top-down modulatory pathways.[8,34] In particular, interictal FC changes in the brainstem descending pain modulatory system between the periaqueductal gray and related pain processing and modulatory regions likely contribute to central sensitization, dysfunctional inhibitory pathways, and allodynia during migraine attacks.[20,25]

Furthermore, FC alterations in hypothalamic-brainstem interactions have been found across different phases of the migraine cycle. By longitudinally monitoring EM in a 2016 case study and 2020 case series, Schulte et al demonstrated that the hypothalamus shows increased preictal FC with the spinal trigeminal nuclei and increased ictal FC with the dorsal rostral pons compared to the interictal phase.[36,37] Meylakh et al in 2018 expanded upon these findings with a case-control study demonstrating increased preictal FC across the periaqueductal gray, thalamus, and hypothalamus.[31] Large-scale network phase-specific changes have also been reported, such as decreased FC strength in the central executive network during the ictal phase.[30] Together, these differences suggest cyclical regulation of complex regional interactions involving periodic changes in pain sensitivity and higher cortical function.[30,31]

Changes in BOLD Activation in Migraine Compared to Healthy Controls

Task-based fMRI studies have investigated BOLD activation in migraine patients using various stimuli, with findings compared against healthy controls listed in Table 2. These studies found functional alterations induced by painful and visual stimulation associated with migraine that can mimic migraine phase patterns, providing additional evidence of regional changes that contribute to sensory hypersensitivities in migraineurs.[14]

Light stimuli at low intensity capable of inducing discomfort in both MA and MwoA reveal a widening photoreactive area in the primary visual cortex, where increased interictal activation has been recognized especially in MA.[23,38,40] Noxious thermal stimulation on EM reveals greater activation of the temporal pole and a reduced threshold for painful heat during the ictal phase.[26] Nociceptive stimulation with ammonia gas does not result in normal habituation in migraineurs, but rather sensitization to pain, accompanied by increased activity in the anterior insula, thalamus, and middle cingulate cortex.[41] Together, these studies support a strong association between regional hyperexcitability and hyperresponsiveness to visual and painful stimuli innocuous to healthy controls.[14] Such alterations likely relate to sensitivities to environmental stimuli during and between migraine attacks and perceptual changes that

Table 1. Functional Connectivity Changes Detected With Resting State Functional MRI in Migraineurs Compared to Healthy Controls.

STUDY	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS AND REGION OF INTEREST	FINDINGS IN MIGRAINEURS
Mainero et al., 2011[20]	17 episodic migraine (with and without aura) 5 with allodynia 5 without allodynia	17	Interictal	Seeds-based analysis Periaqueductal gray	**Periaqueductal gray, against controls:** Increased FC with ventrolateral prefrontal cortex, supramarginal gyrus, anterior insula, precentral gyrus, postcentral gyrus, angular gyrus, thalamus **Periaqueductal gray, in participants with allodynia compared to without allodynia:** Decreased FC with prefrontal cortex, anterior cingulate cortex
Xue et al., 2012[18]	23 episodic migraine without aura	23	Interictal	Independent-component analysis Default mode network Central executive network Salience network	**Default mode network, against controls:** Increased FC with anterior insula **Right central executive network, against controls:** Increased FC with middle frontal gyrus and anterior insula **Left central executive network, against controls:** Increased FC with inferior frontal gyrus **Salience network, against controls:** Decreased FC with supplementary motor area
Yuan et al., 2012[28]	21 episodic migraine without aura	21	Interictal	Seeds-based analysis Anterior cingulate cortex	**Anterior cingulate cortex, against controls:** Decreased FC in corpus callosum
Schwedt et al., 2013[21]	20 chronic migraine	20	Interictal	Seeds-based analysis Anterior cingulate cortex Bilateral anterior insula Bilateral amygdala	**Anterior insula, against controls:** Differing FC with pulvinar, middle temporal cortex, mediodorsal thalamus, precuneus, periaqueductal gray, cingulate cortex, inferior parietal cortex **Amygdala, against controls:** Differing FC with superior frontal cortex and occipital cortex
Tessitore et al., 2013[19]	20 episodic migraine without aura	20	Interictal	Independent component analysis Default mode network	**Default mode network, against controls:** Decreased FC within the prefrontal and temporal cortices
Schwedt et al., 2014[25]	38 episodic migraine 8 with allodynia 8 without allodynia	20	Interictal	Seeds-based analysis Periaqueductal gray Nucleus cuneiformis	**Periaqueductal gray + nucleus cuneiformis, against controls:** Differing FC in 26 connections, with no overlap with differing FC based on allodynia **Periaqueductal gray + nucleus cuneiformis, with allodynia, against without allodynia:** Increased FC with brainstem, thalamic, insula and cerebellar regions, frontal and temporal regions
Coppola et al., 2016[29]	18 episodic migraine without aura	19	Interictal	Independent-component analysis Whole brain	**Default mode network + visuospatial system + medial visual cortical areas, against controls:** Decreased FC between default mode network, visuospatial system, and medial visual cortical areas Negatively correlated with increased FA in thalami

(Continued)

Table 1. Continued.

STUDY	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS AND REGION OF INTEREST	FINDINGS IN MIGRAINEURS
Coppola et al., 2016[30]	13 episodic migraine without aura	19	Ictal	Independent-component analysis Whole brain	**Central executive network + Dorsoventral attention system, against controls:** Decreased FC between central executive network and dorsoventral attention system No correlation with FA in thalami Strength of central executive network negatively correlated with number of migraine days/month
Chong et al., 2017[22]	58 episodic and chronic migraine (with and without aura)	50	Interictal	Seeds-based analysis 33 pain-related regions of interest	**Most discriminatory FC differences in 6 regions of interest, against controls:** Bilateral amygdala, right middle temporal, right posterior insula, right middle cingulate cortex, left ventromedial prefrontal regions (right-sided lateralization in 4 regions)
Meylakh et al., 2018[31]	26 episodic and chronic migraine (with and without aura) 26 Interictal 8 Preictal 11 postictal	78	Interictal Preictal Postictal	Seeds-based analysis Periaqueductal gray	**Periaqueductal gray, in preictal phase, against controls:** Increased FC with hypothalamus, thalamus and between the rostral and caudal regions of periaqueductal gray **Periaqueductal gray in preictal phase, compared to postictal and interictal phases:** Increased FC with hypothalamus, thalamus and between the rostral and caudal regions of periaqueductal gray
Chen et al., 2019[32]	18 episodic migraine without aura 16 chronic migraine without aura	21	Interictal	Seeds-based analysis Hypothalamus	**Posterior hypothalamus, in episodic migraine against controls:** Decreased FC in left inferior temporal gyrus **Anterior hypothalamus, in chronic migraine against controls:** Increased FC in right anterior orbital gyrus
Coppola et al., 2019[16]	20 chronic migraine without aura	20	Interictal	Independent component analysis Default mode network Central executive network Dorsal attention system	**Default mode network, against controls:** Decreased FC with central executive network **Central executive network, against controls:** Decreased FC with default mode network and dorsal attention system **Dorsal attention system, against controls:** Increased FC with default mode network and decreased FC with central executive network
Tu et al., 2020[17]	70 episodic migraine without aura	46	Interictal	Seeds-based analysis Occipital cortex	**Occipital cortex, against controls:** Decreased FC with default mode network, sensorimotor network, frontal-parietal network
Russo et al., 2020[33]	47 episodic migraine without aura 20 with cutaneous allodynia 17 without cutaneous allodynia	19	Interictal	Independent component analysis Default mode network Salience network Central executive network	**In episodic migraine without aura that developed allodynia, against controls and without allodynia:** **Default mode network:** Decreased FC in posterior cingulate cortex and precuneus **Central executive network:** Decreased FC in anterior cingulate cortex and middle frontal gyrus Correlated with FA changes in corpus callosum

(Continued)

Table 1. Continued.

