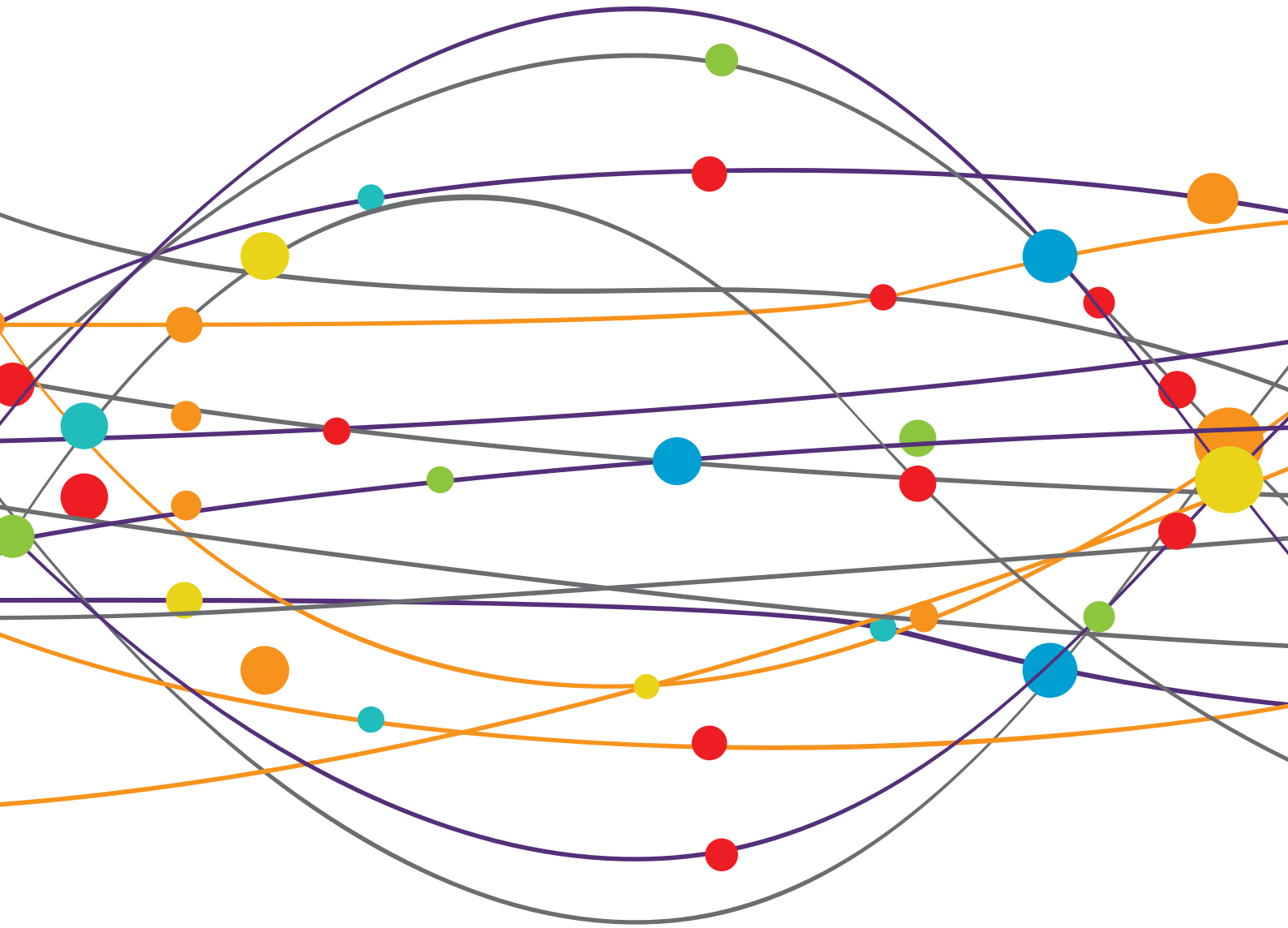
FUNCTIONAL AND STRUCTURAL BRAIN ALTERATIONS IN HEADACHE: A TRAIT OR A STATE?

EDITED BY: Roberta Messina, Peter Goadsby and Massimo Filippi
PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88966-063-6
DOI 10.3389/978-2-88966-063-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

FUNCTIONAL AND STRUCTURAL BRAIN ALTERATIONS IN HEADACHE: A TRAIT OR A STATE?

Topic Editors:
Roberta Messina, Vita-Salute San Raffaele University, Italy
Peter Goadsby, King's College London, United Kingdom
Massimo Filippi, Vita-Salute San Raffaele University, Italy

Citation: Messina, R., Goadsby, P., Filippi, M., eds. (2020). Functional and Structural Brain Alterations in Headache: A Trait or a State?. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88966-063-6

Table of Contents

04 ***Editorial: Functional and Structural Brain Alterations in Headache: A Trait or a State?***
Roberta Messina, Peter J. Goadsby and Massimo Filippi

06 ***Volume of Hypothalamus as a Diagnostic Biomarker of Chronic Migraine***
Zhiye Chen, Xiaoyan Chen, Mengqi Liu, Lin Ma and Shengyuan Yu

17 ***Structural and Functional Brain Alterations in Post-traumatic Headache Attributed to Mild Traumatic Brain Injury: A Narrative Review***
Todd J. Schwedt

24 ***Is There Any MRI Pattern That Discriminates Female From Male Migraine Patients?***
Nasim Maleki and Xiao Michelle Androulakis

30 ***Altered Resting State Functional Activity and Microstructure of the White Matter in Migraine With Aura***
Péter Faragó, Eszter Tóth, Krisztián Kocsis, Bálint Kincses, Dániel Veréb, András Király, Bence Bozsik, János Tajti, Árpád Párdutz, Délia Szok, László Vécsei, Nikoletta Szabó and Zsigmond Tamás Kincses

38 ***Are Migraine With and Without Aura Really Different Entities?***
Zsigmond Tamás Kincses, Dániel Veréb, Péter Faragó, Eszter Tóth, Krisztián Kocsis, Bálint Kincses, András Király, Bence Bozsik, Árpád Párdutz, Délia Szok, János Tajti, László Vécsei, Bernadett Tuka and Nikoletta Szabó

44 ***Application of the Migraine Aura Complexity Score (MACS): Clinical and Neuroimaging Study***
Igor Petrusic, Michele Viana, Marko Dakovic and Jasna Zidverc-Trajkovic

53 ***Imaging the Visual Network in the Migraine Spectrum***
Francesca Puledda, Dominic Ffytche, Owen O'Daly and Peter J. Goadsby

65 ***The Chronic Migraine Brain: What Have We Learned From Neuroimaging?***
Massimo Filippi and Roberta Messina

75 ***Brain Structural and Functional Imaging Findings in Medication-Overuse Headache***
Catherine D. Chong

81 ***Imaging the Premonitory Phase of Migraine***
Nazia Karsan and Peter J. Goadsby

89 ***What We Gain From Machine Learning Studies in Headache Patients***
Roberta Messina and Massimo Filippi

92 ***An Update on Imaging in Idiopathic Intracranial Hypertension***
David Moreno-Ajona, James Alexander McHugh and Jan Hoffmann

99 ***Understanding Cluster Headache Using Magnetic Resonance Imaging***
Stefania Ferraro, Anna Nigri, Greta Demichelis, Chiara Pinardi, Luisa Chiapparini, Luca Giani, Alberto Proietti Cecchini and Massimo Leone

frontiers in Neurology

EDITORIAL
published: 12 August 2020
doi: 10.3389/fneur.2020.00859

Editorial: Functional and Structural Brain Alterations in Headache: A Trait or a State?

Roberta Messina[1,2]*, *Peter J. Goadsby*[3] and *Massimo Filippi*[1,2,4,5]

[1] Neuroimaging Research Unit, Division of Neuroscience, Institute of Experimental Neurology, Milan, Italy, [2] Neurology Unit, Milan, Italy, [3] NIHR-Wellcome Trust King's Clinical Research Facility, King's College London, London, United Kingdom, [4] Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [5] Vita-Salute San Raffaele University, Milan, Italy

Keywords: headache, neuroimaging, migraine, biomarkers, secondary headaches

Editorial on the Research Topic

Functional and Structural Brain Alterations in Headache: A Trait or a State?

Headache disorders affect billions of people and are among the most disabling diseases worldwide (1). The recognition of the significant economic and social impacts of these conditions has increased the interest in understanding their pathophysiology and has led to the development of new treatments. Neuroimaging studies have shed light on the mechanisms of primary and secondary headache disorders, exploring the structure and function of brain regions that mediate the pain and other symptoms present during the headache attacks (2). However, the biology underlying neuroimaging findings in headache patients is not fully understood. Some of the brain alterations might represent a trait that predispose to the development of headache. Others might constitute an adaptive response to the recurrence of headache attacks. This Research Topic aims to outline the current state of the art on functional and structural brain abnormalities in headache disorders, and highlight different opinions and perspectives whether these brain changes might represent headache brain traits, states or a combination of both. Thirteen papers were published as part of the Research Topic covering different forms of primary and secondary headaches.

It is not surprising that most of the articles in the Research Topic were focused on migraine, being the most frequently studied form of headache. Migraine is now widely accepted as a complex neurological disorder characterized by headache and a plethora of sensory, cognitive and neurovegetative symptoms. Many migraine patients experience non-headache symptoms many hours before the onset of the migraine pain, during the premonitory phase of the migraine attack. Karsan and Goadsby reviewed recent functional imaging studies that have attempted to image migraine patients during this early phase. It emerged from the review that changes in the functional connection between the brainstem, hypothalamus, limbic, and pain modulatory regions may account for the symptoms that patients report during the premonitory phase. The authors hypothesized an early activation of subcortical and diencephalic brain areas, which then exert a top-down effect on brainstem regions involved in trigeminovascular nociception, leading ultimately to headache, and associated symptoms.

Between 15–30% of migraine patients experience aura. Migraine aura symptoms can be very heterogenous between patients and among migraine attacks in the same patient. Using a scoring system that evaluates the complexity of aura symptoms, Petrusic et al. have shown that migraine patients with aura can be stratified into different clinical phenotypes. More complex aura symptoms were associated to a thicker visual and somatosensory cortex. Whether migraine with and without aura are two different entities is still a matter of debate. Faragò et al. and Kincses et al. examined functional and structural brain differences between migraine patients with and without aura, suggesting that these two subtypes of migraine should be handled separately in future studies.

Edited and reviewed by:
Cristina Tassorelli, Università di Pavia, Italy

***Correspondence:**
Roberta Messina
messina.roberta@hsr.it

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *16 June 2020*
Accepted: *07 July 2020*
Published: *12 August 2020*

Citation:
Messina R, Goadsby PJ and Filippi M (2020) Editorial: Functional and Structural Brain Alterations in Headache: A Trait or a State? Front. Neurol. 11:859. doi: 10.3389/fneur.2020.00859

The role of the visual network in migraine pathophysiology is well-known. Puledda et al. reviewed the most relevant neuroimaging studies highlighting the involvement of the visual pathways in the broader spectrum of migrainous disorders, including migraine with and without aura, and in the visual snow syndrome, which is not a form of aura. The visual snow syndrome is a recently recognized neurological disorder characterized by the constant vision of tiny flickering dots covering the entire visual field. In the review, the authors hypothesized that a combination of altered peripheral visual stimulation, thalamic and visual cortical dysfunctions could account for the visual illusion experienced by patients with visual snow.

Mechanisms responsible for migraine chronification are still unclear. Two studies of the Research Topic (Filippi and Messina; Chen et al.) highlighted recent imaging studies exploring the function and structure of brain areas that could have a role in migraine evolution into a chronic form.

Another interesting topic that has been discussed by Maleki and Androulakis is the presence of sex-related differences in migraine patients. So far, only few neuroimaging studies have compared female and male patients with migraine showing distinct structural and functional alterations in pain processing brain areas. These preliminary findings may pave the way to further studies that could explain the higher prevalence of migraine in women.

Similar to migraine, the use of advanced imaging techniques have yielded new insights into the pathophysiology of cluster headache. Over the last decades, an increasing number of neuroimaging studies, reviewed by Ferraro et al., have revealed an abnormal activation and morphology of brain regions, including the hypothalamus and midbrain tegmentum, which can explain the typical circadian and circannual rhythms of cluster headache attacks, as well as the predominant presence of autonomic symptoms.

Abnormalities in the structure and function of brain areas involved in the processing of the cognitive, affective and sensory aspects of pain have also been revealed in patients with secondary headaches. Thus, raising the question whether it is possible to identify a specific imaging pattern for each different headache phenotype. The reviews by Schwedt and Chong highlighted imaging similarities and differences between migraine and secondary headaches, like medication overuse and post-traumatic headache. Although, there is evidence showing that patients with post-traumatic headache experience distinct brain alterations compared to patients with migraine, further research is necessary to define better the alterations directly attributable to the underlying brain injury, post-traumatic headache or a possible pre-injury migraine. Patients with medication overuse headache showed brain changes not only in regions that are part of the pain network but also in areas implicated in addiction. Interestingly, some of these abnormalities normalized following discontinuation of the overused medication, while others persisted. These findings suggest that some brain alterations are secondary to the frequent intake of acute treatments and associated headache, whereas others might represent a brain trait that predispose to development of medication overuse.

Although headache diagnosis is mainly based on taking a good clinical history, diagnostic tests, including brain imaging and imaging of the retina, have a pivotal role in the diagnostic work up of secondary headaches, such as headache attributed to idiopathic intracranial hypertension, as suggested by Moreno-Ajona et al.

In conclusion, the articles included in this Research Topic provided an overview on the main neuroimaging findings in primary and secondary headache disorders. It stands out from the Research Topic that headache disorders are complex neurological conditions. Headache patients experience widespread brain functional and structural alterations, some of which can predispose to a specific headache phenotype, while others can be associated to the perception of headache pain and can change dynamically over time. In the future, novel advanced neuroimaging techniques and computational methods, as machine learning approaches (Messina and Filippi), can improve our understanding of the underlying biology of headaches, leading to the development of novel headache-specific treatments.

AUTHOR CONTRIBUTIONS

RM wrote the first draft of the manuscript. PG and MF edited the final version of the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. (2017) 390:1211–59. doi: 10.1016/S0140-6736(17)32154-2
2. Messina R, Filippi M, Goadsby PJ. Recent advances in headache neuroimaging. *Curr Opin Neurol*. (2018) 31:379–85. doi: 10.1097/WCO.0000000000000573

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 06 June 2019
doi: 10.3389/fneur.2019.00606

Volume of Hypothalamus as a Diagnostic Biomarker of Chronic Migraine

Zhiye Chen[1,2,3†], *Xiaoyan Chen*[2†], *Mengqi Liu*[1,3], *Lin Ma*[1*] and *Shengyuan Yu*[2*]

[1] Department of Radiology, Chinese PLA General Hospital, Beijing, China, [2] Department of Neurology, Chinese PLA General Hospital, Beijing, China, [3] Department of Radiology, Hainan Hospital of Chinese PLA General Hospital, Sanya, China

It is believed than hypothalamus (HTH) might be involved in generation of migraine, and evidence from high resolution fMRI reported that the more anterior part of HTH seemed to play an important role in migraine chronification. The current study was aimed to identify the alteration of morphology and resting-state functional connectivity (FC) of the hypothalamus (HTH) in interictal episodic migraine (EM) and chronic migraine (CM). High-resolution structural and resting-state functional magnetic resonance images were acquired in 18 EM patients, 16 CM patients, and 21 normal controls (NC). The volume of HTH was calculated and voxel-based morphometry (VBM) was performed over the whole HTH. Receiver operating characteristics (ROC) curve analysis was applied to evaluate the diagnostic efficacy of HTH volume. Correlation analyses with clinical variables were performed and FC maps were generated for positive HTH regions according to VBM comparison. The volume of the HTH significantly decreased in both EM and CM patients compared with NC. The cut-off volume of HTH as 1.429 ml had a good diagnostic accuracy for CM with sensitivity of 81.25% and specificity of 100%. VBM analyses identified volume reduction of posterior HTH in EM vs. NC which was negatively correlated with headache frequency. The posterior HTH presented decreased FC with the left inferior temporal gyrus (Brodmann area 20) in EM. Decreased volume of anterior HTH was identified in CM vs. NC and CM vs. EM which was positively correlated with headache frequency in CM. The anterior HTH presented increased FC with the right anterior orbital gyrus (AOrG) (Brodmann area 11) in CM compared with NC and increased FC with the right medial orbital gyrus (MOrG) (Brodmann area 11) in CM compared with EM. Our study provided evidence of structural plasticity and FC changes of HTH in the pathogensis of migraine generation and chronification, supporting potential therapeutic target toward the HTH and its peptide.

Keywords: hypothalamus, episodic migraine, chronic migraine, chronicification, volume, voxel-based morphomethy, functional connectivity

OPEN ACCESS

Edited by:
Massimo Filippi,
Vita-Salute San Raffaele University, Italy

Reviewed by:
Gianluca Coppola,
Fondazione G. B. Bietti (IRCCS), Italy
Marco Carotenuto,
Università degli Studi della Campania Luigi Vanvitelli Caserta, Italy

***Correspondence:**
Lin Ma
cjr.malin@vip.163.com
Shengyuan Yu
yusy1963@126.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *07 February 2019*
Accepted: *22 May 2019*
Published: *06 June 2019*

Citation:
Chen Z, Chen X, Liu M, Ma L and Yu S (2019) Volume of Hypothalamus as a Diagnostic Biomarker of Chronic Migraine. Front. Neurol. 10:606. doi: 10.3389/fneur.2019.00606

INTRODUCTION

Migraine is a common disabling primary headache disorder characterized by multiphase attacks of headache and a number of accompanying symptoms. Chronic migraine(CM) is defined as headache occurring on ≥15 days/month for more than 3 months with migraine features on ≥8 days/month (1). CM affects approximately 2% of the adult population in western countries,

imposing substantial burdens on individual sufferers, their families and society. Although this disorder is highly disabling and prevalent, it remains largely underdiagnosed and undertreated (2). The chronification occurs in about 2.5% or more of episodic cases annually (3, 4). A number of potential risk factors may be associated with the transition to CM (3). But the underlying pathophysiologic mechanisms leading to migraine chronification are still unknown.