STUDY	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS AND REGION OF INTEREST	FINDINGS IN MIGRAINEURS
Lim et al., 2021[34]	13 episodic migraine (with and without aura) 7 chronic migraine (with and without aura)	26	Interictal	Seeds-based analysis Spinal trigeminal nucleus Left medial pulvinar and ventral posteromedial nuclei of thalamus Left dorsal posterior insula Left primary somatosensory cortex	**Increased BOLD signal variability, against controls:** Spinal trigeminal nucleus, pulvinar and ventral posteromedial nuclei of the thalamus, primary somatosensory cortex, posterior insula **Decreased BOLD signal variability, against controls:** Dorsolateral prefrontal cortex and inferior parietal cortex **Ventral posteromedial nucleus of thalamus, against controls:** Increased dynamic FC with primary somatosensory cortex **Dorsolateral prefrontal cortex, against controls:** Decreased dynamic FC with inferior parietal cortex
Cao et al., 2022[24]	30 episodic and chronic migraine without aura	40	Interictal	Voxel-mirrored homotopic connectivity Seeds-based analysis Thalamus	**Left thalamus, against controls:** Increased FC with left superior frontal gyrus and right thalamus **Right thalamus, against controls:** Increased FC with left middle frontal gyrus
Yuan et al., 2022[35]	46 chronic migraine without aura 23 episodic migraine without aura	25	Interictal	Seeds-based analysis Caudate nuclei	**Right caudate nucleus, in chronic migraine, against controls:** Increased FC with five clusters in emotion, cognition, and sensory-related brain regions No significant differences between episodic migraine and controls
Yang et al., 2022[27]	27 episodic migraine (with and without aura)	30	Interictal	Seeds-based analysis Thalamus	**Thalamic anterior-medial-posterior subregions, against controls:** Decreased FC with left precuneus, left posterior cingulate gyrus, anterior cingulate cortex
Schulte et al., 2020[36] Case series with longitudinal imaging for 15 cycles	9 episodic migraine (with and without aura)	0	Interictal Preictal Ictal	Seeds-based analysis Whole brain Dorsal rostral pons Spinal trigeminal nuclei	**Right nucleus accumbens, in preictal, against interictal:** Increased FC with left amygdala, left hippocampus, left parahippocampal gyrus, dorsal rostral pons **Dorsal pons, in ictal, against interictal:** Increased FC with hypothalamus

Abbreviations: FC, functional connectivity, FA, fractional anisotropy.

precipitate attacks, including aura, photophobia, phonophobia, and cutaneous allodynia.[14,23,26,38,40]

Of further note, additional phase-specific regional activation has been found in hypothalamic-brainstem interactions that complement phase-specific FC changes.[44] Prior to an attack in the prodrome phase, the spinal trigeminal nuclei, visual cortex, and anterior hypothalamus exhibit increased activity.[37,39,44] In contrast, during the ictal phase, the spinal trigeminal nuclei are more weakly activated whereas the rostral pons and posterior hypothalamus are strongly activated, suggesting their roles in acute pain.[37,42] Given increased FC between the rostral pons and the hypothalamus also recorded during the ictal phase, the rostral pons has been termed in some studies as the "migraine generator."[36,37,39] These varying states of excitability and activation in hypothalamic-brainstem regions help explain the functional changes that occur as migraineurs transition from a pain-free state to a painful state, as well as other disease factors such as perceptual changes and attack frequency.[31,39,42]

fMRI Comparisons Between Migraine with Aura and Migraine without Aura

Many fMRI studies recruited both MA and MwoA to compare against healthy controls. However, these same studies often did

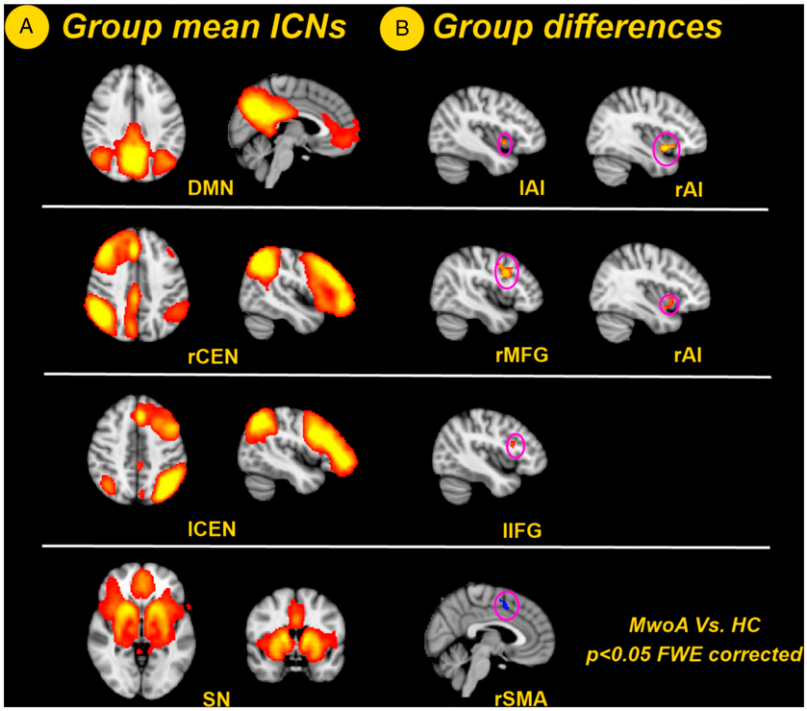

Figure 2. Resting state functional MRI data comparing migraineurs without aura (MwoA) and healthy controls (HC). (A) Spatial group maps of 3 pain-related intrinsic connectivity networks (ICN), including the default mode network (DMN), central executive network (CEN) split into right (rCEN) and left (lCEN), and salience network (SN). (B) Group comparison maps of functional connectivity (FC) in the DMN, CEN, and SN ($P < .05$, family-wise error or FWE corrected). Against HCs, MwoA demonstrate DMN with increased FC to left and right anterior insula (lAI, rAI); rCEN with increased FC to right middle frontal gyrus (rMFG) and right anterior insula (rAI); lCEN with increased FC to left inferior frontal gyrus (lIFG); SN with decreased FC to right supplementary motor area (rSMA). Reprinted from "Intrinsic brain network abnormalities in migraines without aura revealed in resting-state fMRI," by Xue T, Yuan K, Zhao L, et al, 2012, PLoS ONE, 7(12), e52927. DOI: 10.1371/journal.pone.0052927. Copyright (2012) by PLOS One. Permission under the Creative Commons CC BY license. http://creativecommons.org/licenses/by/4.0/.

not perform separate comparisons based on aura presence. Functional studies that have directly compared these two types of migraine are listed in Table 3.

Compared to MwoA, MA demonstrates broad differential FC and BOLD responses in large-scale networks. rs-fMRI studies have uniquely reported increased FC in the anterior cingulate cortex, precentral gyrus, postcentral gyrus, angular gyrus, supramarginal gyrus, insula, and cerebellum.[45,46,49] Task-based fMRI studies have reported increased activation in the primary visual cortex, lateral geniculate nucleus, middle temporal gyrus, lingual gyrus, frontal gyrus, inferior parietal, brainstem, and cerebellum.[40,47,48]

Areas where both FC and BOLD response changes have been recorded include the frontoparietal regions, which may relate to changes in executive function and pain processing and modulation, potentially explaining hypersensitivity symptoms and sensory changes experienced during the aura phase.[45,46,48] Notable overlap with increased FC and BOLD responses in the brainstem and cerebellum also appear to be unique to MA.[47-49] Greater activation of cortical areas involving advanced visual processing, in conjunction with nociceptive trigeminal activation and associated cerebellar changes, may suggest an integrated pathophysiological model specific to MA involving dysfunction in pain-modulating, limbic, and advanced visual regions (Figure 3).[48] Kincses et al in 2019 proposed that more pronounced cortical hyperexcitability due to cortical spreading depression drives greater maladaptive plasticity and neuroinflammatory degeneration, ultimately resulting in more white matter alterations and a more noxious state in MA.[50]

Yet inconsistences have also been found in the brain regions reported to be uniquely affected in MA, such as marked hyperexcitability and interictal activation of the visual cortex and lingual gyrus that have been similarly observed in MwoA.[17,37,40,47] These differing results are likely due to a limited number of direct comparisons between MA and MwoA, with many regional FC and BOLD response changes whose results have not been reproduced. Additional factors of disease course or chronicity are also overlooked.

fMRI Comparisons Between Episodic Migraine and Chronic Migraine

Disease course is crucial in migraine characterization, but many studies in the available literature do not distinguish between EM and CM in their methodologies and therefore do not compare the subtypes. Notable studies that have included direct comparisons between these subtypes are listed in Table 4.

Table 2. Changes in BOLD Responses in Task-Based Functional MRI Using Sensory Stimulation in Migraineurs Compared to Healthy Controls.

STUDY	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	STIMULUS	REGION OF INTEREST	FINDINGS IN MIGRAINEURS
Moulton et al., 2011[26]	11 episodic migraine (with and without aura) 8 ictal and interictal	11	Interictal Ictal	Heat	Whole brain analysis Temporal pole and parahippocampal gyrus FA maps	**Whole brain, interictal, against controls:** Increased activation in temporal pole and parahippocampal gyrus **Temporal pole, interictal, against controls:** Increased FC in anterior cingulate cortex, insula, primary somatosensory cortex, spinal trigeminal nucleus, amygdala, caudate, pulvinar nucleus **Temporal pole and parahippocampal gyrus, in ictal compared to interictal:** Increased activation in temporal pole and parahippocampal gyrus **DTI:** White matter connectivity between temporal pole and pulvinar nucleus
Martín et al., 2011[38]	19 episodic migraine (with and without aura)	19	Interictal	Visual (light)	Occipital cortex	**Occipital cortex, against controls:** Increased activation in occipital cortex at low and low-medium intensity light, without habituation with repetitive stimulation
Stankewitz et al., 2011[39]	20 episodic migraine (with and without aura) 20 interictal 10 preictal 13 ictal	20	Interictal Preictal Ictal	Ammonia	Whole brain analysis Spinal trigeminal nuclei	**Whole brain, in interictal, against controls:** Increased activation in insula, midcingulate and anterior cingulate cortex, secondary somatosensory cortex, amygdala, cerebellum, caudate nuclei, motor areas **Spinal trigeminal nuclei, in preictal and ictal, against interictal and controls:** Increased activation in preictal, weaker activation in ictal Increased activation in rostral pons in ictal
Datta et al., 2013[40]	25 episodic migraine with aura 25 episodic migraine without aura	25	Interictal	Visual (pattern)	Whole brain analysis Primary visual cortex Lateral geniculate nucleus	**Primary visual cortex, in migraine with aura, against controls:** Increased activation in primary visual cortex **Lateral geniculate nucleus, in migraine with aura, against controls:** Increased activation in lateral geniculate nucleus
Stankewitz et al., 2013[41]	20 episodic migraine with aura 20 interictal 10 ictal	20	Interictal Ictal	Ammonia	Whole brain analysis	**Whole brain, in interictal, against controls:** Increased activation in middle cingulate cortex, anterior insula, thalamus, precentral gyrus Controls show decreased activation suggesting habituation

(Continued)

Table 2. Continued.

STUDY	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	STIMULUS	REGION OF INTEREST	FINDINGS IN MIGRAINEURS
Schulte et al., 2017[42]	18 episodic migraine (7 ictal) 17 chronic migraine (12 ictal)	19	Interictal Ictal	Ammonia	Hypothalamus	**In chronic migraine, against controls:** Increased activation of anterior hypothalamus **In ictal, against interictal:** Increased activation of posterior hypothalamus
Schulte and May, 2016[37] Case study with longitudinal imaging for 30 days	1 episodic migraine without aura	0	Interictal Preictal Ictal Postictal	Ammonia Visual (pattern) Olfactory (odor)	Spinal trigeminal nuclei Rostral pons Hypothalamus Primary and secondary visual cortex Seed-based approach Hypothalamus	**Preictal, against interictal:** Increased activation of hypothalamus and visual cortex **Ictal, against interictal:** Increased activation of middle pons, decreased activation of visual cortex **Postictal, against interictal:** Increased activation of visual cortex **Hypothalamus, in preictal, against interictal:** Increased FC with spinal trigeminal nuclei **Hypothalamus, in ictal, against interictal:** Increased FC with rostral pons
Schulte et al., 2020[43] Case series with longitudinal imaging for 30 days	7 episodic migraine (with and without aura)	0	Interictal Preictal Ictal Postictal	Ammonia Visual (pattern) Olfactory (odor)	Whole brain analysis Hypothalamus	**Whole brain, in preictal, against ictal and postictal:** Increased activation in left visual cortex within 24 hours of headache **Hypothalamus, in preictal, against ictal and postictal:** Increased activation in hypothalamus within 48 hours of headache

Abbreviations: FC, functional connectivity, DTI, diffusion tensor imaging, FA, fractional anisotropy.

There is considerable overlap in regional BOLD signal abnormalities related to the sensory-discriminative, cognitive, and integrative domains of the pain experience in both subtypes.[21-23] Another notable similarity finds greater activation of the posterior hypothalamus during headaches in both EM and CM which is not observed during headache-free phases, implying that the posterior hypothalamus plays a major role in acute pain.[42] A crucial difference in regional activation, as reported by Schulte et al in 2017, is increased activation of the anterior hypothalamus in CM.[42]

But differences in functional changes are also apparent between EM and CM on rs-fMRI.[21,22,32,42] For instance, when compared to healthy controls and EM, CM has shown differential FC with the anterior hypothalamus, caudate nucleus, anterior cingulate cortex, middle cingulate cortex, and lingual gyrus.[32,35,42] These regional differences may be suggestive of disruptions to cognitive, emotional, and sensory brain networks unique to migraine chronification. Examples of correlations with clinical factors such as increased body mass index values may partially explain comorbidities found with CM, including obesity, sleep disturbances, and autonomic disorders.[32,35,42]

Also of note, Schwedt et al in 2013 observed that the time since onset of CM is correlated with FC strength involving the anterior insula, mediodorsal thalamus, and periaqueductal gray.[21] In a similar respect, Chong et al in 2017 found FC differences compared with healthy controls to be more accurately determined in migraineurs with a long migraine history of over 14 years compared to migraineurs with a shorter disease history.[22] These changes in CM imply that disease burden and course may drive functional reorganization in the brain, but the number of studies that have examined these changes is limited.[22] More direct comparisons between the migraine states are necessary to track the functional changes that occur during the transition from EM to CM.