Neuroimaging has played a significant role in the current understanding of pathophysiologic processes behind migraine. The processes of migraine attacks seem to lead to increased sensitivity or hyperexcitability of different brain regions, facilitating occurrence of headache and aura (5). The hypersensitivity of attack-generating brain regions may lead to the enhanced susceptibility to attack generation. Recent evidences suggested that the brainstem, central dopaminergic system and hypothalamus (HTH) might be crucially involved in generation of migraine attack (5). The HTH has multiple functions in maintaining homeostasis by controlling the endocrine system, coordinating the activity of the sympathetic and parasympathetic nervous systems, integrating psyche and soma, regulating circadian rhythms and arousal, and in nociceptive processing (6). Some clinical features of migraine point toward HTH involvement, such as yawning, tiredness and mood changes in the premonitory phase (7), the circadian rhythmicity of attacks (8) and the association of attacks with hormonal status and the menstrual cycle (9). Neuroimaging studies revealed activation of HTH and altered functional coupling with the spinal trigeminal nuclei and the region of the migraine generator, i.e., the dorsal rostral pons in the premonitory and acute pain phase of migraine, suggesting that the real driver of migraine attacks might be the functional changes in hypothalamo-brainstem connectivity (10–13). In addition, a recent study found that the more anterior part of HTH seemed to play an important role in migraine chronification (14). Therefore, the HTH might be an important biomarker for the diagnosis and treatment of migraine.

As far as we know, there is no study focusing on morphometric analysis on the HTH in chronic migraine. Structural neuroimaging may provide an easier way than functional neuroimaging in clinical practice and add complementary information in speculating mechanisms of the HTH in the pathogenesis of migraine. We had the following hypothesis: (1) the volume of HTH may change in migraineurs; (2) the volume of HTH sub-regions may change in different patterns for CM and interictal episodic migraine (EM); (3) there might be altered functional connectivity(FC) of the positive sub-regions in HTH. To address these hypotheses, we prospectively conducted a study investigating the morphological changes and FC of the HTH in patients with CM, EM and healthy controls (HC) via high-resolution structural and functional magnetic resonance imaging (MRI) by calculating the volume of HTH, performing voxel-based morphometry (VBM) analysis over the whole HTH, and generating FC maps. By doing this, we aimed to investigate the role and possible mechanisms of HTH in migraine and the chronification.

MATERIALS AND METHODS

Subjects

Eighteen EMs, 16 CMs and 21 normal controls (NCs) were recruited from the International Headache Center, Department of Neurology, Chinese PLA General Hospital. All the patients should fulfill the International Classification of Headache Disorders, 3rd Edition (ICHD-III) criteria of episodic or chronic migraine without aura (1), and the inclusion criteria was as follows: (1)The diagnosis of migraine refers to 1.1 Migraine without aura; (2) EM is defined as migraine attack days being <15 days per month, and diagnosis of CM refers to 1.3 CM in ICHD-III; (3) no migraine preventive medication used in the past 3 months; (4) absence of any chronic disorders, including hypertension, diabetes mellitus, cardiovascular diseases, cerebrovascular disorders, neoplastic diseases, other subtypes of headache, chronic pain other than headache, severe anxiety or depression preceding the onset of headache, psychiatric diseases, etc.; (5) absence of alcohol, nicotine, or other substance abuse. The inclusion criteria of NC were similar to those of patients, except for the first three items. NC should never have any primary headache disorders or other types of headache in the past year. The exclusion criteria were the following: cranium trauma, illness interfering with central nervous system function, psychotic disorder, and regular use of a psychoactive or hormone medication.

All the patients were given with the Visual Analog Scale (VAS) for the pain intensity evaluation, the Migraine Disability Assessment Scale (MIDAS), Hamilton Anxiety Scale (HAMA) for the anxiety evaluation, Hamilton Depression Scale (HAMD) for the depression evaluation and Montreal Cognitive Assessment (MoCA) for the cognitive function evaluation. All the subjects were right-handed and underwent conventional MRI examination to exclude the subjects with cerebral infarction, malacia, or occupying lesions. Alcohol, nicotine, caffeine, and other substances were avoided for at least 12 h before MRI examination. All the patients underwent MRI scanning at least 3 days after last migraine attack. CM patients may have headache but not with migraine feature during MRI scanning. The study protocols were approved by the Ethical Committee of Chinese PLA General Hospital and complied with the Declaration of Helsinki. Informed consents were obtained from all participants before the study.

MRI Acquisition

All the MRI data were acquired on a GE 3.0T MR system (DISCOVERY MR750, GE Healthcare, Milwaukee, WI, USA) and a conventional eight-channel quadrature head coil was used. All subjects were instructed to lie in a supine position, and formed padding was used to limit head movement. High resolution structural images were acquired with a three-dimensional T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) sequence [TR (repetition time) = 6.3 ms, TE (echo time) = 2.8 ms, flip angle = 15°, FOV (field of view) = 25.6 × 25.6 cm, Matrix = 256 × 256, NEX (number of acquisition) = 1]. Resting-state functional MR images were obtained using a gradient echo-planar imaging (EPI) sequence (TR = 2,000 ms,

TE = 30 ms, flip angle = 90°, slice thickness = 3 mm, slice gap = 1 mm, FOV = 24 × 24 cm, Matrix = 64 × 64). One hundred and eighty axial EPI functional volumes were obtained over 6 min. Oblique axial T2-weighted imaging (T2WI), T1 fluid-attenuated inversion recovery (T1-FLAIR) and diffusion weighted imaging (DWI) were also acquired. All imaging protocols were identical for all subjects. No obvious structural damage and T2-visible lesion were observed based on the conventional MR images.

MR Image Processing

All MR structural image data were analyzed with Statistical Parametric Mapping 12 (SPM 12) (http://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB 7.6 (The Mathworks, Natick, MA, USA). The individual HTH segment included following steps: (1) Resliced a high-resolution probabilistic *in vivo* atlas of human HTH (15) into MNI space; (2) Individual structural images were performed with segment using DARTEL methods (16, 17), and generate gray matter, white matter and deformation field; (3) Individual HTH segment by applying the inverse deformation field to the HTH template; (4) Calculated the individual HTH volume by summing over all voxels in the individual HTH (**Figure 1**).

Voxel-based morphometry (VBM) analysis of HTH included following steps: (1) Gray matter images (generated by DARTEL segment) were smoothed with an isotropic 8 mm full width at half maximum Gaussian-kernel; (2) A general linear model was used to compare HTH volume changes on voxel level with age, sex and TIV as covariance; (3) Small volume correction ($P < 0.05$, no cluster size threshold) was applied in a region by the standard HTH template; (4) False discovery rate (FDR) was assessed to perform the multiple comparison corrections ($P < 0.05$)

The volume extraction of the altered volume of the HTH region in VBM processing (**Figure 2**): (1) All the positive clusters of VBM were saved as posterior HTH template for EM vs. NC comparison and anterior HTH template for CM vs. NC comparison, respectively; (2) Individual positive HTH segment by applying the inverse deformation field to the anterior and posterior HTH template to generate the individual anterior and posterior HTH; (3) Calculated the individual positive HTH volume by summing over all voxels in the individual positive HTH region.

The functional connectivity (FC) analysis was processed using DPABI software (V4.3_170105) (18) as following: (1) First 10 volumes of the resting-state functional images were removed; (2) Slice timing correction; (3) Head motion correction; (4) Structural images were coregistered to the functional images; (5) The nuisance regressors were removed according to Yan's methods (19), which included motion parameters and their derivatives, global, white matter, CSF time series; (6) The linear trend removal and temporal band-pass filtering (0.01–0.08 Hz); (7) Spatial normalization using by DARTEL; (8)The clusters were classified as the seeds based on VBM comparisons among EM, CM and NC; (9) FC was calculated and the individual FC maps were normalized to Z-maps using Fisher's Z transformation;(10) Smoothing with a 6 mm Gaussian kernel, and two-sample *t*-test was performed with age and sex as covariables to identify the brain regions with significant difference in FC with the positive HTH regions with altered volume among EM, CM, and NC. Significance was set as $P < 0.001$ without correction. The minimal number of continuous voxels was set based on the expected voxels per cluster. The statistical analysis was performed by SPM12 software.

Statistical Analysis

The statistical analysis was performed by using IBM SPSS Statistics (version 23) and MedCalc (version 11.4.2.0). The normal distribution data presented by mean±standard deviation, and the non-normal distribution data presented by median (minimum, maximum). Age was performed with one-way analysis of variance, sex with Chi-square test, VAS with independent *t*-sample test, MIDAS, disease duration (DD) and headache frequency with Mann-Whitney U test because of non-normal distribution. HAMA, HAMD, and MoCA score were performed with one-way analysis with LSD method for variance homogeneity and Dennett's T3 method for variance non-homogeneity. HTH volume was performed with one-way analysis of covariance with age, sex, and total intracranial volume (TIV) as covariance. Pearson's correlation analysis was applied with the normal distribution data, and Spearman's method was applied with the non-normal distribution data. Significant difference was set at a $P < 0.05$. Receiver operating characteristics (ROC) curve analysis was applied to evaluate the diagnostic efficacy of HTH volume and area under the curve (AUC) was recognized reasonable diagnostic valuable with AUC set at >0.7.

RESULTS

Comparison of Clinical Variables and HTH Volume Among NC, EM, and CM

Table 1 presented that there was significant difference for age between EM and CM, sex between NC and EM ($P = 0.01$ and 0.02, respectively). VAS showed no significance between EM and CM ($P = 0.37$). The disease duration showed no significant difference between EM and CM ($P = 0.485$). The headache frequency was significantly higher in CM than that in EM ($P = 0.000$). CM patients had a higher HAMA and HAMD score than that in EM ($P = 0.003$ and 0.033, respectively). MoCA score showed a significant difference among EM, CM and NC ($P < 0.05$). CM had a significantly higher MIDAS score compared with EM ($P = 0.00$).

CM had the lowest HTH volume (1.38 ± 0.12 ml) than that (1.58 ± 0.08 ml) of NC ($P = 0.03$). EM showed a decreased HTH volume (1.47 ± 0.12) compared with that of NC ($P = 0.00$). There was no significant difference between EM and CM ($P = 0.51$) (**Figure 3**).

ROC Curve Analysis of HTH Volume Among NC, EM, and CM

The area under the receiver operating characteristic (ROC) curve (AUC) for NC vs. EM was 0.77 ± 0.08 (95% Confidence Interval 0.60 ∼ 0.89), and the cut-off value was 1.437 with sensitivity 50%, specificity 100% and negative likelihood ratio 50%.

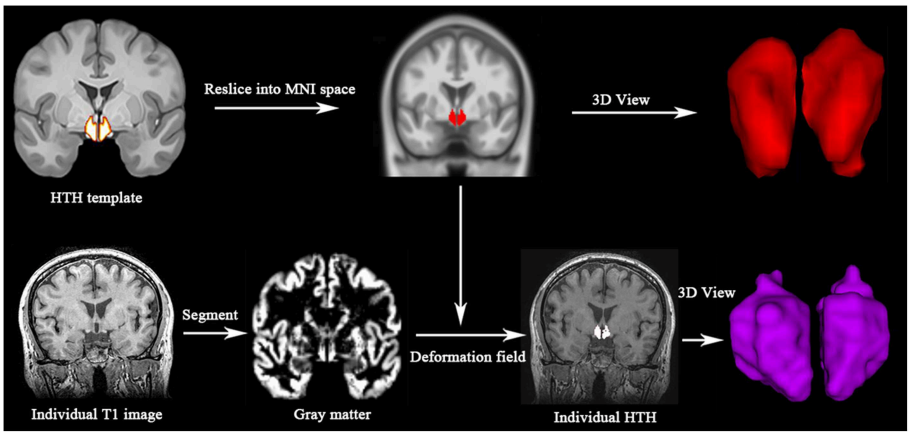


FIGURE 1 | Individual HTH segment. Top line: high resolution probabilistic *in vivo* HTH template was resliced into MNI space; Bottom line: Individual T1 images were segmented, and generated deformation field, which would be used to generate individual HTH using pull-back strategy. Red and purple represent 3D visualization of HTH template and individual HTH.

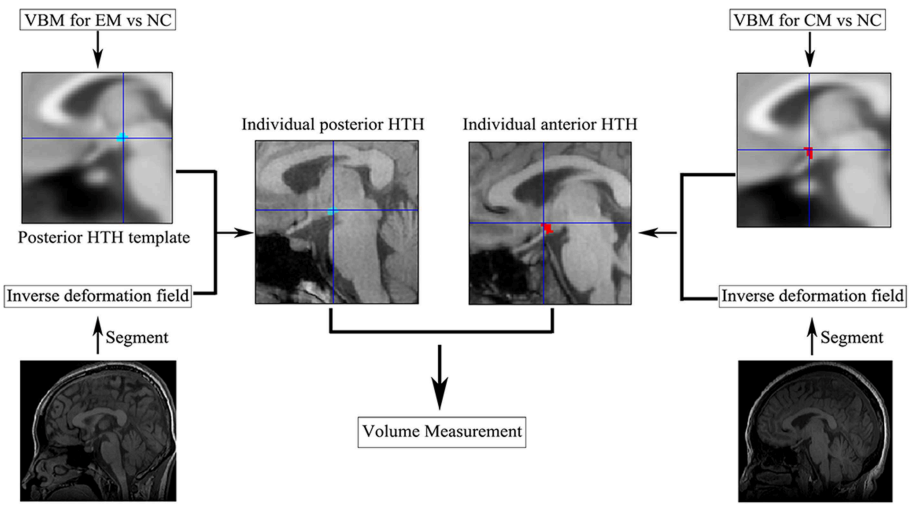


FIGURE 2 | The individual anterior and posterior HTH segment. CM, chronic migraine; EM, episodic migraine; HTH, hypothalamus; NC, normal control; VBM, voxel-based morphometry.

The AUC for NC vs. CM was 0.90 ± 0.06(95% Confidence Interval 0.75 ∼ 0.98), and the cut-off value was 1.429 with sensitivity 81.25%, specificity 100% and negative likelihood ratio 19%.

Pairwise comparison of ROC curves between NC vs. EM and NC vs. CM confirmed that the difference between areas was 0.16 ± 0.09 ($P = 0.08$) (**Figure 4**).

Voxel-Based Morphometry Analysis of HTH Among EM, CM, and NC

VBM analysis identified that the decreased HTH volume of EM located in the posterior HTH (MNI coordinate:−3−12−12; 3−12−11), and the decreased HTH volume of CM located in the anterior HTH (MNI coordinate:−6 0−14; 6 3−14) compared with NC (**Figure 5** and **Table 2**). There was no increased HTH volume of EM and CM compared with NC.

The decreased HTH volume of CM located in the anterior HTH (MNI coordinate:6 3−14;-5 3−12), and there was no increased HTH region in CM compared with EM (**Figure 5**).

Correlation Analysis of the Volume of Anterior and Posterior HTH With the Clinical Variables

The mean decreased volume of the anterior HTH of CM and posterior HTH of EM were 0.162 ± 0.014 ml and 0.109 ± 0.009 ml. In CM patients, the volume of anterior HTH with decreased volume in VBM comparison presented positive correlation with headache frequency ($r = 0.681$, $P = 0.001$), and presented no significant correlation with

TABLE 1 | Comparison of clinical variables and HTH volume among NC, EM, and CM.

	NC	EM	CM	*F*-value	*P*-value
Age[a] (year)	39.61 ± 10.09	33.39 ± 11.00	42.44 ± 8.65	3.69	0.03
Sex (F/M)[b]	18 (7/11)	18 (14/4)	16 (12/4)	7.20[c]	0.03
VAS	NA	8.33 ± 1.50	7.88 ± 1.45	0.90	0.37
DD (year)	NA	10 (0.5,30)[d]	9 (3,30)[d]	124[e]	0.485
HF (times/month)	NA	3 (1,10)[d]	30 (17,30)[d]	0[e]	0.000
HAMA[f]	10.33 (5,16)	15.67 ± 9.85	21.63 ± 10.98	7.334[g]	0.002
HAMD[h]	8.44 ± 4.13	10.89 ± 7.26	16.31 ± 10.52	4.672[g]	0.014
MoCA[i]	27.00 ± 2.52	30 (25,30)[d]	22.94 ± 5.37	14.238[g]	0.000
MIDAS	NA	12 (0,70)[d]	101.81 ± 13.49	8[e]	0.00
HTH (ml)[j]	1.58 ± 0.08	1.47 ± 0.12	1.38 ± 0.12	5.03	0.01

[a] *Significant difference presented between EM and CM (P = 0.01).*
[b] *There is a significant difference between NC and EM (Chi-square value 5.00, P = 0.02).*
[c] *Pearson Chi-square value.*
[d] *Median (minimum, maximum).*
[e] *Mann-Whitney U value.*
[f] *CMhad a higher HAMA score than that in NC (P = 0.003).*
[g] *post hoc multiple comparison using Dennett's T3 because of variance non-homogeneity.*
[h] *CM had a higher HAMD score than that in NC (P = 0.033).*
[i] *There was a significant difference for MoCA score among EM, CM and NC (P< 0.05).*
[j] *NC had a significant higher HTH volume than that of EM (P = 0.004) and CM (P = 0.031).*
NA, not available; VAS, Visual Analog Scale; MIDAS, Migraine Disability Assessment Scale; DD, disease duration; HF, headache frequency; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MoCA, Montreal Cognitive Assessment.