Limitations in Existing fMRI Studies and Future Directions

Although migraine literature has found numerous FC and BOLD response changes related to brain region, migraine phase, and migraine subtype, there is a lack of clear consensus on reported functional changes in migraine.[15] The reported findings are diverse with some overlap, but differences across studies are cited across affected regions, trends in FC strength, and lateralized activity.[22,23,37,39] Many results have not been reproduced and may not be specific to migraine and migraine subtype.[15] Other limitations include limited sample sizes, few

Table 3. Functional MRI Studies Comparing Migraine With Aura Against Migraine Without Aura.

STUDY	fMRI TYPE	MIGRAINE WITH AURA	MIGRAINE WITHOUT AURA	MIGRAINE PHASE	ANALYSIS	FINDINGS
Datta et al., 2013[40]	Sensory-evoked BOLD response with visual stimulus	25	25	Interictal	Whole brain analysis Primary visual cortex Lateral geniculate nucleus	**Primary visual cortex, in migraine with aura, against migraine without aura:** Increased activation in primary visual cortex **Lateral geniculate nucleus, in migraine with aura, against migraine without aura:** Increased activation in lateral geniculate nucleus
Lo Buono et al., 2017[45]	Resting state fMRI	14	14	Interictal	Independent component analysis Default mode network	**In migraine with aura, against migraine without aura:** Increased FC in left angular gyrus, left supramarginal gyrus, right precentral gyrus, right postcentral gyrus, right insular cortex
Faragó et al., 2017[46]	Resting state fMRI	18	35	Interictal	Independent component analysis Resting state networks in MELODIC toolbox	**In migraine with aura, against migraine without aura:** Higher amplitudes of resting state activity in fronto-parietal regions, anterior cingulate cortex, and cerebellum
Kreczmanski et al., 2019[47]	Sensory-evoked BOLD response with visual stimulus	8	8	Interictal	Whole brain analysis	**In migraine with aura, against migraine without aura:** Increased activation in right brainstem, left cerebellum, right middle temporal gyrus Similar activation in occipital lobe, cuneus, lingual gyrus
Russo et al., 2019[48]	Sensory-evoked BOLD response with noxious heat stimulus	17	18	Interictal	Whole brain analysis	**In migraine with aura, against migraine without aura:** Increased activation in left lingual gyrus, inferior parietal lobe, inferior frontal gyrus, cerebellum
Gollion et al., 2022[49]	Resting state fMRI	21	12	Interictal	Seeds-based analysis 12 seeds in insula	**Antero-dorsal insula, in migraine with aura, against migraine without aura:** Increased FC with upper cerebellum corresponding to vermis VI

Abbreviations: FC, functional connectivity, fMRI, functional MRI, BOLD, blood oxygen level-dependent.

direct comparisons between migraine types, technical limitations of 1.5T or 3T MRI scanners with limited resolution of BOLD images, and unaccounted migraine comorbidities.

Future studies with a stricter and uniform methodology should focus on finding reproducible migraine-specific FC patterns and consider longitudinal follow-up to track imaging findings in conjunction with clinical progression. While migraine neuroimaging has previously failed to produce a robust and reliable fMRI biomarker, Tu et al in 2020 recently found a fMRI-based neural marker for MwoA that supports the existing data, using discriminatory FC patterns with good accuracy, sensitivity, specificity, and retest reliability.[12,17] Continued investigation into phase- and course-specific biomarkers with similar criteria are recommended, and other imaging modalities such as DTI would identify associated structural differences for a more coherent understanding about reported functional changes.

White Matter Microstructural Changes in Migraine

Diffusion imaging studies of migraine have primarily focused on DTI, which is widely available in clinical MRI settings and suited for analyzing white matter microstructural abnormalities. By utilizing the sensitivity of the diffusion sequences to the anisotropic diffusion of water molecules, DTI measures the directional alignment of white matter tract fibers where displacement of the molecules is greatest.[5,51] With the standard

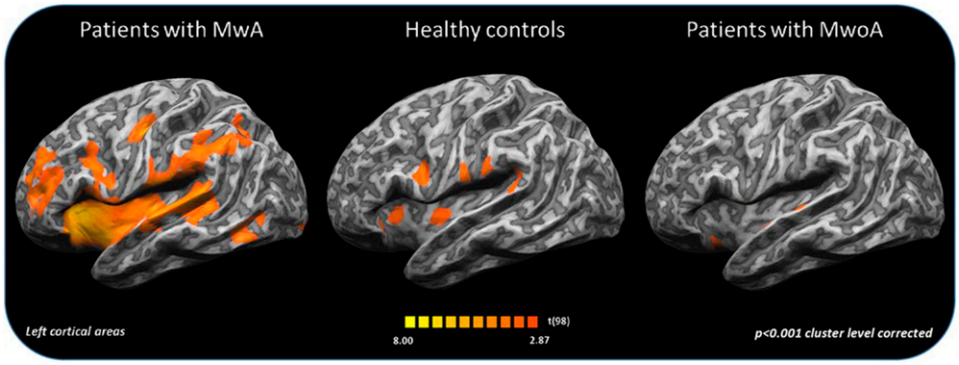

Figure 3. Group comparison of blood oxygen level-dependent (BOLD) response in advanced visual network (including lingual gyrus, inferior parietal lobe, inferior frontal gyrus, and medial frontal gyrus) between migraineurs with aura (MwA), migraineurs without aura (MwoA), and healthy controls during trigeminal heat stimulation. Increased BOLD activation observed in MwA. Reprinted from "Advanced visual network and cerebellar hyperresponsiveness to trigeminal nociception in migraine with aura," by Russo A, Tessitore A, Silvestro M, et al, 2019, J Headache Pain, 20(1), 46. DOI: 10.1186/s10194-019-1002-3. Copyright (2019) by BioMed Central. Permission under the Creative Commons CC BY license. http://creativecommons.org/licenses/by/4.0/.

Table 4. Functional MRI Studies Comparing Chronic Migraine Against Episodic Migraine.

STUDY	fMRI TYPE	EPISODIC MIGRAINE	CHRONIC MIGRAINE	MIGRAINE PHASE	ANALYSIS	FINDINGS
Schwedt et al., 2013[21]	Resting state fMRI	0	20	Interictal	Seeds-based analysis Anterior cingulate cortex Bilateral anterior insula Bilateral amygdala	**Significant correlations between disease duration and FC strength:** Anterior insula with mediodorsal thalamus and periaqueductal gray
Schulte et al., 2017[42]	Sensory-evoked BOLD response with nociceptive stimulus	18	17	Interictal Ictal	Hypothalamus	**In chronic migraine, against episodic migraine:** Increased activation of anterior hypothalamus
Chen et al., 2019[32]	Resting state fMRI	18	16	Interictal	Seeds-based analysis Hypothalamus	**Anterior hypothalamus, in chronic migraine, against episodic migraine:** Increased FC in right medial orbital gyrus
Lim et al., 2021[34]	Resting state fMRI	13	7	Interictal	Seeds-based analysis Spinal trigeminal nucleus Left medial pulvinar and ventral posteromedial nuclei of thalamus	**In chronic migraine, against episodic migraine:** Decreased BOLD signal variability in spinal trigeminal nucleus and hippocampus **In episodic migraine, against chronic migraine:** Decreased dynamic FC between dorsolateral prefrontal cortex and inferior parietal cortex
Yuan et al., 2022[35]	Resting state fMRI	23	46	Interictal	Seeds-based analysis Caudate nuclei	**Right caudate nucleus, in chronic migraine, against episodic migraine:** Increased FC with precuneus, left anterior cingulate gyrus, right middle cingulate cortex, right lingual gyrus FC differences with calcarine cortex and lingual gyrus positively correlated with BMI and negatively correlated with visual analogue scale score