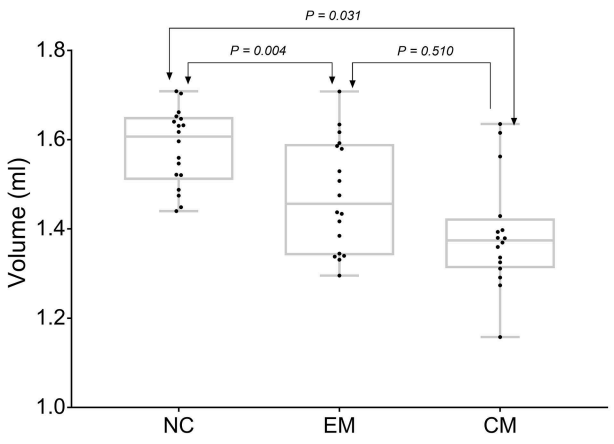


FIGURE 3 | HTH volume distribution plot of NC, EM and CM patients.

the other clinical variables including VAS score, diseased duration, HAMA, HAMA and MoCA score ($P > 0.05$) (**Table 3**). In contrast, the volume of posterior HTH with decreased volume in VBM comparison for EM vs. NC showed significant negative correlation with headache frequency ($r = -0.457$, $P = 0.028$), and showed no significant relation with the other clinical variables including VAS score, diseased duration, HAMA, HAMA and MoCA score ($P > 0.05$).

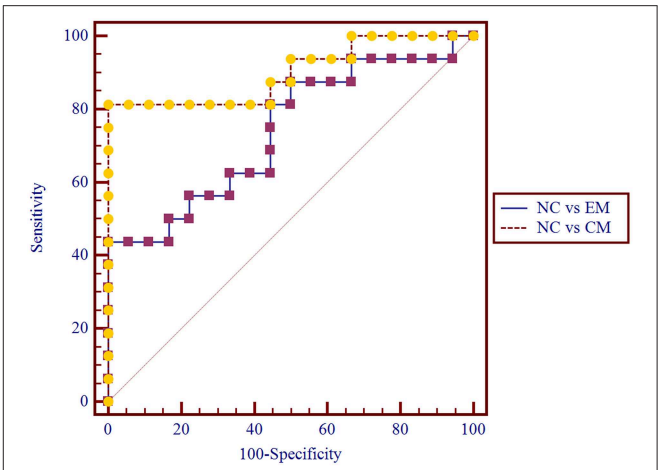


FIGURE 4 | Pairwise comparison of ROC curve for NC vs. EM and NC vs. CM. The AUC for NC vs. CM was 0.90 ± 0.06, and for NC vs. EM was 0.77 ± 0.08.

Altered Functional Connectivity (FC) of Positive HTH Region According to VBM Comparison Among EM, CM, and NC

Table 4 presented that the decreased FC of posterior HTH located in the left inferior temporal gyrus (Brodmann area 20) in EM compared with NC, and there was no increased FC in EM compared with NC (**Figure 6**). The increased FC of anterior HTH of CM located in the right anterior orbital gyrus (AOrG) (Brodmann area 11) compared with NC, and the increased FC of anterior HTH of CM anchored in the right medial orbital gyrus (MOrG) (Brodmann area 11) compared with EM (**Figure 6**). There was no decreased FC of anterior HTH in CM compared with NC and EM. **Figure 7** presented the contrast estimates for the significant voxel.

DISCUSSION

To our knowledge, this is the first study conducted to identify the changes of morphology and functional connectivity (FC) of the HTH in interictal EM and CM. In this study, both EM and CM patients had lower HTH volume than NC. The cut-off volume of HTH as 1.429 ml showed a good level for the diagnosis of CM by ROC analysis. VBM analysis further identified that the decreased HTH volume located in posterior HTH for EM and in anterior HTH for CM compared with NC. The altered volume in these HTH regions had association with headache frequency and presented altered FC with different brain regions, respectively. As a whole, our study added evidence that HTH may play an important role in migraine and migraine chronification.

HTH serves as a crucial center for the integration and coordination of various brain functions. Despite its relatively small size, the HTH expresses a large number of different neurotransmitters and peptide hormones and has wide connection to other brain regions (20). Anatomically HTH can be divided into the lateral and medial level and four rostrocaudal levels: preoptic, anterior, tuberal, and posteror HTH (21). Each

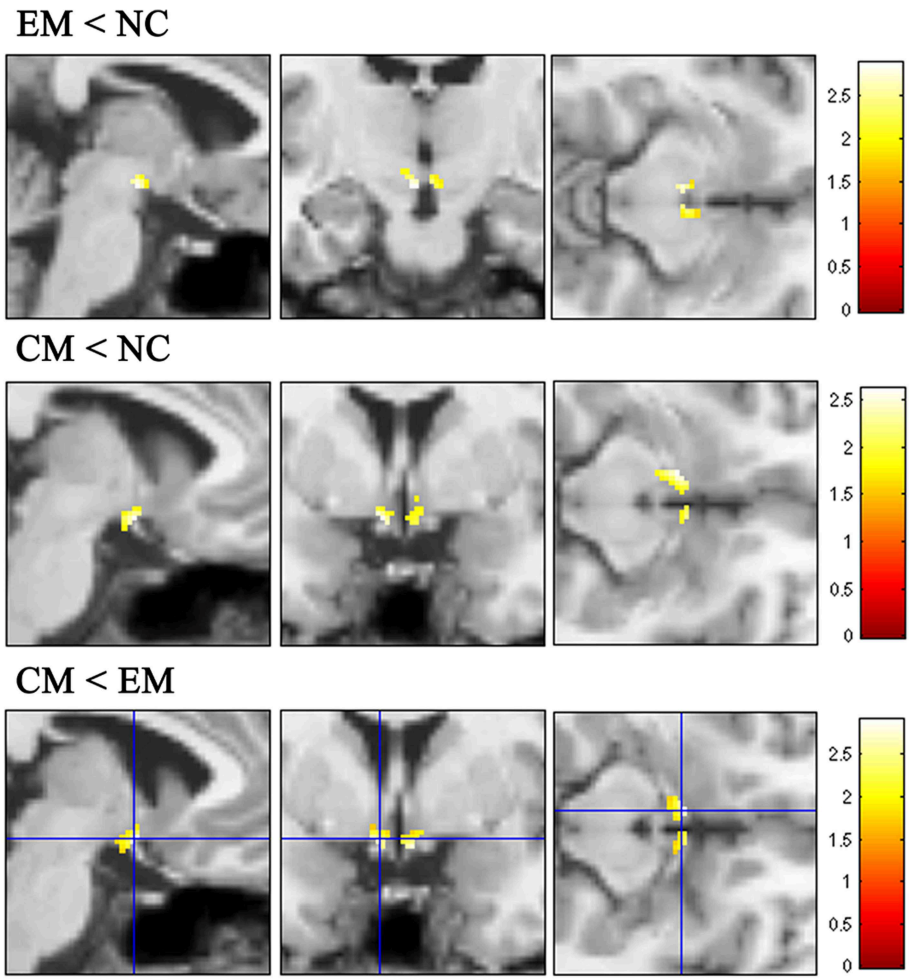


FIGURE 5 | The decreased HTH volume of EM located in the posterior HTH (top line), while the decreased HTH volume of CM located in the anterior HTH (middleline) compared with NC. Compared with EM, the decreased HTH region located in the anterior HTH (bottom line).

TABLE 2 | The decreased HTH regions in EM and CM compared with NC.

Group	Anatomic region	MNI-space			Cluster size	P_{uncorr}	Peak T value
		X	Y	Z			
EM < NC							
	Posterior HTH	−3	−12	−12	22	0.004	2.88
	Posterior HTH	3	−12	−11	22	0.010	2.43
CM < NC							
	Anterior HTH	−6	0	−14	47	0.007	2.62
	Anterior HTH	6	3	−14	21	0.010	2.44
CM < EM							
	Anterior HTH	6	3	−14	38	0.003	2.91
	Anterior HTH	−5	3	−12	46	0.004	2.80

TABLE 3 | Correlation analysis between decreased HTH regions in EM and CM.

	EM		CM	
	r	*P*-value	*r*	*P*-value
VAS	0.059	0.409	0.011	0.483
DD	0.133	0.3	−0.037	0.442
HF	−0.457	0.028	0.681	0.001
HAMA	0.028	0.456	0.319	0.099
HAMD	0.279	0.131	−0.033	0.448
MoCA	0.057	0.412	−0.245	0.163

VAS, visual analog scale; DD, disease duration; HF, headache frequency; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MoCA, Montreal Cognitive Assessment.

region has distinct patches of nuclei and associated functions (22). The preoptic area contains medial preoptic nucleus, uncinate nucleus, intermediate nucleus, and is known to control thermoregulation, reproduction, and electrolyte balance. The anterior HTH, including the supraoptic nucleus, suprachiasmatic nucleus, paraventricular nucleus and anterior periventricular

TABLE 4 | The altered resting-state functional connectivity of HTH subregions with altered volume among EM, CM, and NC.

Group	Brodmann area	Anatomic region	MNI-space			Cluster size	P_{uncorr}	Peak T value
			X	Y	Z			
EM < NC								
	BA 20	Left ITG	−57	−15	−36	13	0.000	4.63
CM > NC								
	BA 11	Right AOrG	21	57	−21	16	0.000	4.29
CM > EM								
	BA11	Right MOrG	18	51	−21	24	0.000	3.86

AOrG, anterior orbital gyrus; MOrG, medial orbital gyrus; ITG, inferior temporal gyrus.

nucleus, regulates feeding, circadian rhythms, autonomic system, and other homeostatic processes. The tuberal HTH includes the arcuate nucleus, median eminence, and ventromedial and dorsomedial hypothalamus, and plays a role in energy balance, stress response, menstrual cycle, pain modulation and aggression. The posterior HTH, which includes the mammillary bodies and the dorsally located posterior hypothalamic nucleus, is involved in processing emotion, as well as spatial and episodic memory (6, 20, 21, 23).

The role of HTH in cluster headache (CH) and other trigeminal autonomic cephalalgias (TACs) has been identified in many studies. Positron emission tomography (PET) and functional MRI studies demonstrated that the posterior HTH is activated during attacks of CH and some other TACs (24, 25). Resting-state functional MRI studies also found altered FC of HTH with the salience network (SN) (26) and a number of diencephalic-mesencephalic dopaminergic structures (27) in CH. VBM MRI has found significant structural differences in the HTH posterior gray matter compared with controls (28). Considering the important role of posterior HTH in CH, deep brain stimulation (DBS) of posterior HTH has been developed as an optional treatment which produced a decrease in attack frequency of more than 50% in 60% of chronic CH patients (29). In recent years, the important role of HTH in migraine has also been revealed by functional neuroimaging studies (10–13, 30) implicating a potential therapeutic target for migraine. HTH has shown co-activation and altered FC with brainstem immediately before or during migraine attack (10–12) suggesting that hypothalamo–brainstem connectivity may be the real driver of migraine attacks. Even in interictal phase of migraine, HTH showed increased FC with a number of brain regions involved in regulation of autonomic functions, including the locus coeruleus, caudate, parahippocampal gyrus, cerebellum, and the temporal pole, which may explain some of the hypothalamic-mediated autonomic symptoms that accompany or precede migraine attacks (30). The altered HTH volume in our study further supported the role of HTH in the pathogenesis of migraine. Different from the increased HTH volume of CH (28, 31), patients of both EM and CM in our study had decreased HTH volume, indicating different neuromechanism of migraine from CH. Unlike the previous study analyzing FC of the whole HTH in interictal migraine (30), our study focused on the FC of the positive HTH regions detected in VBM comparisons and thus may further reveal the mechanism of HTH sub-regions in migraine and its chronification.

The sub-regions of HTH related to CH and migraine mainly located in posterior HTH (13, 14, 24, 25, 28) and anterior HTH (14, 31) as reported in the neuroimaging studies. The posterior HTH may be involved in headache generation (12, 13) and acute pain (14). In our study, the reduced volume of posterior HTH was only present in interictal EM and the volume reduction was negatively correlated with headache frequency in EM, suggesting that the decreased volume of posterior HTH may reflect some deficit in pain processing or modulating systems and lead patients vulnerable to migraine generation while repetitive migraine attacks may vise verse contribute to the volume regain of posterior HTH. The volume regain was considered to be related to neuronal or glial cell genesis, cell size increase, changes in cortical synaptic connectivity, neurogenic inflammation and changes in blood flow or interstitial fluids due to repetitive migraine attacks (32, 33). But the underlying mechanism of the structural alteration is yet to be elucidated. Further functional MRI in our study found decreased FC of the posterior HTH with the left inferior temporal gyrus (Brodmann area 20). The inferior temporal gyrus (ITG) is associated with visual object recognition and has been suggested as the final location of the ventral cortical visual system, which acts as a link between auditory and visual processing, perception, and memory (34). The ITG has been reported to present lower gray matter density (35), and hyperperfusion (36) in interictal migraine. The decreased FC of posterior HTH with the left ITG in EM may suggest the connection of migraine driver with silent cortical spreading depression (37) and may reflect migrainuers' hypersensitivity to visual and auditory stimuli.

One functional MRI study found a significantly stronger activation of the anterior right hypothalamus in CM compared to HC indicating that the more anterior part seemed to play an important role in migraine chronification (14). In consistency with this study, we identified that the volume of anterior HTH decreased in CM compared with both EM and NC in VBM analysis and the volume reduction was positively correlated with headache frequency in CM, which further supported the participation of anterior HTH in migraine chronification. The anterior HTH presented increased FC with the right anterior orbital gyrus (AOrG) (Brodmann area 11) and the right medial orbital gyrus (MOrG) (Brodmann area 11) compared with NC and EM, respectively. The OrG is responsible for very complex emotional and cognitive functions. Brodmann area 11 also receives olfactory and auditory information (38). Previous studies have provided neuropsychological evidence of OrG dysfunction in CM with medication overuse such as depression, dependence, impaired task performance and decision making (39–42). Neuroimaging studies identified hypometabolism (42) and volume reduction of the OrG in CM with medication overuse (43) and without medication overuse (44). The OrG has been proven in animal experiment to exert a direct influence on the anterior HTH (45). The OrG–HTH interaction has also been identified in resting-state fMRI data of human subjects

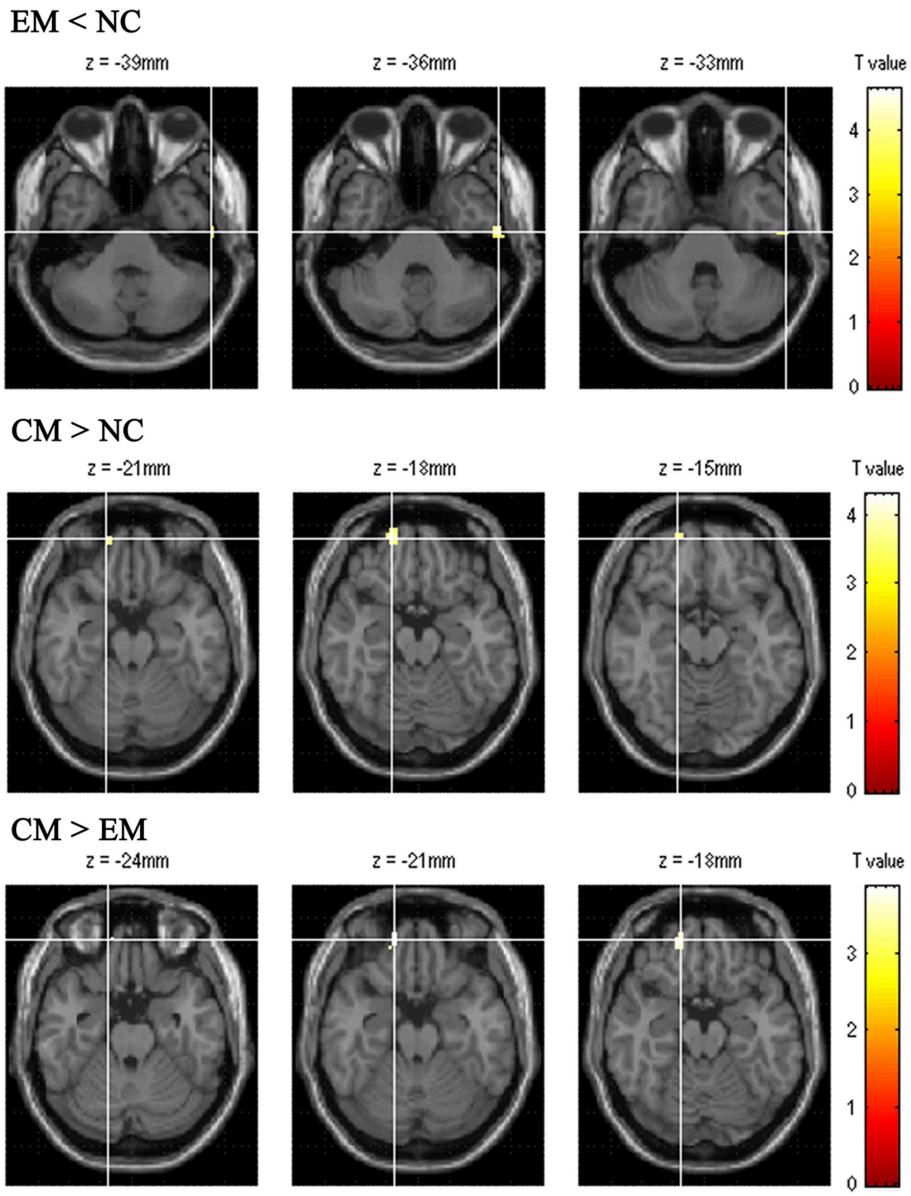


FIGURE 6 | The altered functional connectivity of positive HTH region among EM, CM and NC. The top line presented the decreased functional connectivity of posterior HTH located in the left inferior temporal gyrus in EM compared with that in NC. The middle line presented the increased functional connectivity of anterior HTH of CM located in the right anterior orbital gyrus compared with NC. Bottom line showed that the increased functional connectivity of anterior HTH of CM located in the right medial orbital gyrus compared with EM.