Abbreviations: FC, functional connectivity, fMRI, functional MRI, BOLD, blood oxygen level-dependent.

analysis approaches of tract-based spatial statistics, region of interest analysis, or whole brain voxel-wise analysis, the measures obtained from DTI include fractional anisotropy (FA), mean diffusivity (MD) or apparent diffusion coefficient (ADC), axial diffusivity (AD), and radial diffusivity (RD).[51-53]

Differences in these measures between migraineurs and healthy controls reflect white matter microstructural differences associated with migraine. FA is highly sensitive to changes to axonal integrity, fiber density, and myelin but often nonspecific, suggesting cell death, cell shrinkage or swelling, axonal loss, demyelination, and more.[29,53] MD is often measured in conjunction with FA, indicating changes in the extracellular space due to cell shrinkage or loss of axonal or dendritic connections.[29,53] AD is reflective of axonal integrity and affected by axonal injury and brain maturation, while RD is more reflective of axonal myelination and susceptible to demyelination and axonal degeneration.[53,54] It is debated whether such changes contribute to a predisposition to migraine or result from repeated attacks, which may be explained as maladaptive plastic modifications, accumulated white matter damage, or secondary functional alterations after repeated stimulation.[55,56]

Microstructural Changes to White Matter Tracts in Migraine Compared to Healthy Controls

Changes in major cortical white matter tracts are evident and diffuse in migraine compared to healthy controls, as listed in Table 5.[53,55-57] Reduced FA in the genu and splenium of the corpus callosum, correlated with decreased FC in the anterior cingulate cortex, suggest structural and associated functional disruptions between the bilateral hemispheres (Figure 4).[28,33,58,59] Other white matter changes have been observed in the thalamus, anterior thalamic radiations, trigeminal tracts, cingulum, corticospinal tract, superior and inferior longitudinal fasciculus, frontooccipital fasciculus, and optic radiations.[29,55,57,60-63]

These alterations extend to the cerebellum and brainstem, involving vermis VI extended to lobules V and VI, the inferior cerebellum peduncle tract, spinal trigeminal nuclei, red nuclei, and periaqueductal gray.[64,66,67] The affected white matter tracts indicate a diffuse and concomitant involvement of visual, trigeminal, and thalamic pathways, which support the proposal of dysfunctional trigeminovascular-related visual and pain processing pathways in migraine, with interference in transmission, modulation, and multimodal conduction and integration.[55,66]

White matter microstructural changes in the visual pathway provide several interesting insights into migraine. Granziera et al in 2006 found increased cortical thickness in the middle temporal visual area and visual area 3 accessory motion processing pathways to be correlated with reduced FA in the underlying white matter, superior colliculus, and lateral geniculate nucleus.[68] These findings suggest that structural changes to white matter are accompanied by changes to gray matter.[57,68] Additionally, visual area 3 accessory has been previously suggested as the source of cortical spreading depression manifested during the aura phase, but changes to visual area 3 accessory in both MA and MwoA imply that cortical spreading depression may be an underlying phenomenon even if aura is absent.[8,68]

White Matter Microstructural Differences Based on Presence of Aura, Migraine Phase, and Age

However, it remains important to distinguish between these two migraine subtypes as white matter microstructural differences have been found in MA and MwoA.[61] Differences in FA depending on aura presence have been reported in the corpus callosum, optic radiations, parieto-occipital regions, trigeminothalamic tract, and periaqueductal gray.[11,58,61-63] Yet, existing DTI studies involving direct comparisons between MA and MwoA have been limited in number and do not appear to demonstrate a replicable pattern of white matter microstructural changes, with Granziera et al even finding no significant FA differences between these subgroups.[68]

Studies on phase-specific white matter microstructural changes have been limited, but Coppola et al in 2014 found increased interictal FA values in the thalamus that were positively correlated with the number of days since the previous migraine attack, but were normalized during the ictal phase.[65] Coppola et al followed up with 2016 studies that used both fMRI and DTI, observing that increased FA in the thalamus is negatively correlated with interictal FC changes in the default mode network and visuospatial system, compared to nonsignificant FA values and the absence of such a correlation during the ictal phase.[29,30] Together, these findings may highlight a decrease in neuronal connections in the thalamus that may underlie functional network changes during attack-free periods and onset of the ictal phase.[29,30,65] Additionally, these transient FA values suggest dynamic changes in water mobility that shift with migraine phase, which may help explain the heterogeneous DTI results within the migraine literature.[11]

Microstructural contributions to migraine are further complicated when comparing white matter changes in pediatric and adult migraineurs. Most notable is increased FA in the optic radiations of pediatric subjects reported by Messina et al in 2015, compared to reduced FA in adults reported by Rocca et al in 2008.[55,62] Together, these structural findings help demonstrate that the pathophysiological changes in migraine appear scattered and diffuse, alter visual perception, and may differ depending on aura presence, migraine phase, and patient age.[55,57,62,68]

White Matter Microstructural Differences Between Episodic Migraine and Chronic Migraine

DTI analysis also provides further insight into the structural differences between EM and CM. CM appears to involve global white matter changes when compared to EM, differing in numerous white matter tracts that include the corpus callosum, cerebral peduncles, thalamic radiations, superior and inferior longitudinal fasciculi, corona radiata, external capsule, anterior and posterior limbs of the internal capsule, cerebellar peduncles,

Table 5. DTI Studies of Migraineurs vs Healthy Controls, Including Comparisons Based on Presence of Aura and Chronicity.

STUDY AND COMPARISON	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS	FINDINGS IN MIGRAINEURS
Moulton et al., 2011[26] Migraine/Controls	11 episodic migraine (with and without aura)	11	Interictal Ictal	Tract-based spatial statistics Whole brain	**In controls:** FA maps show white matter connectivity between temporal pole and pulvinar nucleus (may serve as nociceptive pathway contributing to temporal pole functional changes in migraine patients)
Yuan et al., 2012[28] Migraine/Controls	21 episodic migraine without aura	21	Interictal	Tract-based spatial statistics Whole brain	**Against controls:** Decreased FA in genu and left splenium of corpus callosum (correlated with decreased FC in corpus callosum)
Kara et al., 2013[64] Migraine/Controls	14 episodic and chronic migraine without aura	15	Ictal	Region of interest Red nuclei Periaqueductal gray Thalami Posterior limb of internal capsule Subcortical white matter	**Against controls:** Increased ADC in red nuclei
Coppola et al., 2014[65] Migraine/Controls	24 episodic migraine without aura 14 interictal 10 ictal	15	Interictal Ictal	Region of interest Right and left thalami	**In interictal, against controls:** Increased FA in bilateral thalami No significant differences in FA between ictal and controls Positive correlation between FA of thalamus and number of days elapsed since last migraine attack
Chong and Schwedt, 2015[60] Migraine/Controls	23 episodic and chronic migraine (with and without aura)	18	Interictal	Tractography Anterior thalamic radiations Corticospinal tracts Inferior longitudinal fasciculi	**Against controls:** Increased MD in anterior thalamic radiations, left corticospinal tract, right inferior longitudinal fasciculus (correlated with disease duration) Increased RD in left anterior thalamic radiations, left corticospinal tract, inferior longitudinal fasciculi
Messina et al., 2015[55] Migraine/Controls	15 pediatric episodic migraine (with and without aura)	15 pediatric	Interictal	Tract-based spatial statistics Tractography Whole brain	**Against controls:** Increased FA in optic radiations Decreased MD, AD, RD in brainstem, thalami, fronto-temporo-occipital regions
Coppola et al., 2016[29] Migraine/Controls	18 episodic migraine without aura	19	Interictal	Region of interest Right and left thalami	**Against controls:** Increased FA in bilateral thalami Negatively correlated with FC changes in default mode network, visuospatial system, and medial visual cortical areas
Coppola et al., 2016[30] Migraine/Controls	13 episodic migraine without aura	19	Ictal	Region of interest Right and left thalami	**Against controls:** No significant differences across group comparisons of FA and MD No correlation with FC changes in central executive network, dorsoventral attention system

(Continued)

Table 5. Continued.