(46). Therefore, the increased FC of anterior HTH and OrG in CM in our study may indicate the role of anterior HTH in the relationship of emotional and execution dysfunction with overweight, autonomic disorder and sleep problem in CM (47). However, the altered volume and FC of anterior HTH is the cause or outcome of migraine chronification is still a debate.

The HTH has an important role in pain perception. There is evidence of anatomical connections between the HTH and the trigeminal nucleus (48). More evidences confirmed the important role of the posterior HTH in regulating trigeminovascular processing through the analgesic effect by injection of opioids, or resection, or neurostimulation of this region (49). The HTH hosts many key neuropeptide systems, such as orexins, oxytocin, neuropeptide Y, and pituitary adenylate cyclase activating protein(PACAP), etc., which have been postulated to play a role in migraine pathophysiology. Potential therapeutic compounds targeting these systems may have efficacy in treating migraine (50). Oxytocin is synthesized in magnocellular neurosecretory cells in both the supraoptic and paraventricular nuclei of the anterior HTH (51). Oxytocin

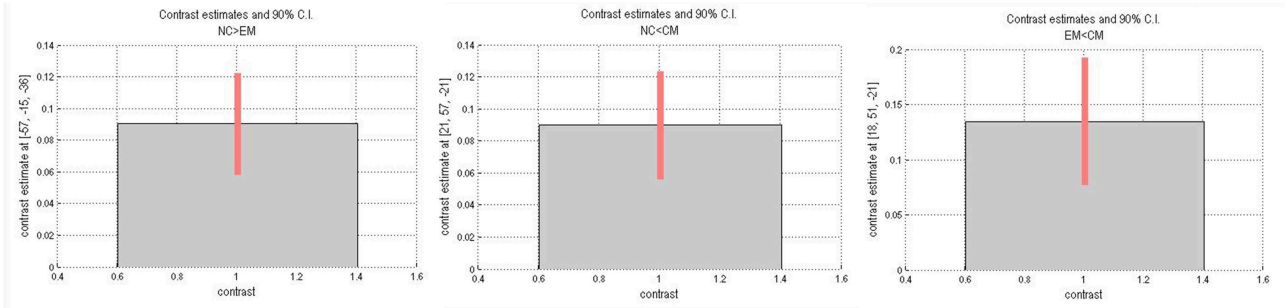


FIGURE 7 | Contrast estimates and 90% CI for the significant voxels.

receptors located in numerous brain and spinal cord regions including dorsal root and calcitonin gene-related peptide (CGRP)-expressing trigeminal ganglia neurons, suggesting a role in pain modulation (52, 53). Intranasal oxytocin was associated with strong analgesic effect for CM possibly by upregulating oxytocin receptors on trigeminal neurons following inflammatory or noxious stimulation and reducing CGRP release (52). The decreased volume of anterior HTH in CM detected in our study may in part reflect structural plasticity of Oxytocin neurons and the deficit in OrG–HTH-brainstem pain modulatory system may be one of the pathogensis of CM. Both anterior and posterior HTH also contain PACAP neurons. Descending projections of PACAP neurons from the posterior, paraventricular, lateral, dorsomedial and pre-optic hypothalamic nuclei to the trigeminocervical neurons and superior salivatory nucleus, are thought to be involved in mediating cranial autonomic symptoms and dural neuro-inflammatory mechanisms of primary headache (54). Besides, PACAP was involved in control of circadian rhythms, learning, memory, and stress (54), which may also be related to migraine pathophysiology. PACAP can induce migraine-like headache (55, 56) and the PACAP system is the subject of significant interest as a potential therapeutic target for migraine (57). Researches on these HTH neuropeptide systems, the HTH structural plasticity and functional alteration may extend our knowledge to migraine pathogenesis and treatment.

Our study has some limitations. Firstly, the age and sex were not compatible among the groups. To diminish the influence on volume and FC analysis, we used age, sex and TIV as covariance. Secondarily, we did not compare the volume difference between patients suffering headache and not suffering headache because only 2 of the 16 CM patients were headache free when taking MRI scanning. Therefore, it is unknown how headache influence the HTH volume in CM. Thirdly, we did not measure the migraine-associated neuropeptide released from the HTH in the blood. Further studies may measure these peptides to better elucidate the alteration of the HTH in neuroimaging findings.

In conclusion, we provided neuroimaging evidence that the structural plasticity and FC alteration of HTH happened in interictal EM and CM. HTH volume <1.429 ml may have a good diagnostic value for CM and would be considered as a biomarker of CM. Migraine generation may be triggered by the abnormal structure and function of the posterior HTH while the anterior HTH seemed to be associated with migraine chronification. The role of the HTH in migraine pathogenesis may be due to its connection with multiple pain processing areas and the key neuropeptide systems related to migraine. Therapeutic targets toward these peptides or abnormal HTH regions as detected in this study may be tested in future studies.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of Chinese PLA General Hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Chinese PLA General Hospital.

AUTHOR CONTRIBUTIONS

ZC conceive and wrote the paper. XC collected clinical data and wrote part of the paper. ML collected clinial data. ZC analyzed the data. LM and SY revised the paper.

FUNDING

This work was supported by supported by Hainan Provincial Natural Science Foundation of China (818MS153), the Special Financial Grant from the China Postdoctoral Science Foundation (2014T70960), the Foundation for Medical and Health Sci & Tech innovation Project of Sanya (2016YW37).

REFERENCES

1. HCCotIHS(IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* (2018) 38:1–211. doi: 10.1177/0333102417738202
2. Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. *Headache.* (2011) 51(Suppl. 2):77–83. doi: 10.1111/j.1526-4610.2011.01954.x
3. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. *Neurology.* (2009) 72:S3–7. doi: 10.1212/WNL.0b013e3181974b19
4. Lipton RB, Manack Adams A, Buse DC, Fanning KM, Reed ML. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache-related disability. *Headache.* (2016) 56:1280–9. doi: 10.1111/head.12878
5. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. *Neurol Sci.* (2017) 38:125–30. doi: 10.1007/s10072-017-2866-0
6. Alstadhaug KB. Migraine and the hypothalamus. *Cephalalgia.* (2009) 29:809–17. doi: 10.1111/j.1468-2982.2008.01814.x
7. Schulte LH, Jurgens TP, May A. Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? *J Headache Pain.* (2015) 16:14. doi: 10.1186/s10194-015-0495-7
8. van Oosterhout W, van Someren E, Schoonman GG, Louter MA, Lammers GJ, Ferrari MD, et al. Chronotypes and circadian timing in migraine. *Cephalalgia.* (2018) 38:617–25. doi: 10.1177/0333102417698953
9. Maasumi K, Tepper SJ, Kriegler JS. Menstrual migraine and treatment options: review. *Headache.* (2017) 57:194–208. doi: 10.1111/head.12978
10. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. *Headache.* (2007) 47:1418–26. doi: 10.1111/j.1526-4610.2007.00776.x
11. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain.* (2016) 139:1987–93. doi: 10.1093/brain/aww097
12. Meylakh N, Marciszewski KK, Di Pietro F, Macefield VG, Macey PM, Henderson LA. Deep in the brain: changes in subcortical function immediately preceding a migraine attack. *Hum Brain Mapp.* (2018) 39:2651–63. doi: 10.1002/hbm.24030
13. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain.* (2014) 137:232–41. doi: 10.1093/brain/awt320
14. Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: evidence from high-resolution fMRI. *Neurology.* (2017) 88:2011–16. doi: 10.1212/WNL.0000000000003963
15. Pauli WM, Nili AN, Tyszka JM. A high-resolution probabilistic *in vivo* atlas of human subcortical brain nuclei. *Sci Data.* (2017) 5:180063. doi: 10.17605/OSF.IO/JKZWP).
16. Ashburner J, Friston KJ. Voxel-based morphometry–the methods. *Neuroimage.* (2000) 11:805–21. doi: 10.1006/nimg.2000.0582
17. Chen Z, Li L, Sun J, Ma L. Mapping the brain in type II diabetes: voxel-based morphometry using DARTEL. *Eur J Radiol.* (2012) 81:1870–6. doi: 10.1016/j.ejrad.2011.04.025
18. Yan CG, Wang XD, Zuo XN, Zang YF. DPABI: data processing & analysis for (resting-state) brain imaging. *Neuroinformatics.* (2016) 14:339–51. doi: 10.1007/s12021-016-9299-4
19. Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage.* (2013) 76:183–201. doi: 10.1016/j.neuroimage.2013.03.004
20. Xie Y, Dorsky RI. Development of the hypothalamus: conservation, modification and innovation. *Development.* (2017) 144:1588–99. doi: 10.1242/dev.139055
21. Baroncini M, Jissendi P, Balland E, Besson P, Pruvo JP, Francke JP, et al. MRI atlas of the human hypothalamus. *Neuroimage.* (2012) 59:168–80. doi: 10.1016/j.neuroimage.2011.07.013
22. Burbridge S, Stewart I, Placzek M. Development of the neuroendocrine hypothalamus. *Compr Physiol.* (2016) 6:623–43. doi: 10.1002/cphy.c150023
23. Vann SD, Nelson AJ. The mammillary bodies and memory: more than a hippocampal relay. *Progr Brain Res.* (2015) 219:163–85. doi: 10.1016/bs.pbr.2015.03.006
24. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. *Neurology.* (2000) 55:1328–35. doi: 10.1212/wnl.55.9.1328
25. Iacovelli E, Coppola G, Tinelli E, Pierelli F, Bianco F. Neuroimaging in cluster headache and other trigeminal autonomic cephalalgias. *J Headache Pain.* (2012) 13:11–20. doi: 10.1007/s10194-011-0403-8
26. Qiu E, Tian L, Wang Y, Ma L, Yu S. Abnormal coactivation of the hypothalamus and salience network in patients with cluster headache. *Neurology.* (2015) 84:1402–8. doi: 10.1212/WNL.0000000000001442
27. Ferraro S, Nigri A, Bruzzone MG, Brivio L, Proietti Cecchini A, Verri M, et al. Defective functional connectivity between posterior hypothalamus and regions of the diencephalic-mesencephalic junction in chronic cluster headache. *Cephalalgia.* (2018) 2018: 1048. doi: 10.1177/0333102418761048
28. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med.* (1999) 5:836–8.
29. Lainez MJ, Guillamon E. Cluster headache and other TACs: pathophysiology and neurostimulation options. *Headache.* (2017) 57:327–35. doi: 10.1111/head.12874
30. Moulton EA, Becerra L, Johnson A, Burstein R, Borsook D. Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. *PLoS ONE.* (2014) 9:e95508. doi: 10.1371/journal.pone.0095508
31. Arkink EB, Schmitz N, Schoonman GG, van Vliet JA, Haan J, van Buchem MA, et al. The anterior hypothalamus in cluster headache. *Cephalalgia.* (2017) 37:1039–50. doi: 10.1177/0333102416660550
32. May A. Experience-dependent structural plasticity in the adult human brain. *Trends Cogn Sci.* (2011) 15:475–82. doi: 10.1016/j.tics.2011.08.002
33. Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, et al. Long-term *in vivo* imaging of experience-dependent synaptic plasticity in adult cortex. *Nature.* (2002) 420:788–94. doi: 10.1038/nature01273
34. Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M. The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends Cogn Sci.* (2013) 17:26–49. doi: 10.1016/j.tics.2012.10.011
35. Coppola G, Di Renzo A, Tinelli E, Iacovelli E, Lepre C, Di Lorenzo C, et al. Evidence for brain morphometric changes during the migraine cycle: a magnetic resonance-based morphometry study. *Cephalalgia.* (2015) 35:783–91. doi: 10.1177/0333102414559732
36. Arkink EB, Bleeker EJ, Schmitz N, Schoonman GG, Wu O, Ferrari MD, et al. Cerebral perfusion changes in migraineurs: a voxelwise comparison of interictal dynamic susceptibility contrast MRI measurements. *Cephalalgia.* (2012) 32:279–88. doi: 10.1177/0333102411435985
37. Woods RP, Iacoboni M, Mazziotta JC. Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. *N Engl J Med.* (1994) 331:1689–92. doi: 10.1056/NEJM199412223312505
38. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol.* (2004) 72:341–72. doi: 10.1016/j.pneurobio.2004.03.006
39. Biagianti B, Grazzi L, Gambini O, Usai S, Muffatti R, Scarone S, et al. Orbitofrontal dysfunction and medication overuse in patients with migraine. *Headache.* (2012) 52:1511–9. doi: 10.1111/j.1526-4610.2012.02277.x
40. Fuh JL, Wang SJ. Dependent behavior in patients with medication-overuse headache. *Curr Pain Headache Rep.* (2012) 16:73–9. doi: 10.1007/s11916-011-0240-0
41. Gomez-Beldarrain M, Carrasco M, Bilbao A, Garcia-Monco JC. Orbitofrontal dysfunction predicts poor prognosis in chronic migraine with medication overuse. *J Headache Pain.* (2011) 12:459–66. doi: 10.1007/s10194-011-0340-6
42. Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, et al. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain.* (2006) 129:543–50. doi: 10.1093/brain/awh691
43. Lai TH, Chou KH, Fuh JL, Lee PL, Kung YC, Lin CP, et al. Gray matter changes related to medication overuse in patients with chronic migraine. *Cephalalgia.* (2016) 36:1324–33. doi: 10.1177/0333102416630593

44. Coppola G, Petolicchio B, Di Renzo A, Tinelli E, Di Lorenzo C, Parisi V, et al. Cerebral gray matter volume in patients with chronic migraine: correlations with clinical features. *J Headache Pain.* (2017) 18:115. doi: 10.1186/s10194-017-0825-z
45. Rempel-Clower NL, Barbas H. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J Comp Neurol.* (1998) 398:393–419.
46. Hirose S, Osada T, Ogawa A, Tanaka M, Wada H, Yoshizawa Y, et al. Lateral-medial dissociation in orbitofrontal cortex-hypothalamus connectivity. *Front Hum Neurosci.* (2016) 10:244. doi: 10.3389/fnhum.2016.00244
47. Camara-Lemarroy CR, Rodriguez-Gutierrez R, Monreal-Robles R, Marfil-Rivera A. Gastrointestinal disorders associated with migraine: a comprehensive review. *World J Gastroenterol.* (2016) 22:8149–60. doi: 10.3748/wjg.v22.i36.8149
48. Malick A, Strassman RM, Burstein R. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J Neurophysiol.* (2000) 84:2078–112. doi: 10.1152/jn.2000.84.4.2078
49. Costa A, Antonaci F, Ramusino MC, Nappi G. The neuropharmacology of cluster headache and other trigeminal autonomic cephalalgias. *Curr Neuropharmacol.* (2015) 13:304–23. doi: 10.2174/1570159x13666150309233556
50. Strother LC, Srikiatkhachorn A, Supronsinchai W. Targeted orexin and hypothalamic neuropeptides for migraine. *Neurotherapeutics.* (2018) 15:377–90. doi: 10.1007/s13311-017-0602-3
51. Vandesande F, Dierickx K. Identification of the vasopressin producing and of the oxytocin producing neurons in the hypothalamic magnocellular neurosecretroy system of the rat. *Cell Tissue Res.* (1975) 164:153–62.
52. Tzabazis A, Kori S, Mechanic J, Miller J, Pascual C, Manering N, et al. Oxytocin and migraine headache. *Headache.* (2017) 57 64–75. doi: 10.1111/head.13082
53. Tzabazis A, Mechanic J, Miller J, Klukinov M, Pascual C, Manering N, et al. Oxytocin receptor: expression in the trigeminal nociceptive system and potential role in the treatment of headache disorders. *Cephalalgia.* (2016) 36:943–50. doi: 10.1177/0333102415618615
54. Waschek JA, Baca SM, Akerman S. PACAP and migraine headache: immunomodulation of neural circuits in autonomic ganglia and brain parenchyma. *J Headache Pain.* (2018) 19:23. doi: 10.1186/s10194-018-0850-6
55. Guo S, Vollesen AL, Hansen RD, Esserlind AL, Amin FM, Christensen AF, et al. Part I: pituitary adenylate cyclase-activating polypeptide-38 induced migraine-like attacks in patients with and without familial aggregation of migraine. *Cephalalgia.* (2017) 37:125–35. doi: 10.1177/0333102416639516
56. Tfelt-Hansen PC. PACAP-induced migraine: a possible CNS effect? *Brain.* (2014) 137:e304. doi: 10.1093/brain/awu166
57. Vollesen ALH, Amin FM, Ashina M. Targeted pituitary adenylate cyclase-activating peptide therapies for migraine. *Neurotherapeutics.* (2018) 15:371–76. doi: 10.1007/s13311-017-0596-x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 14 June 2019
doi: 10.3389/fneur.2019.00615

Structural and Functional Brain Alterations in Post-traumatic Headache Attributed to Mild Traumatic Brain Injury: A Narrative Review

*Todd J. Schwedt**

Department of Neurology, Mayo Clinic, Scottsdale, AZ, United States

Introduction: By definition, post-traumatic headache (PTH) attributed to mild traumatic brain injury (mTBI) is not associated with brain structural abnormalities that are seen on routine clinical inspection of brain images. However, subtle brain structural abnormalities, as well as functional abnormalities, detected via research imaging techniques yield insights into the pathophysiology of PTH. The objective of this manuscript is to summarize published findings regarding research imaging of the brain in PTH attributed to mTBI.

Methods: For this narrative review, PubMed was searched using the terms "post-traumatic headache" or "post-concussion headache" and "imaging" or "magnetic resonance imaging" or "research imaging" or "positron emission tomography". Articles were chosen for inclusion based on their relevance to the topic.

Results: Ten articles were ultimately included within this review. The studies investigated white matter tract integrity and functional connectivity in acute PTH, structural measures, white matter tract integrity, cerebral blood flow, and functional connectivity in persistent PTH (PPTH), and proton spectroscopy in both acute and persistent PTH. The articles demonstrate that acute and persistent PTH are associated with abnormalities in brain structure, that acute and persistent PTH are also associated with abnormalities in brain function, that it might be possible to predict the persistence of PTH using brain imaging findings, and that there are differences in imaging findings when comparing PTH to healthy controls and when comparing PTH to migraine. Although it is not entirely clear if the imaging findings are directly attributable to PTH as opposed to the underlying TBI or other post-TBI symptoms, correlations between the imaging findings with headache frequency and headache resolution suggest a true relationship between the imaging findings and PTH.

Conclusions: PTH attributed to mTBI is associated with abnormalities in brain structure and function that can be detected via research imaging. Additional studies are needed to determine the specificity of the findings for PTH, to differentiate findings attributed to PTH from those attributed to the underlying TBI and coexistent post-TBI symptoms, and to determine the accuracy of imaging findings for predicting the development of PPTH.

Keywords: post-traumatic headache, traumatic brain injury, concussion, brain imaging, migraine, functional magnetic resonance imaging, diffusion tensor imaging, functional connectivity

OPEN ACCESS

Edited by:
Massimo Filippi,
Vita-Salute San Raffaele University, Italy

Reviewed by:
Gianluca Coppola,
Fondazione G. B. Bietti (IRCCS), Italy
Marco Carotenuto,
Università degli Studi della Campania Luigi Vanvitelli Caserta, Italy

***Correspondence:**
Todd J. Schwedt
schwedt.todd@mayo.edu

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *01 April 2019*
Accepted: *24 May 2019*
Published: *14 June 2019*

Citation:
Schwedt TJ (2019) Structural and Functional Brain Alterations in Post-traumatic Headache Attributed to Mild Traumatic Brain Injury: A Narrative Review. Front. Neurol. 10:615. doi: 10.3389/fneur.2019.00615

INTRODUCTION

Post-traumatic headache (PTH) attributed to traumatic injury to the head is defined by the International Classification of Headache Disorders 3 (ICHD-3) as a headache that is reported to have developed within 7 days of the head injury, regaining consciousness following the head injury, or discontinuation of medication(s) impairing the ability to sense or report headache following the head injury (1). PTH can be a new headache that develops after the injury or it can be significant worsening of a pre-existing headache, such as when there is substantial worsening of migraine patterns following the injury. PTH is considered "acute" when it has been present for 3 months or less, and "persistent" when it has been present for more than 3 months. According to the ICHD-3, PTH can be attributed to mild traumatic head (brain) injury or to moderate or severe traumatic head (brain) injury. An essential component of the ICHD-3 definition for mild traumatic brain injury (mTBI) is that there is no imaging evidence of a traumatic head injury such as skull fracture, intracranial hemorrhage, and/or brain contusion. Thus, by this definition, brain images from individuals with mTBI are clinically interpreted as "normal." However, as discussed within this article, advanced imaging techniques and imaging data analyses reveal abnormalities in brain structure and function in individuals with PTH attributed to mTBI.

PTH is a highly prevalent symptom following TBI; likely, it is the most common acute and persistent symptom following mTBI (2). Although PTH may be the only symptom during the acute and persistent phases following TBI, often PTH is accompanied by cognitive, mood, sleep, and autonomic symptoms (3, 4). The phenotype of PTH most commonly resembles that of migraine, due to the presence of moderate to severe headache and sensory hypersensitivities, or tension-type headache, although less commonly it resembles other primary headaches (5, 6). Given the phenotypic overlap with primary headaches, like migraine, it is presumed that there are shared underlying mechanisms between PTH and the primary headaches.

Given the high incidence of PTH following TBI, the significant impact that PTH has on individuals, and the absence of PTH-specific therapies, it is essential that we continue to investigate mechanisms for acute PTH and PTH persistence. Research neuroimaging of brain structure and function is one useful method by which to conduct such investigations. In this manuscript, published findings from research neuroimaging studies of acute and persistent PTH are summarized and interpreted, and future directions are discussed.

METHODS

For this narrative review, articles were identified by searching PubMed using the terms "post-traumatic headache" or "post-concussion headache" and "imaging" or "magnetic resonance imaging" or "research imaging" or "positron emission tomography." The resulting list was reviewed by the author and abstracts and full manuscripts were further reviewed based on the author's judgment of the relevance of each article to the topic. The reference lists of each selected article were reviewed to identify additional publications not identified via the PubMed search. Ultimately, 10 articles were included in this Review.

IMAGING ACUTE PTH (TABLE 1)

Diffusion tensor imaging (DTI) allows for assessment of white matter integrity. Alhilali and colleagues performed a DTI analysis of 58 individuals who had PTH of a migraine phenotype attributed to mTBI vs. 17 individuals who had mTBI without PTH of a migraine phenotype (although they could have PTH of a non-migraine phenotype) (7). The median time from injury to evaluation was 20 days. The cohort with PTH of a migraine phenotype had lower fractional anisotropy (FA) in the corpus callosum and fornix/septohippocampal circuit. Furthermore, FA within regions of the fornix/septohippocampal circuit correlated positively with visual memory performance ($r = 0.325$, $p = 0.01$). The corpus callosum and the fornix/septohippocampal circuit have previously been implicated in migraine or cortical spreading depression pathophysiology (10, 11). A major strength of this study is the use of a mTBI group without PTH of a migraine phenotype as a comparator group, theoretically controlling for potential effects of the mTBI on white matter tract integrity. However, it is not clear what proportion of this control group had PTH of a phenotype other than migraine and how the presence of such headaches could impact DTI findings. Furthermore, the correlation between DTI measures in the fornix/septohippocampal circuit with visual memory performance could suggest that the DTI finding is not (entirely) related to the presence of PTH of a migraine phenotype.

A principal components analysis of DTI FA data was performed to identify white matter injury patterns associated with PTH attributed to mTBI (9). Sixty-four patients with mTBI were included, 40 with PTH and 24 without PTH. Median duration between injury and presentation was between 3 and 4 weeks. A principal component that included decreased FA in the splenium and increased FA in the genu of the corpus callosum was associated with an increased risk of PTH (odds ratio 2.32, 95% confidence interval 1.29–4.67, $p = 0.01$). This principal component accurately classified those who had PTH with an area under the curve of 0.73.

Delic and colleagues investigated the performance of a classifier based on Shannon entropy (SE) that used FA DTI data in differentiating individuals who had PTH of a migraine phenotype attributed to mTBI from those who had mTBI without PTH of a migraine phenotype and from healthy controls (8). SE measures the complexity of a dataset—the more information or complexity within a dataset, the higher the SE. In the realm of white matter integrity, higher SE of FA data could be reflective of a mixed pattern of white matter tract injury, swelling, and remyelination. It has been hypothesized that SE provides a more accurate measurement of axonal changes that occur after neurologic injury. For this analysis, 57 participants with mTBI and PTH of a migraine phenotype, 17 with mTBI without PTH

TABLE 1 | Imaging findings during acute post-traumatic headache.

References	PTH phase	Imaging modality or sequence	Comparison group(s)	Main findings
Alhilali et al. (7)	Acute	DTI	mTBI with PTH of migraine phenotype vs. mTBI without PTH of migraine phenotype	PTH of migraine phenotype: lower FA in corpus callosum and fornix/septohippocampal circuit.
Delic et al. (8)	Acute	DTI	1) mTBI with PTH of migraine phenotype vs. mTBI without PTH of migraine phenotype 2) mTBI with PTH of migraine phenotype vs. migraine controls and vs. HC	mTBI with PTH of migraine phenotype vs. all other groups: lower SE of FA data Inverse correlation between SE and time to recovery. Accuracy for differentiating PTH of migraine phenotype from a) controls: specificity 95%, sensitivity 77% b) mTBI without PTH of a migraine phenotype: specificity 75%, sensitivity 81%
Ghodadra et al. (9)	Acute	DTI	mTBI with PTH vs. mTBI without PTH	PTH: lower FA in splenium of corpus callosum; higher FA in genu of corpus callosum

Diffusion tensor imaging studies demonstrate anomalies in white matter tract integrity in acute PTH due to mild traumatic brain injury.
DTI, diffusion tensor imaging; mTBI, mild traumatic brain injury; PTH, post-traumatic headache; FA, fractional anisotropy; HC, healthy control subject; SE, Shannon Entropy.

TABLE 2 | Imaging studies that investigated acute and persistent post-traumatic headache or prediction of persistent post-traumatic headache.

References	PTH phase	Imaging modality or sequence	Comparison group(s)	Main findings
Obermann et al. (12)*	1) Acute 2) Persistent	Gray matter density	1) Acute PTH vs. HC 2) PTH-acute vs. persistent	Acute PTH vs. HC: no differences PPTH vs. HC: less gray matter density in anterior cingulate cortex and dorsolateral prefrontal cortex in PPTH 12 months: those who had PPTH at 3 months, but resolved prior to 12 months had normal gray matter density
Sarmento et al. (13)	1) Acute 2) Persistent	MRS	HC	Reduced NAA/creatinine in frontal lobes (anterior, anterior and posterior medial), parietal lobes (medial). Increased choline/creatinine in frontal lobes (posterior, anterior medial), parietal lobes (medial).
Niu et al. (14)	Acute: predicting development of PPTH	Functional connectivity	PPTH vs. PTH resolution during acute phase	Connectivity of PAG with inferior parietal lobule and with precuneus predicted persistence of PTH: 100% sensitivity and 78% specificity

A study of gray matter density in those with PTH attributed to whiplash showed less gray matter in PPTH, but not acute PTH, compared with healthy controls. An MRS study that combined individuals with acute PTH with those who had PPTH into one group, found evidence for reduced neuronal vitality, increased membrane turnover and cell proliferation in PTH. A functional connectivity study demonstrated promise for using measures of periaqueductal gray connectivity for predicting the persistence of PTH.
*PTH, post-traumatic headache; HC, healthy control subject; MRS, magnetic resonance spectroscopy; NAA, N-acetylspartate; PPTH, persistent post-traumatic headache; PAG, periaqueductal gray. *PTH attributed to whiplash.*

of a migraine phenotype, 22 healthy control subjects, and 20 control subjects with migraine were included. All mTBI patients had acute PTH with a median time from injury to clinical presentation of 20 days and with 83% of patients presenting within 2 months of injury. Those with mTBI were found to have lower SE compared to controls and there was an inverse correlation between SE and time to patient recovery. PTH of a migraine phenotype was associated with lower SE compared to mTBI without PTH of a migraine phenotype. SE measures provided high accuracy for differentiating those with mTBI from controls (Area under the curve = 0.92, specificity 95%, sensitivity 77%) and for differentiating mTBI with PTH of a migraine phenotype from mTBI without PTH of a migraine phenotype (Area under the curve = 0.85, specificity 75%, sensitivity 81%). This study suggests that SE analyses of DTI data may be particularly useful for investigating white matter pathology and repair following mTBI and for building classification models (i.e., diagnostic biomarkers) for PTH.

COMBINED STUDY OF ACUTE AND PERSISTENT PTH USING MR SPECTROSCOPY (TABLE 2)

MRI proton spectroscopy (MRS) was used to compare N-acetylspartate (NAA, an indicator of neuronal vitality) and choline (a marker of membrane turnover) ratios with creatinine in 17 individuals with PTH attributed to mTBI vs. 12 healthy controls (13). Nine individuals had acute PTH while the remaining 8 had PPTH. Compared to controls, PTH was associated with reduced NAA/creatinine in the anterior regions of the frontal lobe white matter, anterior and posterior medial

regions of the frontal lobes, and medial regions of the parietal lobes. Choline/creatinine was increased in regions of the posterior frontal lobe white matter, anterior medial frontal lobe, and medial parietal lobes. Authors concluded that decreased NAA is suggestive of reduced neuronal vitality, likely due to the underlying head trauma, while the increased choline is a marker of membrane turnover and cell proliferation developing around the injured neurons.

PREDICTING THE PERSISTENCE OF PTH USING BRAIN IMAGING

Fortunately, many individuals with acute PTH have headache resolution during the first few days to weeks following PTH onset and thus do not have persistence of PTH (2). However, up to 60% do not have PTH resolution, their PTH endures for more than 3 months, and they are classified as having PPTH (2). The ability to predict who will have persistence of PTH could be valuable for several reasons: (1) those at high risk for PPTH might benefit from closer clinical follow-up; (2) early intervention might reduce the impact of PTH and might prevent PTH persistence (although specific interventions for preventing PTH persistence have yet to be identified); and (3) those individuals at high risk for PPTH would be appropriate for clinical trials of therapeutics aimed at treating acute PTH and reducing the risk for PTH persistence.

An MRI resting-state functional connectivity study by Niu and colleagues suggests that prediction of PPTH is possible (14). In this study, 54 patients with mTBI and acute PTH had brain MRIs including functional connectivity measurements within 7 days of their injury, and they had a 3-month follow-up evaluation to assess for PTH persistence. Investigators analyzed functional connectivity with the right ventrolateral periaqueductal gray (PAG), since this region has been shown to have abnormal connectivity in other pain studies, since it is vulnerable to mTBI, and since it plays a role in opioid antinociception (15–17). At baseline, compared to healthy controls, those with acute PTH had weaker right ventrolateral PAG functional connectivity with several regions of the default mode network, including regions in the right and left precuneus, right inferior parietal lobule, and right angular gyrus, and stronger connectivity with a region in the left middle temporal gyrus. There were significant negative correlations between PAG with right precuneus connectivity and Headache Impact Test 6 scores and between PAG with right inferior parietal lobule and Headache Impact Test 6 scores when measured at baseline. Furthermore, baseline connectivity between the PAG with the right inferior parietal lobule and with the right precuneus were predictors for having persistence of PTH measured at 3 months. A logistic regression model including age, sex, years of education, loss of consciousness duration, and functional connectivity of the PAG with the default mode network predicted PPTH with 100% sensitivity (95% confidence interval (CI) 66%−100%) and 78% specificity (95% CI 63%−89%). This study demonstrates that acute PTH is associated with altered functional connectivity of the PAG with regions of the default mode network, that the connectivity strength correlates with PTH burden, and that functional connectivity measured during the acute post-TBI phase contributes to prediction of PTH persistence.

IMAGING PERSISTENT PTH (TABLE 3)

An MRI study by Chong and colleagues compared vertex-by-vertex cortical thickness measurements in 33 patients with PPTH due to mTBI with 33 healthy controls (18). Those with PPTH had a median of 7 years with PPTH and 16 days per month with headache and had no history of migraine prior to TBI. After adjustment for several factors that could impact cortical thickness, including age, sex, depression scores, and anxiety scores, the PPTH group had significantly less cortical thickness in left and right frontal (superior frontal, caudal middle frontal, precentral) and right parietal (precuneus, supramarginal, inferior parietal, superior parietal) regions compared to healthy controls. Considering these regions that differed between subject groups, there were significant negative correlations between the thickness of the left and right superior frontal regions with headache frequency. There were no significant correlations between the cortical thickness of these regions and years lived with PPTH. These findings suggest a relationship between the severity of PTH (measured as headache frequency in this case) with brain structure. Relationships between the severity of post-TBI symptoms with measures of brain structure have been suggested in other studies, although not specifically investigating PTH (23, 24). The association between headache frequency with cortical thickness, but not years of PTH with cortical thickness, at least suggests that the finding of less cortical thickness is attributable to PTH as opposed to the underlying mTBI.

Studies that compare brain imaging findings in those with PPTH to individuals with other headache types, like migraine, can provide insights into shared and distinct pathophysiology. Regional cerebral blood flow, measured by the xenon-133 inhalation technique, was investigated in 35 individuals with PPTH attributed to mTBI vs. 49 non-headache controls and 92 individuals with migraine (20). Compared to healthy controls and individuals with migraine, those with PPTH had reduced regional cerebral blood flow, and greater regional and hemispheric asymmetries. The authors suggested that cerebral blood flow changes and vasomotor instability may be contributing mechanisms to the development of PTH and other post-TBI symptoms.

An MRI investigation of regional volumes, cortical thickness, surface area, and brain curvature found structural differences between PPTH and migraine cohorts in the right lateral orbitofrontal lobe, left caudal middle frontal lobe, left superior frontal lobe, left precuneus, and right supramarginal gyrus (21). Amongst these regions that differed between PPTH and migraine, the structure of regions in the right lateral orbitofrontal lobe, right supramarginal gyrus, and left superior frontal lobe also differed between PPTH and healthy controls who had no history of head trauma or migraine. A DTI study by Chong and colleagues investigated node-by-node white matter tract integrity in PPTH vs. migraine and vs. healthy controls (19).