STUDY AND COMPARISON	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS	FINDINGS IN MIGRAINEURS
Qin et al., 2019[66] Migraine/Controls	46 episodic migraine without aura	46	Interictal	Voxel-based morphometry Whole brain	**Against controls:** Decreased FA in vermis VI extending to bilateral cerebellar lobules V and VI Increased AD, MD, RD in right inferior cerebellum peduncle tract Increased AD, MD, RD in spinal trigeminal nucleus (correlated with reduced gray matter volume)
Russo et al., 2020[33] Migraine/Controls	47 episodic migraine without aura 20 with cutaneous allodynia 17 without cutaneous allodynia	19	Interictal	Voxel-based morphometry Tract-based spatial statistics Whole brain	**In episodic migraine without aura that developed allodynia, against controls and without allodynia:** Decreased FA in corpus callosum Correlated with FC changes in default mode network and central executive network
Pak et al., 2022[59] Migraine/Controls	51 episodic migraine with and without aura	44	Interictal	Region of interest Genu, splenium, and body of corpus callosum	**Against controls:** Decreased FA in genu of corpus callosum
Mungoven et al., 2022[67] Migraine/Controls	38 episodic migraine with and without aura	38	Interictal	Voxel-based morphometry Region of interest Whole brain Trigeminal nerve root entry zone in pons	**Against controls:** Both groups show trend of inverse FA and MD linear correlation in: spinal trigeminal nucleus, dorsolateral pons, posterior cingulate cortex, primary somatosensory cortex, insula, hypothalamus, putamen, primary visual cortex Migraineurs show no inverse correlation in periaqueductal gray seen in controls
Yang et al., 2022[27] Migraine/Controls	27 episodic migraine with and without aura	30	Interictal	Region of interest Thalamus	**Against controls:** No significant differences across group comparisons of FA, MD, RD, AD
Granziera et al., 2006[68] Migraine/Controls Migraine with aura/ Migraine without aura	12 episodic migraine with aura 12 episodic migraine without aura	12	Interictal	Region of interest Whole brain Motion-processing regions of middle temporal visual area and visual area 3	**Both migraine groups, against controls:** Decreased FA in white matter directly below middle temporal visual area and visual area 3, and in superior colliculus and left lateral geniculate nucleus Increased cortical thickness of motion-processing visual areas and visual area 3 No significant differences in FA between migraine groups
DaSilva et al., 2007[63] Migraine/Controls Migraine with Aura/ Migraine without aura	12 episodic migraine with aura 12 episodic migraine without aura	12	Interictal	Region of interest Whole brain	**In migraine with aura, against controls:** Decreased FA in ventroposterior medial thalamus **In migraine with aura, against migraine without aura:** Decreased FA in trigeminothalamic tracts Increased FA in periaqueductal gray

(Continued)

Table 5. Continued.

STUDY AND COMPARISON	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS	FINDINGS IN MIGRAINEURS
Rocca et al., 2008[62] Migraine/Controls Migraine with aura/ Migraine without aura	7 episodic migraine with aura 8 episodic migraine without aura	11	Interictal	Tractography Optic radiations Corpus callosum Corticospinal tract	**In migraine with aura, against controls:** Decreased FA in both optic radiations Increased MD in right optic radiation **In migraine with aura, against migraine without aura:** Decreased FA in right optic radiation
Szabó et al., 2018[61] Migraine/Controls Migraine with aura/ Migraine without aura	18 episodic and chronic migraine with aura 25 episodic and chronic migraine without aura	28	Interictal	Tract-based spatial statistics Whole brain	**In migraine with aura, against controls:** Decreased RD in parieto-occipital regions, corpus callosum, cingulate cortex **In migraine with aura, against migraine without aura:** Increased FA in left parieto-occipital white matter **In migraine with aura:** AD in superior longitudinal fascicle negatively correlated with disease duration and attack frequency
Faragó et al., 2019[58] Migraine/Controls Migraine with aura/ Migraine without aura	18 episodic migraine with aura 33 episodic migraine without aura	32	Interictal	Voxel-based morphometry Whole brain	**In migraine with aura, against controls:** Differing diffusion indices in frontal region, right occipital pathways **In migraine with aura, against migraine without aura:** Differing diffusion indices in genu and body of corpus callosum, occipital bundles **In migraine with aura:** Changes in FA and RD correlated with FC changes in frontal region
Neeb et al., 2015[69] Migraine/Controls Chronic migraine/ Episodic migraine	34 chronic migraine without aura 39 episodic migraine without aura	39	Interictal	Tract-based spatial statistics Whole brain	No significant differences across group comparisons of FA, MD, RD, AD
Gomez-Beldarrain et al., 2016[70] Migraine/Controls Chronic migraine/ Episodic migraine	19 episodic migraine (with and without aura) 18 episodic migraine (with and without aura)	15	Interictal	Tract-based spatial statistics Region of interest Cingulate gyri Uncinate fasciculi	**In chronic migraine, against controls:** After 6 months, decreased FA in right anterior insula, right uncinate gyrus, cingulate gyri **Higher cognitive reserve score:** Increased FA in right anterior insula and cingulate gyri **On preventive therapy:** Decreased FA in left anterior insula, left uncinate fasciculus, right cingulate gyrus **Higher anxiety:** Decreased FA in anterior insula **Higher physical component score in quality of life:** Increased FA in uncinate fasciculi

(Continued)

Table 5. Continued.

STUDY AND COMPARISON	MIGRAINEURS	CONTROLS	MIGRAINE PHASE	ANALYSIS	FINDINGS IN MIGRAINEURS
Planchuelo-Gómez et al., 2020[56] Migraine/Controls Chronic migraine/ Episodic migraine Migraine with aura/ Migraine without aura	54 episodic migraine with aura and without aura 56 chronic migraine with and without aura	50	Interictal	Tract-based spatial statistics Whole brain White matter tracts in Johns Hopkins University ICBM-DTI-81 White-Matter Atlas and White-Matter Tractography Atlas	**In episodic migraine, against controls:** No significant differences across group comparisons of FA, MD, RD, AD **In chronic migraine, against episodic migraine:** Decreased AD in 44 white matter regions, including corpus callosum, cerebral peduncles, thalamic radiations, superior and inferior longitudinal fasciculi, external capsule, anterior and posterior limbs of internal capsule, corona radiata, pontine crossing tract, cerebellar peduncles, corticospinal tract **In chronic migraine, external capsule:** Disease duration positively correlated with FA and negatively correlated with RD Exclusion of migraine with aura yielded no significant differences from original analysis
Coppola et al., 2020[71] Migraine/Controls Chronic migraine/ Episodic migraine	19 episodic migraine without aura 18 chronic migraine	18	Interictal	Tract-based spatial statistics Whole brain	**In episodic migraine, against controls:** No significant differences across group comparisons of FA, MD, RD, AD **In chronic migraine, against controls:** Increased RD in superior and posterior corona radiata, genu of corpus callosum, posterior limb of internal capsule, superior longitudinal fasciculi Increased MD in right superior and posterior corona radiata, right superior longitudinal fasciculus, and right splenium of corpus callosum **In chronic migraine, against episodic migraine:** Decreased FA in superior and posterior corona radiata, body of corpus callosum, right superior longitudinal fasciculus, right forceps minor Increased MD in superior corona radiata, right posterior corona radiata, right body and splenium of corpus callosum, right superior longitudinal fasciculus, and right posterior limb of internal capsule