TABLE 3 | Imaging findings during persistent post-traumatic headache.

References	PTH phase	Imaging modality or measure	Comparison group(s)	Main findings
Chong et al. (18)	Persistent	Cortical thickness	HC	Less thickness in frontal (superior, caudal middle, precentral) and parietal lobes (precuneus, supramarginal, inferior, superior). Negative correlations between superior frontal thickness with headache frequency.
Chong et al. (19)	Persistent	DTI	1) Migraine 2) HC	vs. Migraine: DTI differences in anterior thalamic radiations, cingulum, inferior and superior longitudinal fasciculi, uncinate fasciculi, corticospinal tract. Positive correlation between cingulum angular bundle MD and RD with headache frequency. vs. HC: DTI differences in anterior thalamic radiations, cingulum, corticospinal tract, inferior longitudinal fasciculus, uncinate fasciculus, forceps major and minor.
Gilkey et al. (20)	Persistent	CBF	1) Migraine 2) HC	vs. Migraine + HC: reduced regional CBF; greater regional and hemispheric CBF asymmetries.
Schwedt et al. (21)	Persistent	Regional volumes, cortical thickness, surface area, curvature	1) Migraine 2) HC	vs. Migraine: structural differences in frontal (lateral orbitofrontal, caudal middle, superior) and parietal lobes (precuneus, supramarginal). vs. HC (only considering regions that differed between PPTH vs. Migraine): frontal (lateral orbitofrontal, superior) and parietal lobes (supramarginal).
Dumkrieger et al. (22)	Persistent	Static and dynamic functional connectivity	1) Migraine 2) HC	vs. Migraine (static connectivity): 17 region pairs that included somatosensory, insula, hypothalamus, anterior and middle cingulate, temporal pole, supramarginal, superior parietal, middle occipital, lingual, pulvinar, precuneus, cuneus, somatomotor, ventromedial prefrontal, and dorsolateral prefrontal regions. Correlations between years with headache and headache frequency with static connectivity of a few region pairs. vs. Migraine (dynamic connectivity): 10 region pairs that included somatosensory, hypothalamus, middle cingulate, temporal pole, supramarginal, superior parietal, lingual gyrus, somatomotor, precentral, posterior cingulate, middle frontal, fusiform, parieto-occipital, and amygdala regions. Correlations between headache frequency and pain intensity with dynamic connectivity with a couple region pairs. vs. HC (only considering regions that differed between PPTH vs. Migraine; static connectivity): dorsolateral prefrontal, ventromedial prefrontal, middle cingulate, somatomotor, pulvinar, insula, hypothalamus. vs. HC (only considering regions that differed between PPTH vs. Migraine; dynamic connectivity): somatosensory, lingual, middle cingulate, supramarginal, temporal pole, middle frontal.

Studies investigating brain structure and regional cerebral blood flow demonstrate differences between those with PPTH vs. healthy controls and vs. those with migraine. Correlations between some of the structural measures with headache frequency provide additional evidence for a relationship between the structural changes with PPTH.
HC, healthy control subject; DTI, diffusion tensor imaging; MD, mean diffusivity; RD, radial diffusivity; CBF, cerebral blood flow; PPTH, persistent post-traumatic headache.

DTI measures (mean diffusivity or radial diffusivity) differed in PPTH vs. migraine for several white matter tracts including the anterior thalamic radiations, cingulum, inferior longitudinal fasciculi, uncinate fasciculi, corticospinal tract, and superior longitudinal fasciculi. Amongst those with PPTH there was a positive correlation between cingulum angular bundle mean diffusivity and radial diffusivity with headache frequency, a relationship not seen amongst those with migraine. A study by Dumkrieger and colleagues compared static and dynamic functional connectivity of 59 regions of interest involved in pain processing in PPTH vs. migraine (22). Between group differences in static and dynamic functional connectivity were identified for several regions and correlations between connectivity strength and headache burden (i.e., years with headache, headache frequency) were found. These studies demonstrate that despite significant overlap in symptoms between migraine and PPTH (89–96% of those with PPTH in these studies had a phenotype consistent with "migraine" or "probable migraine"), there are identifiable differences in brain structure and function, perhaps suggesting distinct underlying pathophysiology. Further studies are necessary to determine the specificity of the differences for PPTH and to determine if the findings are directly related to PPTH vs. being attributable to the underlying mTBI irrespective of PPTH.

LIMITATIONS AND FUTURE DIRECTIONS

One of the biggest challenges in research imaging of PTH is differentiating imaging findings associated with PTH vs. those attributable to the underlying TBI vs. those associated with other post-TBI symptoms. mTBI is associated with acute, subacute and perhaps even chronic changes in brain structure

and function (25). The persistence of post-TBI symptoms is associated with the presence and duration of these imaging abnormalities (26, 27). When symptoms are present, PTH is often just one symptom of many that the individual with mTBI experiences. In addition to PTH, mTBI is often associated with alterations in mood, cognition, sleep patterns, and non-headache pain (28). The presence of brain imaging abnormalities due to the mTBI itself and the common scenario of PTH being one of a constellation of symptoms, makes it challenging to isolate the brain imaging findings associated with PTH from those associated with the mTBI or other symptoms. Research designs that include cohorts who have mTBI without active symptoms and mTBI with symptoms not including headache, as well as longitudinal designs that include imaging before and after resolution of symptoms could help identify imaging findings specifically associated with PTH.

Additional studies are necessary to determine if imaging findings associated with PTH are shared by primary headaches, by other secondary headaches, or by non-headache pain types, or if there are imaging findings that are specific for PTH. This determination would lend insights into the pathophysiology of PTH and could contribute to the objective classification of PTH via models that include brain imaging data.

It is not yet known if the mechanism of brain injury leading to PTH impacts research imaging findings. A study by Obermann and colleagues measured regional gray matter using voxel based morphometry in 32 patients who had PTH attributed to whiplash (12). In this longitudinal study, patients were imaged within 14 days of injury and again after 3 months; those with headaches that lasted longer than 3 months ($n = 12$) were imaged again at 1 year post-injury. When imaged within the first 14 days post-injury, there were no significant regional differences in gray matter density between those with PTH and controls. For those who went on to have PPTH, there were significant decreases in gray matter density in the anterior cingulate cortex and dorsolateral prefrontal cortex when comparing the 14 days to 3 months post-injury scans. The 3-month changes in gray matter density resolved by 1 year, coinciding with headache resolution in all but one patient. The temporal correlation between the structural findings with the presence, persistence and resolution of PTH strongly suggest that the imaging findings are directly related to PTH. Furthermore, although no direct comparisons have been made between PTH attributed to whiplash with PTH attributed to TBI, the anterior cingulate cortex and dorsolateral prefrontal cortex are regions that have been commonly identified as participating in headache physiology as well as non-headache pain physiology (29, 30).

The ability to predict which individuals with acute PTH will have persistence of PTH would be a major advance for the clinical management of individuals with acute PTH and for optimizing enrollment of individuals into clinical trials of PTH therapeutics. Although much work needs to be done to understand the optimal treatments for acute and persistent PTH, presumably, the early identification of the patient who is likely to have persistence of PTH would allow for earlier and more aggressive management of acute PTH with pharmacologic and non-pharmacologic therapies. Earlier therapeutic intervention might be more effective than treatment that is started after PTH has already become persistent and might even prevent the persistence of PTH. Furthermore, to reduce unnecessary risks and to limit required patient sample sizes, it would be optimal if clinical trials of preventive therapies for acute PTH could enroll patients who are at high risk of having PTH persistence, excluding those likely to have natural PTH resolution. A prognostic biomarker for PPTH could assist with appropriate enrollment into such clinical trials.

CONCLUSIONS

Research neuroimaging is starting to provide insights into the pathophysiology of acute and persistent PTH. Further work is needed to determine if there are imaging findings that are specific to PTH, as opposed to being attributable to the underlying trauma or post-injury symptoms that accompany PTH. Determining the specificity of imaging findings for PTH will deepen our understanding of PTH pathophysiology and might contribute to the ability to diagnostically classify new onset PTH from worsening of a pre-injury primary headache. Furthermore, imaging might contribute to models that predict which individuals with acute PTH are likely to develop PPTH, a prediction that would be useful for determining how aggressive to manage those with acute PTH and for determining a cohort of individuals who would be most appropriate for clinical trials of PTH therapeutics.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202
2. Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. *Cephalalgia*. (2014) 34:93–102. doi: 10.1177/0333102413499645
3. Dwyer B. Posttraumatic headache. *Semin Neurol*. (2018) 38:619–26. doi: 10.1055/s-0038-1673692
4. Howard L, Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Symptoms of autonomic dysfunction among those with persistent posttraumatic headache attributed to mild traumatic brain injury: a comparison to migraine and healthy controls. *Headache*. (2018) 58:1397–407. doi: 10.1111/head.13396
5. Lane R, Davies P. Post traumatic headache (PTH) in a cohort of UK compensation claimants. *Cephalalgia*. (2018) 39:641–7. doi: 10.1177/0333102418812091
6. Lucas S, Ahn AH. Posttraumatic headache: classification by symptom-based clinical profiles. *Headache*. (2018) 58:873–82. doi: 10.1111/head.13311

7. Alhilali LM, Delic J, Fakhran S. Differences in callosal and forniceal diffusion between patients with and without postconcussive migraine. *Am J Neuroradiol*. (2017) 38:691–5. doi: 10.3174/ajnr.A5073
8. Delic J, Alhilali LM, Hughes MA, Gumus S, Fakhran S. White matter injuries in mild traumatic brain injury and posttraumatic migraines: diffusion entropy analysis. *Radiology*. (2016) 279:859–66. doi: 10.1148/radiol.2015151388
9. Ghodadra A, Alhilali L, Fakhran S. Principal component analysis of diffusion tensor images to determine white matter injury patterns underlying postconcussive headache. *Am J Neuroradiol*. (2016) 37:274–8. doi: 10.3174/ajnr.A4505
10. Yuan K, Qin W, Liu P, Zhao L, Yu D, Zhao L, et al. Reduced fractional anisotropy of corpus callosum modulates inter-hemispheric resting state functional connectivity in migraine patients without aura. *PLoS ONE*. (2012) 7:e45476. doi: 10.1371/journal.pone.0045476
11. Moskowitz MA, Nozaki K, Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. *J Neurosci*. (1993) 13:1167–77. doi: 10.1523/JNEUROSCI.13-03-01167.1993
12. Obermann M, Nebel K, Schumann C, Holle D, Gizewski ER, Maschke M, et al. Gray matter changes related to chronic posttraumatic headache. *Neurology*. (2009) 73:978–83. doi: 10.1212/WNL.0b013e3181b8791a
13. Sarmento E, Moreira P, Brito C, Souza J, Jevoux C, Bigal M. Proton spectroscopy in patients with post-traumatic headache attributed to mild head injury. *Headache*. (2009) 49:1345–52. doi: 10.1111/j.1526-4610.2009.01494.x
14. Niu X, Bai L, Sun Y, Wang S, Cao J, Sun C, et al. Disruption of periaqueductal grey-default mode network functional connectivity predicts persistent post-traumatic headache in mild traumatic brain injury. *J Neurol Neurosurg Psychiatry*. (2019) 90:326–32. doi: 10.1136/jnnp-2018-318886
15. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci*. (1984) 7:309–38. doi: 10.1146/annurev.ne.07.030184.001521
16. Jang SH, Park SM, Kwon HG. Relation between injury of the periaqueductal gray and central pain in patients with mild traumatic brain injury: observational study. *Medicine*. (2016) 95:e4017. doi: 10.1097/MD.0000000000004017
17. Chen Z, Chen X, Liu M, Liu S, Ma L, Yu S. Disrupted functional connectivity of periaqueductal gray subregions in episodic migraine. *J Headache Pain*. (2017) 18:36. doi: 10.1186/s10194-017-0747-9
18. Chong CD, Berisha V, Chiang CC, Ross K, Schwedt TJ. Less cortical thickness in patients with persistent post-traumatic headache compared with healthy controls: an MRI study. *Headache*. (2018) 58:53–61. doi: 10.1111/head.13223
19. Chong CD, Peplinski J, Berisha V, Ross K, Schwedt TJ. Differences in fibertract profiles between patients with migraine and those with persistent post-traumatic headache. *Cephalalgia*. (2019) 2019:333102418815650. doi: 10.1177/0333102418815650
20. Gilkey SJ, Ramadan NM, Aurora TK, Welch KM. Cerebral blood flow in chronic posttraumatic headache. *Headache*. (1997) 37:583–7. doi: 10.1046/j.1526-4610.1997.3709583.x
21. Schwedt TJ, Chong CD, Peplinski J, Ross K, Berisha V. Persistent post-traumatic headache vs. migraine: an MRI study demonstrating differences in brain structure. *J Headache Pain*. (2017) 18:87. doi: 10.1186/s10194-017-0796-0
22. Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Static and dynamic functional connectivity differences between migraine and persistent post-traumatic headache: a resting-state magnetic resonance imaging study. *Cephalalgia*. (2019) 2019:333102419847728. doi: 10.1177/0333102419847728
23. Albaugh MD, Orr C, Nickerson JP, Zweber C, Slauterbeck JR, Hipko S, et al. Postconcussion symptoms are associated with cerebral cortical thickness in healthy collegiate and preparatory school ice hockey players. *J Pediatr*. (2015) 166:394–400 e1. doi: 10.1016/j.jpeds.2014.10.016
24. D'Souza MM, Trivedi R, Singh K, Grover H, Choudhury A, Kaur P, et al. Traumatic brain injury and the post-concussion syndrome: a diffusion tensor tractography study. *Indian J Radiol Imaging*. (2015) 25:404–14. doi: 10.4103/0971-3026.169445
25. Chong CD, Schwedt TJ. Research imaging of brain structure and function after concussion. *Headache*. (2018) 58:827–35. doi: 10.1111/head.13269
26. Messe A, Caplain S, Pelegrini-Issac M, Blancho S, Montreuil M, Lévy R, et al. Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. *Brain Imaging Behav*. (2012) 6:283–92. doi: 10.1007/s11682-012-9159-2
27. Hartikainen KM, Waljas M, Isoviita T, Dastidar P, Liimatainen S, Solbakk AK, et al. Persistent symptoms in mild to moderate traumatic brain injury associated with executive dysfunction. *J Clin Exp Neuropsychol*. (2010) 32:767–74. doi: 10.1080/13803390903521000
28. Ruff RL, Riechers RG II, Wang XF, Piero T, Ruff SS. A case-control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI. *BMJ Open*. (2012) 2:e000312. doi: 10.1136/bmjopen-2011-000312
29. Becerra L, Veggeberg R, Prescot A, Jensen JE, Renshaw P, Scrivani S, et al. A 'complex' of brain metabolites distinguish altered chemistry in the cingulate cortex of episodic migraine patients. *Neuroimage Clin*. (2016) 11:588–94. doi: 10.1016/j.nicl.2016.03.020
30. Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci*. (2005) 6:533–44. doi: 10.1038/nrn1704

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 06 September 2019
doi: 10.3389/fneur.2019.00961

Is There Any MRI Pattern That Discriminates Female From Male Migraine Patients?

Nasim Maleki[1]* *and Xiao Michelle Androulakis*[2,3]

[1] Psychiatric Neuroimaging Division, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2] Columbia VA Health Care System, Columbia, SC, United States, [3] Department of Neurology, School of Public Health, University of South Carolina, Columbia, SC, United States

There has been accumulating evidence on sex disparity in incidence, prevalence, symptomology, and burden of migraine. Several neuroimaging studies on migraine patients attempted to unravel the mechanisms of the disease, yet very few of them examined the sex-related differences. Here, we will first discuss some of the reported neuroimaging patterns that discriminate females from males in migraine. We will then re-examine the salient neuroimaging findings in migraine and discuss them in relation to sex-related influences. Finally, we will discuss some of the intriguing recent data suggesting the presence of sex-specific traits in migraineurs. These findings may have potential implications for future neuroimaging studies to identify underlying correlating patterns in the brain to (1) explain the neural basis for higher prevalence of migraine in women, and (2) better understand migraine-specific changes during different stages of life in both men and women.

Keywords: brain, neuroimaging, magnetic resonance imaging, sex, migraine, sex-related differences

OPEN ACCESS

Edited by:
Massimo Filippi, Vita-Salute San Raffaele University, Italy

Reviewed by:
Catherine D. Chong, Mayo Clinic Arizona, United States
Francesca Puledda, King's College London, United Kingdom

***Correspondence:**
Nasim Maleki
nmaleki@mgh.harvard.edu

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *02 July 2019*
Accepted: *21 August 2019*
Published: *06 September 2019*

Citation:
Maleki N and Androulakis XM (2019) Is There Any MRI Pattern That Discriminates Female From Male Migraine Patients? Front. Neurol. 10:961. doi: 10.3389/fneur.2019.00961

INTRODUCTION

Despite advances in understanding of the migraine pathophysiology (1), as one of the most prevalent disabling disorders worldwide, migraine disease continues to be an unresolved major public health problem for both men and women (2–6). Of the 38 million migraine sufferers in the US, two-thirds are estimated to be female (7, 8) with differences in the incidence pattern appearing around puberty (9). Sex differences in migraine also extend to greater symptomology, higher rate of visual auras, higher headache-related disability, and greater healthcare resource utilization by females (10). In the past two decades, several neuroimaging studies have attempted to identify potential differences in the brains of migraineurs, however only a very limited number of studies have examined the sex-specific differences in the brains of migraineurs. In this review: (i) We will first discuss neuroimaging findings on the patterns that discriminate women from men in migraine to date; (ii) We will then re-examine some of the salient neuroimaging findings in migraine and discuss them in relation to the sex-related influences; (iii) Finally, we will discuss some of the intriguing recent findings that seem to suggest presence of sex-specific traits in migraineurs, which may have potential implications for future neuroimaging studies. These together may not only hold

clues to the sex disparity in migraine, but also consequently shed more light on the mechanisms of the disease.

NEUROIMAGING FINDINGS ON SEX-RELATED BRAIN DIFFERENCES IN MIGRAINE

There are very limited neuroimaging studies with considerably small sample sizes that have examined sex-related differences in migraine. In a study on episodic migraineurs and matched healthy control individuals, increased cortical thickness in the insula and precuneus in female migraineurs and a smaller volume of the parahippocampal gyrus in male migraineurs were observed despite both male and female migraineurs having comparable disease frequency and duration (11). Functionally, women with migraine showed stronger response to pain in brain regions involved in emotional processing such as the amygdala, which was consistent with increased measures of pain related unpleasantness for them compared to men with migraine. In a follow up study, abnormality in the insula was again observed in women between the ages of 20–65 years with migraine. It was found that there was a lack of age-related thinning in the insular cortex in female migraineurs compared to female healthy controls (12). A meta-analysis of nine voxel-based morphometry neuroimaging studies (222 migraineurs and 230 healthy controls), suggested sex-influence on some of the observed differences in the gray matter volume between migraineurs and healthy subjects. The analysis showed that a higher percentage of females in the patient sample was associated with decreased gray matter in the right dorsolateral prefrontal cortex (13).

Sex-related differences in the topological properties of the brain functional networks have also been reported recently. In one study, a noxious stimulation paradigm utilizing a thermal probe was applied to the back of the hand in order to evoke a painful response (11). Female migraineurs showed greater brain activation in response compared to men with migraine in certain brain regions such as the amygdala, parahippocampus, basal ganglia, and posterior cingulate cortex. These regions are involved in processing of the emotional aspects of pain. The same study indicated significant differences between the functional connectivity of these structures with the rest of the brain (using a seed-based functional connectivity analysis approach), specifically with the areas involved in pain processing. Using graph theory analysis, one study revealed network level differences that may reflect faulty communication within and between brain regions in female migraineurs (14). Another study has further revealed widespread disrupted functional connectivity in female migraineurs compared to healthy women primarily in brain regions involved in discriminating sensory features of pain, pain modulation, and sensory integration (15). Sex-related differences have also been reported in the incidence of white matter abnormalities in female migraine patients compared to age-matched healthy female controls with no such difference in males (16).

NEUROIMAGING FINDINGS IN MIGRAINE AND POTENTIAL SEX-RELATED INFLUENCES

Hypothalamic Involvement

One of the most consistent and salient findings in neuroimaging studies of migraine is abnormal hypothalamic activity preceding (17, 18), during (18–20) and even in between the migraine attacks (21). Most of the premonitory autonomic symptoms associated with a migraine attack are indeed thought to be of hypothalamic origin (22, 23). The hypothalamic orexinergic system in particular is thought to be a key regulator of the modulatory effects of the hypothalamus on the trigeminovascular system implicated in migraine pathophysiology (24). Orexin, a neuropeptide solely synthesized in the hypothalamus, plays a major role in modulating brain activity and a variety of complex functions including sleep, reward, feeding behavior, and stress response (24). Functional changes in hypothalamo–brainstem connectivity (22) including changes in functional coupling with the spinal trigeminal nuclei and the dorsal rostral pons (25) are shown to precede a migraine attack. The hypothalamus also serves as an interface between the neural system and the peripheral endocrine systems. It is likely that cyclic activation of trigeminovascular system by sex hormones during menstrual cycles may be one of the contributing factors to the incidence of migraine attacks via coupling with the hypothalamus in women. However, to the best of our knowledge there have not been any reports on neuroimaging differences between male vs. female migraineurs involving the hypothalamus.

Insular Involvement

Insular abnormalities in association with migraine have been reported in several neuroimaging studies (26–31). There is abnormal intrinsic connectivity between the anterior insula and primary sensory cortices, and the pons (32). There is abnormal connectivity of the default mode network and central executive network in migraineurs compared to healthy subjects (29). Chronic migraine disease duration is correlated with intrinsic functional connectivity strength between the anterior insula and mediodorsal thalamus and the anterior insula and periaqueductal gray. Higher frequency of migraine attacks mediates increased connectivity between the somatosensory cortex and the anterior insula in response to evoked pain (31). Aberrant functional connectivity between right orbitofrontal insula and prefrontal regions is also observed within the salience network in women with chronic migraine (33). The insula is one of the regions that has been implicated in neuroimaging studies of sex-related differences in migraine.

Brainstem Involvement

Multiple studies have reported abnormal brainstem function in ictal and interictal migraineurs. This includes increased neuronal activity in the brainstem during migraine attacks (26, 34–36) and dysfunctional descending modulation, involving the periaqueductal gray (PAG) and dorsal rostral pons (36), during and between migraine attacks (37–39). Moreover, during the

pre-headache phase of a migraine attack (<24 h), increased infra-slow oscillation and homogeneity in dorsal pons, spinal trigeminal nucleus, and hypothalamus are observed in migraine patients (40). Interictally, the dorsal pons show increased connectivity with the bilateral anterior insula in migraineurs (32). In an animal study, CGRP expression increased within the PAG in ovariectomized female rats, and CGRP level remained elevated even after receiving hormone replacement therapy (41). To the best of our knowledge, no studies evaluated male vs. female brainstem functional/structural differences in migraine. Given that a lack of female sex hormone increased CGRP expression in PAG in ovariectomized female rats (41), it is likely that descending pain modulation is affected differently in opposite sexes. Therefore, investigation of neuroimaging patterns in migraine should shed light on how sex influences pain modulation.

Extended Amygdala Involvement

The extended amygdala, which consists of the central medial amygdala, sublenticular substantia innominata, the nucleus accumbens shell, and the bed nucleus of the stria terminalis, regulates nociception, aversive motivational state, reward, memory, and learning (42). It interconnects extensively with the thalamus, hypothalamus, and cortical regions (43) and as such plays an important role in neural circuitry of emotion regulation (44). In a resting state fMRI study that investigated salience network connectivity in women with chronic migraine, the bilateral central and medial amygdala were found to be significantly less connected functionally with each other, and the overall salient network circuitry dys-synchronization was found to be centered on the extended amygdala among 351 salient intranetwork connectivities investigated (33). Using PET scan with u-opioid receptor tracer, researchers found that right amygdala opioid dysfunction is largely explained by migraine frequency and severity (45). Cortical spreading depression, a pathophysiological substrate of migraine with aura, was elicited in rats with NMDA administrated to the amygdala (46). The amygdala also shows sex differences in animal and human studies (47). These sex-specific differences in regional anatomy may explain the inconsistent findings amongst studies when including mixed (male and female) cohorts.

It seems reasonable to postulate that the extended amygdala is crucial (but not sufficient by itself) for the lack of habituation to salient information seen in migraine. Therefore, it contributes to the maladaptive response to head pain and promotes pain catastrophizing and recurrent negative thoughts commonly seen in female migraine patients.

Network Level Differences

Intrinsic functional brain networks (IFBN) such as the Default Mode Network, Salience Network, and Central Executive Network are brain state-dependent, spatial topographies representing inter-regional connectivity patterns, and consisting of functionally correlated brain regions. The diverse symptomatology of migraine suggests that multiple functional brain regions are at play. Interestingly, decades of migraine neuroimaging research failed to confirm a single brain region responsible for its pathogenesis. From an evolutionary standpoint, each human brain region has adapted to take on multiple roles in different contexts in order to perform a variety of functions (48). Taken together, it is unlikely that one isolated part of the nervous system is sufficient or necessary to orchestrate such complex brain process as migraine. The unique advantage of the functional brain network approach in studying migraine and chronic migraine is that it allows for a systemic and comprehensive approach to map out migraine symptoms to the underlying brain circuitry. This is a far better approach compared to the localization approach using a whole brain atlas, which likely results in missing the "forest" by only examining the "tree(s)."

Decreases in salience network and central executive network connectivity are correlated with chronic migraine headache frequency in women, suggesting that improving synchronization of these networks through therapeutic interventions may improve clinical symptoms and have potential to be used as a biomarker for monitoring disease progression and treatment response (49). The intrinsic functional connectivity between the brain networks can be modulated by the phase of the menstrual cycle and by the usage of oral contraceptive pills (50). Therefore, it is likely that the migraine burden or treatment response in women would be influenced by these factors.

SEX SPECIFIC TRAITS IN MIGRAINEURS AND IMPLICATIONS FOR NEUROIMAGING

Perimenopausal Migraineurs

Perimenopause as a midlife transitional period in women is associated with significant changes in certain brain networks' underlying processes such as thermoregulation, circadian rhythms, sleep, and sensory processing (51). Fluctuations and decline in the levels of ovarian hormones during this period also have significant modulatory influences on brain function (52–55), which could have significant implications for neurological disorders, including migraine (56, 57). A recent study provides evidence for increased incidence of vasomotor symptoms in aging women with a history of migraine (58). This finding may be concordant with neuroimaging findings that have shown sex-specific and disease specific abnormalities in the structure and function of the insular cortex, the core cortical region for autonomic integration, in women with migraine. This further emphasizes a need for neuroimaging studies of migraine in the aging population (59).

Trait Estradiol Decline

In migraine, decline in estrogen levels is thought to be one of the most potent triggers for occurrence of a migraine attack and is commonly referred to as the "estrogen withdrawal hypothesis" (60, 61). A recent study has shown that women with a history of migraine have faster decline of estradiol prior to menses than women with no history of migraine, irrespective of whether they had experienced a headache in that cycle or not (62), suggesting there exists an endogenous trait in women with migraine. Changes in estrogen levels could have modulatory effects on neurons containing estrogen receptors

and may increase nociception (63, 64). Estrogen receptors are widely expressed in the trigeminal sensory system (65). The effects of estrogen on the receptors could be through modulating expression of nociceptive mediators, as well as through receptor coupling. Increased release of excitatory neurotransmitters can lead to the sensitization of the trigeminovascular system leading to peripheral and central sensitization (66, 67).

Neuroimaging studies in menstrual cycling women with migraine according to the phase of their menstrual cycle should provide insights on how decline in estrogen might modulate or affect functional activity or connectivity. Studying the interactions between sex hormones and brain activity should also extend to men as the dynamics of such interactions might not be the same in men and women. In fact, estrogen may also play a role in migraine for men but surprisingly men with migraine exhibit increased levels of estradiol while exhibiting clinical evidence of relative androgen deficiency (68).

Pubertal Development and Onset of Migraines

The highest incidence of migraine coincides with pubertal development period, which is also a critical period for brain reorganization. The sex-specific differences in timing and speed of these changes may be critical in reorganization of connections in the brain, and therefore, may predispose individuals to various diseases, such as migraine, with sex disparity. Recent studies provide support for this notion by revealing that the "timing" of the onset of menarche matters in migraine: earlier age at menarche increases the risk of migraine, but not other types of headaches, in women by adulthood (69). It is likely that sex-specific differences in the brain of adults with migraine (11, 12) may have started to appear around the onset of puberty (70) and that the sex-specific traits in female migraineurs may have begun to crystalize during the same time. Sex-specific differences in the trajectory of development of brain regions that are implicated in migraine pathophysiology, such as brainstem nuclei, may also increase the susceptibility to migraine (71).

Treatment Response Differences

FDA has recently approved several anti-calcitonin gene-related peptide (CGRP) therapies following successful randomized, placebo controlled, double blinded trials, all of which had predominantly female participants. None of these studies evaluated the treatment response differences in women vs. men. In animal models, CGRP triggers migraine-like response in female but not male rodents, suggesting that female-specific mechanisms may be involved consequent to CGRP receptor activation and that blocking CGRP is probably unlikely to work in males (72). There is also evidence for sex differences in the expression of CGRP receptor components in the spinal trigeminal nucleus with higher levels of expression in females (73). Therefore, we question if monoclonal antibody blocking CGRP may be as effective for migraine in men compared to women.

Very few studies have looked at the neuroimaging changes following migraine treatment. In a pilot longitudinal fMRI study, the impact of SPG treatment on salience and executive networks in women with chronic migraine was examined (74). It was found that total network synchronization improved in the executive network but not in the salient network. There was a trend toward improvement in the salient network but its insignificance was probably due to small sample size. Moreover, within the salience network, connectivity between prefrontal to limbic regions greatly improved. Comparing chronic migraine patients who responded to Botox vs. those who did not, responders showed improved functional connectivity in a small case control study (75).

CONCLUSION

The sex-related differences in migraine go beyond the difference in prevalence of the disease and extend to sex-related differences in incidence and disease progression as well as in pharmacologic treatment response patterns. Given the sex differences in migraine, it may be more informative if researchers studied male and female migraineurs separately, such as using stratification in the study designs, to better delineate the underlying pathophysiology and treatment response. Statistical adjustment for sex differences in regression models does not and cannot adjust for the complexity of the underlying biological differences between males vs. females, and the sex-influences should be considered from the conception of neuroimaging studies to the analysis and interpretation of the results. This is certainly a dilemma when designing a migraine study given the already 1:3 male to female ratio in migraine and lesser engagement of men in research studies. At this point, it almost seems that we know less about male-specific compared to female-specific neuropathology. It is likely that despite the major overlap in the neural "culprits" involved, the modulatory influence of sex-influences will have a wider impact on the functional dynamics of the known players in migraine pathophysiology and as such findings in one sex may not simply and directly translate or extend to another sex.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. Neurobiology of migraine. *Neuroscience*. (2009) 161:327–41. doi: 10.1016/j.neuroscience.2009.03.019
2. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. (2001) 41:646–57.
3. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. *Headache*. (2005) 45(Suppl 1):S3–13. doi: 10.1111/j.1526-4610.2005.4501001.x