Abbreviations: FA, fractional anisotropy, MD, mean diffusivity, ADC, apparent diffusion coefficient, RD, radial diffusivity, AD, axial diffusivity, FC, functional connectivity.

and corticospinal tract (Figure 5).[56,71] More specifically, reduced AD in these regions suggest decreased fiber density and axonal loss.[56] Interestingly, these same studies demonstrate no significant differences in diffusion indices between EM and controls, which suggest that migraine chronification involves more diffuse and pronounced white matter microstructural changes detectable through diffusion imaging.[56,71]

This proposed explanation is supported with more white matter differences that involve reduced FA in the anterior insula, anterior cingulate gyrus, and uncinate fasciculus associated with components of pain processing, including modulation, resilience, emotion, and cognition.[70] Given that higher FA in these regions is correlated with individuals with a higher cognitive reserve, Gomez-Beldarrain et al in 2016 proposed that individuals without CM and with intact cognition likely possess stronger white matter tracts with higher pain resilience.[70] Therefore, while EM may involve white matter alterations, the transition to CM may involve a much greater loss of axonal integrity that contributes to pain hypersensitivity, decreased cognition, and dysfunctional

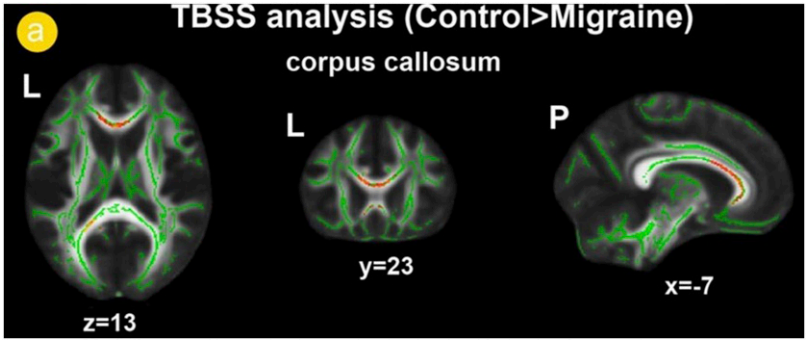

Figure 4. Reduced fractional anisotropy is found in the genu and splenium of the corpus callosum in migraineurs without aura compared to healthy controls, using tract-based spatial statistics (TBSS) analysis. The normal white matter skeleton is shown in green, and voxels with significant differences are shown as red-yellow. Reprinted from "Reduced fractional anisotropy of corpus callosum modulates inter-hemispheric resting state functional connectivity in migraine patients without aura," by Yuan K, Qin W, Liu P, et al, 2012, PLoS One, 7(9), e45476. DOI: 10.1371/journal.pone.0045476. Copyright (2012) by PLoS One. Original image cropped to include top half only. Permission under the Creative Commons CC BY license. http://creativecommons.org/licenses/by/4.0/.

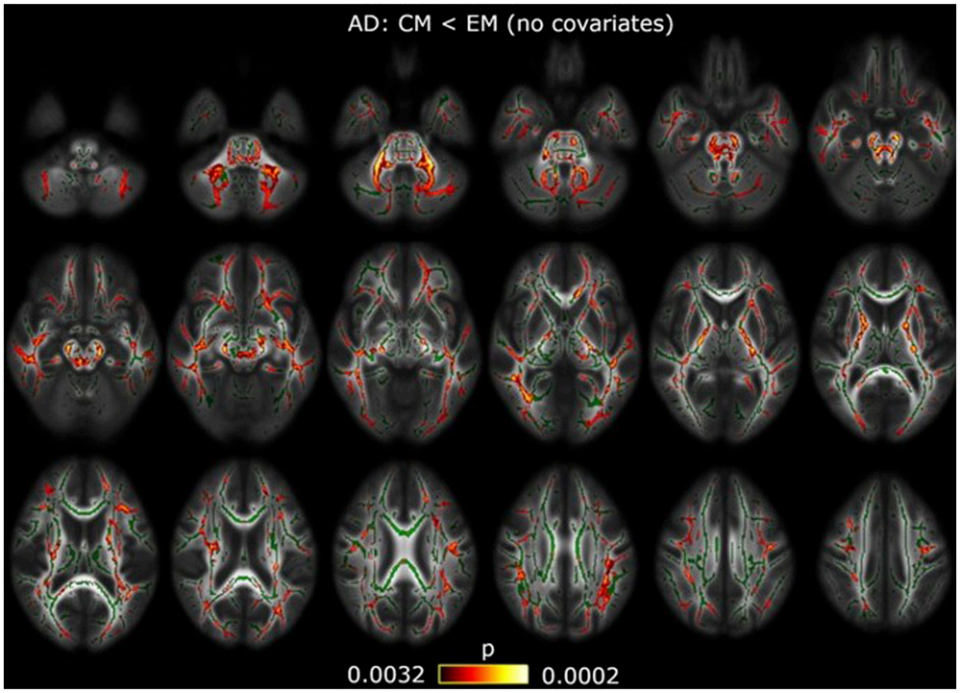

Figure 5. Reduced axial diffusivity (AD) is found in 44 regions in the Johns Hopkins University ICBM-DTI-81 White Matter Atlas and White-Matter Tractography Atlas in chronic migraineurs (CM) compared to episodic migraineurs (EM). The normal white matter skeleton is shown in green, and voxels with significant differences are shown as red-yellow. Reprinted from "White matter changes in chronic and episodic migraine: a diffusion tensor imaging study," by Planchuelo-Gómez Á, García-Azorín D, Guerrero ÁL, et al, 2020, J Headache Pain, 21(1), 7. DOI: 10.1186/s10194-019-1071-3. Copyright (2020) by BioMed Central. Original image cropped to include top half only. Permission under the Creative Commons CC BY license. http://creativecommons.org/licenses/by/4.0/.

inhibition.[56,70] Moreover, Planchuelo-Gómez et al in 2020 also found increased FA and reduced RD in the external capsule in correlation with time since the onset of CM, suggesting neural plasticity and reorganization for adapting to a more continuous painful state in CM.[56,57]

Limitations in Existing DTI Studies and Future Directions

On the other hand, conflicting trends in FA and other DTI measures have been reported across different studies.[27,55,56,61,62] These apparently contradictory results may suggest a coexistence of both debilitated and enhanced white matter networks within the brain, involving both axonal damage and plastic adaptation.[57] However, a study in 2015 by Neeb et al has even found no significant differences in DTI measures across CM, EM, and healthy controls.[69] Consequently, existing studies using DTI face many limitations in methodology that may explain these different results within the literature. These flaws include small sample sizes, few replication studies, few comparisons between migraine types, participant usage of

medication and frequency of usage, and unaccounted comorbidities including anxiety and depression.[57,69]

There is no migraine-specific biomarker tracking white matter microstructural changes, necessitating future studies to distinguish migraine subtypes and minimize confounding variables. Longitudinal studies are also needed to evaluate phase-specific structural changes and long-term alterations that occur beginning at youth and during the transition from EM to CM.

Furthermore, more advanced diffusion modalities may be implemented that overcome DTI limitations. In 2020, Planchuelo-Gómez et al used apparent measures using reduced acquisitions (AMURA), utilizing the ensemble average diffusion propagator to provide better modeling of the white matter fiber architecture, yielding initial results that complement DTI analysis of migraine.[57] Other more advanced diffusion imaging techniques such as high angular resolution diffusion imaging (HARDI) may also provide more accurate characterization of white matter changes in future studies. Moreover, multi-shell diffusion MRI can also be used to decompose the neurite signal from the rest of the voxels to indirectly measure the neurite density index.[72] These techniques would provide information about the microscopic damages to white matter that are hidden to structural imaging techniques. Doing so would calculate several metrics including neurite density and the degree of axonal fanning, estimate microglial and myelin contents, and determine white matter tract integrity. These proposed research directions with an improved methodology may elucidate an identifiable biomarker of white matter changes, as well as any interactions with changes in gray matter and functional connectivity.

Utility of Combined fMRI and DTI Imaging in Migraine

Pairing DTI and fMRI in the same studies to examine coexisting functional and white matter microstructural differences should also be considered in future investigation. While these imaging modalities have traditionally been studied separately, existing studies of healthy volunteers have observed that applying such multimodal imaging may have useful research and clinical application in relation to migraine. Lanyon et al in 2009 used fMRI and DTI to identify visual motion perception pathways between the middle temporal area and superior temporal cortex with the pulvinar nucleus of the posterior thalamus, active in the setting of a dysfunctional primary visual cortex.[73] Zou et al in 2022 combined imaging to identify prominent prefrontal-parietal and insula-cingulate connectivity that more accurately predicts individualized pain threshold compared to using fMRI and DTI alone, highlighting key roles of the insula, precuneus, and calcarine in pain sensitivity.[74] These regional connectivity features related to visual and pain modulatory pathways support reported changes to FC and diffusion indices in the migraine literature.

In combined imaging studies on migraine patients, Moulton et al in 2011 investigated the role of the temporal pole in the transition between interictal and ictal phases, observing extensive white matter connectivity between the temporal pole and pulvinar nucleus that may serve as an afferent pathway for transmitting nociceptive information and the basis for observed phase-specific functional changes.[26] Coppola et al in 2014 and 2016 supported these results with correlations between increased FA in the thalamus and FC changes in the default mode network, visuospatial system, and medial visual cortical areas, proposing that deficient thalamic microstructural connections contribute to interictal changes to functional networks.[29,30,65] More recently, Faragó et al in 2019 and Russo et al in 2020 also demonstrate how FA and RD differences correlated with FC changes in large-scale brain networks, suggesting a joint role of neuroanatomic and brain activity-related alterations in migraine pathophysiology.[33,58] More specifically, functional and white matter microstructural disruptions co-occurring in central pain modulatory circuits may ultimately contribute to presence of aura and development of allodynia.[33,58]

Consequently, multimodal imaging using both fMRI and DTI carries exciting potential in migraine research by providing better pathophysiological explanations for nonspecific FC and white matter microstructural differences currently being reported. Examining the interplay between brain structure and function can help elucidate existing knowledge gaps and reconcile discrepancies between studies.

Discussion

Our fMRI and DTI literature search resulted in many diverse findings—some reproduced, many others not. By performing a comprehensive review, we deduced several noteworthy functional and white matter microstructural trends and related them to migraine clinical presentation and subtype. However, while most studies we included demonstrated some degree of significant result, many findings did not overlap. Several studies demonstrated no significant differences across comparisons against controls or between migraine subgroups.[27,35,56,68,69,71] In turn, our ability to gather these findings into a coherent pathological pattern was limited.

Some of these discrepancies can be explained by the differences in study designs. We ensured that all our included studies defined migraine based on the *International Classification of Headache Disorders* criteria, but we were still limited by the heterogeneity of this disorder. Studies vary in their recognition of specific migraine characteristics, including presence or absence of aura, episodic or chronic definition, nature of aura, lateralization of headache, disease duration, attack frequency, time since previous attack, and other important clinical variables including age and sex, family history of migraine, medication intake, cognitive testing, and psychiatric comorbidities. This nonuniform recruitment, which subsequently affects whether regression analyses with these confounding variables are performed, certainly impacts the final results of each study.

Additionally, we ensured most of our included studies took similar approaches in analysis, but the type of analysis performed inevitably can affect results. While both seeds-based and independent component analyses in fMRI yield similar results in primary resting state networks, results can vary in secondary subnetworks depending on factors such as regional seed placement, scan time, and FC metrics within networks vs between networks.[75,76] Functional changes observed with rs-fMRI vs task-based fMRI can be difficult to connect as well, with differences focusing on temporal statistical relationships between brain regions vs triggered regional activation. Similarly, tract-based spatial statistics and region of interest labeling in DTI share many of the same advantages in detecting FA changes but differ based on automated or manual region of interest selection, whole brain vs regional analysis, and registration of white matter microstructural differences unique to individual participants.[77] Furthermore, we omitted studies utilizing less conventional methods, such as Granger causality analysis of fMRI, that may help explain some of these assorted findings.[78]

Ultimately, current limitations of fMRI and DTI studies may be overcome with a standardized uniform protocol in migraineur recruitment, analysis of important demographic and clinical factors related to migraine, and collaboration between different investigating parties on methodology and data. Longitudinal studies and utility of combined fMRI and DTI imaging, as well as more advanced functional and diffusion imaging modalities, should also be considered to bridge existing gaps in results and interpretation.

Conclusion

rs-fMRI and task-based fMRI migraine studies have observed a wide array of alterations in functional connectivity and regional activation in pain-related networks. These functional changes can be phase-specific and likely disrupt multimodal sensory-integrative pathways in pain processing and modulation. MA appears to entail unique pathogenesis mechanisms involving the frontoparietal, brainstem, and cerebellar regions associated with pain modulation and executive function. CM can be distinguished from EM based on diencephalic, insular, limbic, and occipitotemporal changes which may reflect comorbidities associated with chronicity.

DTI studies on brain imaging in migraineurs have observed white matter microstructural changes in major cortical white matter tracts extending to the brainstem and cerebellum. These alterations are associated with functional and structural gray matter changes, supporting proposed dysfunction of multimodal visual and pain processing pathways. White matter differences are more diffuse and extensive in CM, suggestive of pathogenic or adaptive differences unique to chronicity.

However, interpretations of the reported fMRI and DTI measure trends have not achieved a clear consensus. Future studies should establish a uniform methodology to reproduce existing results and conduct more direct comparisons between migraineurs with different subtypes of the disease. Alternative fMRI and advanced diffusion imaging techniques may overcome some of these limitations. Combining fMRI and DTI imaging has related the co-occurrence of functional and white matter microstructural changes to migraine phase and pain sensitivity; increased utilization of combined imaging will improve understanding of the underlying structural and functional interplay in migraine pathophysiology.

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Appendix

Abbreviations

MA	migraine with aura
MwoA	migraine without aura
EM	episodic migraine
CM	chronic migraine
fMRI	functional MRI
DTI	diffusion tensor imaging
rs-fMRI	resting state fMRI
FC	functional connectivity
BOLD	blood oxygen level-dependent
FA	fractional anisotropy
MD	mean diffusivity
ADC	apparent diffusion coefficient
AD	axial diffusivity
RD	radial diffusivity