4. McIntyre RS, Konarski JZ, Wilkins K, Bouffard B, Soczynska JK, Kennedy SH. The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian Community Health Survey. *Headache*. (2006) 46:973–82. doi: 10.1111/j.1526-4610.2006.00469.x
5. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. (2012) 380:2163–96. doi: 10.1016/S0140-6736(12)61729-2
6. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache*. (2013) 53:427–36. doi: 10.1111/head.12074
7. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the subtypes of migraine. *Int J Epidemiol*. (1995) 24:612–8.
8. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA*. (2006) 295:1824–30. doi: 10.1001/jama.295.15.1824
9. Stewart WF, Linet MS, Celentano DD, Van Natta M, Ziegler D. Age- and sex-specific incidence rates of migraine with and without visual aura. *Am J Epidemiol*. (1991) 134:1111–20. doi: 10.1093/oxfordjournals.aje.a116014
10. Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, Fanning KM, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. (2013) 53:1278–99. doi: 10.1111/head.12150
11. Maleki N, Linnman C, Brawn J, Burstein R, Becerra L, Borsook, D. Her versus his migraine: multiple sex differences in brain function and structure. *Brain*. (2012) 135(Pt 8):2546–59. doi: 10.1093/brain/aws175
12. Maleki N, Barmmetler G, Moulton EA, Scrivani S, Spierings EL, Becerra L, et al. Female migraineurs show lack of insular thinning with age. *Pain*. (2015) 156:1232–9. doi: 10.1097/j.pain.0000000000000159
13. Dai Z, Zhong J, Xiao P, Zhu Y, Chen F, Pan P, et al. Gray matter correlates of migraine and gender effect: a meta-analysis of voxel-based morphometry studies. *Neuroscience*. (2015) 299:88–96. doi: 10.1016/j.neuroscience.2015.04.066
14. Liu J, Qin W, Nan J, Li J, Yuan K, Zhao L, et al. Gender-related differences in the dysfunctional resting networks of migraine suffers. *PLoS ONE*. (2011) 6:e27049. doi: 10.1371/journal.pone.0027049
15. Zhang J, Su J, Wang M, Zhao Y, Zhang QT, Yao Q, et al. The posterior insula shows disrupted brain functional connectivity in female migraineurs without aura based on brainnetome Atlas. *Sci Rep*. (2017) 7:16868. doi: 10.1038/s41598-017-17069-8
16. Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. *Cephalalgia*. (2010) 30:129–36. doi: 10.1111/j.1468-2982.2009.01904.x
17. Maniyar FH, Sprenger T, Monteith T, Schankin CJ, Goadsby PJ. The premonitory phase of migraine–what can we learn from it? *Headache*. (2015) 55:609–20. doi: 10.1111/head.12572
18. Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: evidence from high-resolution fMRI. *Neurology*. (2017) 88:2011–6. doi: 10.1212/WNL.0000000000003963
19. Deecher DC. Physiology of thermoregulatory dysfunction and current approaches to the treatment of vasomotor symptoms. *Expert Opin Investig Drugs*. (2005) 14:435–48. doi: 10.1517/13543784.14.4.435
20. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. *Headache*. (2007) 47:1418–26. doi: 10.1111/j.1526-4610.2007.00776.x
21. Moulton EA, Becerra L, Johnson A, Burstein R, Borsook D. Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. *PLoS ONE*. (2014) 9:e95508. doi: 10.1371/journal.pone.0095508
22. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. (2014) 137(Pt 1):232–41. doi: 10.1093/brain/awt320
23. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. *Neurol Sci*. (2017) 38(Suppl 1):125–30. doi: 10.1007/s10072-017-2866-0
24. Holland P, Goadsby PJ. The hypothalamic orexinergic system: pain and primary headaches. *Headache*. (2007) 47:951–62. doi: 10.1111/j.1526-4610.2007.00842.x
25. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain*. (2016) 139(Pt 7):1987–93. doi: 10.1093/brain/aww097
26. Bahra A, Matharu MS, Buchel C, Frackowiak RS, Goadsby PJ. Brainstem activation specific to migraine headache. *Lancet*. (2001) 357:1016–7. doi: 10.1016/s0140-6736(00)04250-1
27. Schmidt-Wilcke T, Ganssbauer S, Neuner T, Bogdahn U, May A. Subtle grey matter changes between migraine patients and healthy controls. *Cephalalgia*. (2008) 28:1–4. doi: 10.1111/j.1468-2982.2007.01428.x
28. Kim JH, Kim S, Suh SI, Koh SB, Park KW, Oh K. Interictal metabolic changes in episodic migraine: a voxel-based FDG-PET study. *Cephalalgia*. (2010) 30:53–61. doi: 10.1111/j.1468-2982.2009.01890.x
29. Xue T, Yuan K, Zhao L, Yu D, Zhao L, Dong T, et al. Intrinsic brain network abnormalities in migraines without aura revealed in resting-state fMRI. *PLoS ONE*. (2012) 7:e52927. doi: 10.1371/journal.pone.0052927
30. Yang J, Zeng F, Feng Y, Fang L, Qin W, Liu X, et al. A PET-CT study on the specificity of acupoints through acupuncture treatment in migraine patients. *BMC Complement Altern Med*. (2012) 12:123. doi: 10.1186/1472-6882-12-123
31. Maleki N, Becerra L, Brawn J, Bigal M, Burstein R, Borsook D. Concurrent functional and structural cortical alterations in migraine. *Cephalalgia*. (2012) 32:607–20. doi: 10.1177/0333102412445622
32. Tso AR, Trujillo A, Guo CC, Goadsby PJ, Seeley WW. The anterior insula shows heightened interictal intrinsic connectivity in migraine without aura. *Neurology*. (2015) 84:1043–50. doi: 10.1212/WNL.0000000000001330
33. Androulakis XM, Rorden C, Peterlin BL, Krebs K. Modulation of salience network intranetwork resting state functional connectivity in women with chronic migraine. *Cephalalgia*. (2018) 38:1731–41. doi: 10.1177/0333102417748570
34. Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med*. (1995) 1:658–60.
35. Afridi SK, Matharu MS, Lee L, Kaube H, Friston KJ, Frackowiak RS, et al. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. *Brain*. (2005) 128(Pt 4):932–9. doi: 10.1093/brain/awh416
36. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci*. (2011) 12:570–84. doi: 10.1038/nrn3057
37. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? *Headache*. (2001) 41:629–37. doi: 10.1046/j.1526-4610.2001.041007629.x
38. Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A. Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies. *Headache*. (2007) 47:996–1003. doi: 10.1111/j.1526-4610.2007.00853.x
39. Moulton EA, Burstein R, Tully S, Hargreaves R, Becerra L, Borsook D. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. *PLoS ONE*. (2008) 3:e3799. doi: 10.1371/journal.pone.0003799
40. Meylakh N, Marciszewski KK, Di Pietro F, Macefield VG, Macey PM, Henderson LA. Deep in the brain: changes in subcortical function immediately preceding a migraine attack. *Hum Brain Mapp*. (2018) 39:2651–63. doi: 10.1002/hbm.24030
41. Wang D, Zhao J, Wang J, Li J, Yu S, Guo X. Deficiency of female sex hormones augments PGE2 and CGRP levels within midbrain periaqueductal gray. *J Neurol Sci*. (2014) 346:107–11. doi: 10.1016/j.jns.2014.08.002
42. Koepp MJ, Hammers A, Lawrence AD, Asselin MC, Grasby PM, Bench CJ. Evidence for endogenous opioid release in the amygdala during positive emotion. *Neuroimage*. (2009) 44:252–6. doi: 10.1016/j.neuroimage.2008.08.032
43. Sah P, Faber ES, Lopez De Armentia M, Power J. The amygdaloid complex: anatomy and physiology. *Physiol Rev*. (2003) 83:803–34. doi: 10.1152/physrev.00002.2003
44. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. (2000) 23:155–84. doi: 10.1146/annurev.neuro.23.1.155

45. Jassar H, Nascimento T, DaSilva AF. Impact of chronic migraine attacks and their severity on the endogenous μ-opioid neurotransmission in the limbic system. *Neuroimage*. (2019) 23:101905. doi: 10.1016/j.nicl.2019.101905
46. Akcali D, Sayin A, Sara Y, Bolay H. Does single cortical spreading depression elicit pain behaviour in freely moving rats? *Cephalalgia*. (2010) 30:1195–206. doi: 10.1177/0333102409360828
47. Pfau DR, Hobbs NJ, Breedlove SM, Jordan CL. Sex and laterality differences in medial amygdala neurons and astrocytes of adult mice. *J Comp Neurol*. (2016) 524:2492–502. doi: 10.1002/cne.23964
48. Pearson JM, Watson KK, Platt ML. Decision making: the neuroethological turn. *Neuron*. (2014) 82:950–65. doi: 10.1016/j.neuron.2014.04.037
49. Androulakis XM, Krebs K, Peterlin BL, Zhang T, Maleki N, Sen S, et al. Modulation of intrinsic resting-state fMRI networks in women with chronic migraine. *Neurology*. (2017) 89:163–9. doi: 10.1212/WNL.0000000000004089
50. Petersen N, Kilpatrick LA, Goharzad A, Cahill L. Oral contraceptive pill use and menstrual cycle phase are associated with altered resting state functional connectivity. *Neuroimage*. (2014) 90:24–32. doi: 10.1016/j.neuroimage.2013.12.016
51. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. (2015) 11:393–405. doi: 10.1038/nrendo.2015.82
52. Goldstein JM, Jerram M, Poldrack R, Ahern T, Kennedy DN, Seidman LJ, et al. Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. *J Neurosci*. (2005) 25:9309–16. doi: 10.1523/JNEUROSCI.2239-05.2005
53. Choi JC, Park SK, Kim YH, Shin YW, Kwon JS, Kim JS, et al. Different brain activation patterns to pain and pain-related unpleasantness during the menstrual cycle. *Anesthesiology*. (2006) 105:120–7. doi: 10.1097/00000542-200607000-00021
54. Goldstein JM, Jerram M, Abbs B, Whitfield-Gabrieli S, Makris N. Sex differences in stress response circuitry activation dependent on female hormonal cycle. *J Neurosci*. (2010) 30:431–8. doi: 10.1523/JNEUROSCI.3021-09.2010
55. Pletzer B, Kronbichler M, Aichhorn M, Bergmann J, Ladurner G, Kerschbaum HH. Menstrual cycle and hormonal contraceptive use modulate human brain structure. *Brain Res*. (2010) 1348:55–62. doi: 10.1016/j.brainres.2010.06.019
56. Scott EL, Zhang QG, Vadlamudi RK, Brann DW. Premature menopause and risk of neurological disease: basic mechanisms and clinical implications. *Mol Cell Endocrinol*. (2014) 389:2–6. doi: 10.1016/j.mce.2014.01.013
57. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric*. (2015) 18:483–91. doi: 10.3109/13697137.2015.1020484
58. Maleki N, Cheng YC, Tu Y, Locascio JJ. Longitudinal course of vasomotor symptoms in perimenopausal migraineurs. *Ann Neurol*. (2019) 85:865–74. doi: 10.1002/ana.25476
59. Bernstein C, Shifren J, Maleki N. Need for migraine/perimenopausal research. *Headache*. (2018) 58:1670–4. doi: 10.1111/head.13406
60. Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology*. (1972) 22:355–65.
61. MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. *Neurology*. (2004) 63:351–3. doi: 10.1212/01.wnl.0000133134.68143.2e
62. Pavlovic JM, Allshouse AA, Santoro NF, Crawford SL, Thurston RC, Neal-Perry GS, et al. Sex hormones in women with and without migraine: evidence of migraine-specific hormone profiles. *Neurology*. (2016) 87:49–56. doi: 10.1212/WNL.0000000000002798
63. Liverman CS, Brown JW, Sandhir R, McCarson KE, Berman NE. Role of the oestrogen receptors GPR30 and ERalpha in peripheral sensitization: relevance to trigeminal pain disorders in women. *Cephalalgia*. (2009) 29:729–41. doi: 10.1111/j.1468-2982.2008.01789.x
64. Gupta S, McCarson KE, Welch KM, Berman NE. Mechanisms of pain modulation by sex hormones in migraine. *Headache*. (2011) 51:905–22. doi: 10.1111/j.1526-4610.2011.01908.x
65. Cairns BE. The influence of gender and sex steroids on craniofacial nociception. *Headache*. (2007) 47:319–24. doi: 10.1111/j.1526-4610.2006.00708.x
66. Karki P, Webb A, Zerguine A, Choi J, Son DS, Lee E. Mechanism of raloxifene-induced upregulation of glutamate transporters in rat primary astrocytes. *Glia*. (2014) 62:1270–83. doi: 10.1002/glia.22679
67. Bottger P, Glerup S, Gesslein B, Illarionova NB, Isaksen TJ, Heuck A, et al. Glutamate-system defects behind psychiatric manifestations in a familial hemiplegic migraine type 2 disease-mutation mouse model. *Sci Rep*. (2016) 6:22047. doi: 10.1038/srep22047
68. van Oosterhout WPJ, Schoonman GG, van Zwet EW, Dekkers OM, Terwindt GM, MaassenVanDenBrink A, et al. Female sex hormones in men with migraine. *Neurology*. (2018) 91:e374–81. doi: 10.1212/WNL.0000000000005855
69. Maleki N, Kurth T, Field A. Age at menarche and risk of developing migraine or non-migraine headaches by young adulthood: a prospective cohort study. *Cephalalgia*. (2017) 37:1257–63. doi: 10.1177/0333102416677999
70. Maleki N, Retzepi K, Lessard A, Berna-Renella C, Gollub R. Evidence that structural differences in amygdala and insula associated with migraine emerge as early as adolescence to young adulthood. In: *Annual Meeting of the Organization for Human Brain Mapping*. Honolulu, HI (2015).
71. Maleki N, Bernstein C, Napadow V, Field A. Migraine and puberty: potential susceptible brain sites. *Semin Pediatr Neurol*. (2016) 23:53–9. doi: 10.1016/j.spen.2016.01.011
72. Avona A, Burgos-Vega C, Burton MD, Akopian AN, Price TJ, Dussor G. Dural calcitonin gene-related peptide produces female-specific responses in rodent migraine models. *J Neurosci*. (2019) 39:4323–31. doi: 10.1523/JNEUROSCI.0364-19.2019
73. Ji Y, Rizk A, Voulalas P, Aljohani H, Akerman S, Dussor G, et al. Sex differences in the expression of calcitonin gene-related peptide receptor components in the spinal trigeminal nucleus. *Neurobiol Pain*. (2019) 6:100031. doi: 10.1016/j.ynpai.2019.100031
74. Krebs K, Rorden C, Androulakis XM. Resting state functional connectivity after sphenopalatine ganglion blocks in chronic migraine with medication overuse headache: a pilot longitudinal fMRI study. *Headache*. (2018) 58:732–43. doi: 10.1111/head.13318
75. Hubbard CS, Becerra L, Smith JH, DeLange JM, Smith RM, Black DF, et al. Brain changes in responders vs. non-responders in chronic migraine: markers of disease reversal. *Front Hum Neurosci*. (2016) 10:497. doi: 10.3389/fnhum.2016.00497

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 01 October 2019
doi: 10.3389/fneur.2019.01039

Altered Resting State Functional Activity and Microstructure of the White Matter in Migraine With Aura

*Péter Faragó [1,2], Eszter Tóth [1], Krisztián Kocsis [1], Bálint Kincses [1], Dániel Veréb [1], András Király [1,2], Bence Bozsik [1], János Tajti [1], Árpád Párdutz [1], Délia Szok [1], László Vécsei [1,3], Nikoletta Szabó [1,2] and Zsigmond Tamás Kincses [1,4]**

[1] Department of Neurology, Faculty of Medicine, Interdisciplinary Excellent Centre, University of Szeged, Szeged, Hungary, [2] Central European Institute of Technology, Brno, Czechia, [3] MTA-SZTE, Neuroscience Research Group, Szeged, Hungary, [4] Department of Radiology, Faculty of Medicine, University of Szeged, Szeged, Hungary

Introduction: Brain structure and function were reported to be altered in migraine. Importantly our earlier results showed that white matter diffusion abnormalities and resting state functional activity were affected differently in the two subtypes of the disease, migraine with and without aura. Resting fluctuation of the BOLD signal in the white matter was reported recently. The question arising whether the white matter activity, that is strongly coupled with gray matter activity is also perturbed differentially in the two subtypes of the disease and if so, is it related to the microstructural alterations of the white matter.

Methods: Resting state fMRI, 60 directional DTI images and high-resolution T1 images were obtained from 51 migraine patients and 32 healthy volunteers. The images were pre-processed and the white matter was extracted. Independent component analysis was performed to obtain white matter functional networks. The differential expression of the white matter functional networks in the two subtypes of the disease was investigated with dual-regression approach. The Fourier spectrum of the resting fMRI fluctuations were compared between groups. Voxel-wise correlation was calculated between the resting state functional activity fluctuations and white matter microstructural measures.

Results: Three white matter networks were identified that were expressed differently in migraine with and without aura. Migraineurs with aura showed increased functional connectivity and amplitude of BOLD fluctuation. Fractional anisotropy and radial diffusivity showed strong correlation with the expression of the frontal white matter network in patients with aura.

Discussion: Our study is the first to describe changes in white matter resting state functional activity in migraine with aura, showing correlation with the underlying microstructure. Functional and structural differences between disease subtypes suggest at least partially different pathomechanism, which may necessitate handling of these subtypes as separate entities in further studies.

Keywords: migraine, resting state, fMRI, white matter, diffusion, ALFF

OPEN ACCESS

Edited by:
Massimo Filippi, Vita-Salute San Raffaele University, Italy

Reviewed by:
Emanuele Tinelli, Sapienza University of Rome, Italy
Lars Neeb, Charité Medical University of Berlin, Germany

***Correspondence:**
Zsigmond Tamás Kincses
kincses.zsigmond.tamas@med.u-szeged.hu

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *30 June 2019*
Accepted: *13 September 2019*
Published: *01 October 2019*

Citation:
Faragó P, Tóth E, Kocsis K, Kincses B, Veréb D, Király A, Bozsik B, Tajti J, Párdutz Á, Szok D, Vécsei L, Szabó N and Kincses ZT (2019) Altered Resting State Functional Activity and Microstructure of the White Matter in Migraine With Aura. Front. Neurol. 10:1039. doi: 10.3389/fneur.2019.01039

INTRODUCTION

Migraine is the most widely known primary headache disorder, which affects nearly 10% of the population (1). The clinical appearance of attack is similar in most cases, however 20% of the patients report focal neurological symptoms (aura) before headache (migraine with aura; MWA). Different theories claimed to explain the pathomechanism of MWA and migraine without aura (MWoA) and the two forms of the headache may have distinct triggers (2). Malfunction of the trigemino-vascular complex, dysfunctional brainstem nuclei and altered metabolism of several neuropeptides may all play a part in the initiation of the migraineous headache. Aura symptoms are supposed to be originated from cortical spreading depression (CSD), a spreading wave of depolarization throughout the cortex that is thought to cause the focal symptoms associated with aura (3). CSD that is more prevalent in MWA is reportedly associated with the imbalance of excitation/inhibition in the migrainous brain (4). The altered excitability in MWA patients can cause increased amplitude of visual evoked potentials (5, 6), and also altered motion perception, where they have to judge certain properties of stimuli against a noisy background (7). Several studies also report enhanced responsiveness of the cortex to visual stimuli in a functional MRI setting (8, 9). Functional imaging placed the differences between the two subtypes on new foundations. Such methods were able to detect CSD during the aura phase (3, 10), and also revealed altered responses to sensory (11) or painful stimuli (12–14).

Resting state fMRI showed conflicting results about the alterations of brain activity during rest in interictal period. While some studies presented increased connectivity (15), some of them found the connectivity to be decreased (16). The fact, that these studies used heterogeneous populations of both MWA and MWoA patients, might explain this discrepancy. Our earlier investigation showed that the amplitude of the resting BOLD fluctuation, presumably a signature of increased excitability, was increased in MWA but not in MWoA (17).

Apart from gray matter functional networks, previous studies suggested that the white matter responds to external stimuli in a fashion similar to the gray matter, and this activation can also be measured with fMRI (18–20). Such fluctuations in activity are also present during rest, organized into distinct, consistently identifiable white matter resting state fMRI networks that bear close resemblance to gray matter functional networks (21–23). Several studies report that these networks function differently in neurological or psychiatric diseases (24–26). Since white matter microstructure is affected in migraine (27) and also differs between disease subtypes (28), a couple of questions arise. Does the functional activity of the white matter differs in disease comparing to the healthy population? Is there any difference between the various forms of migraine and if there it is, is it related to the microstructural alterations?

Resting state fMRI usually focus on the analysis of the whole frequency range of the time courses. However, it might be prudent to analyse different frequency ranges separately, since resting state networks were shown to be organize across several frequency bands (29). Several publications report resting state network abnormalities throughout several frequency bands in neuropsychiatric diseases and investigate the amplitude of low frequency fluctuations (30–33).

In our study, we aimed to explore differences in white matter resting state functional activity between the two migraine subtypes (MWA and MWoA) and healthy individuals. Considering the previously reported abnormalities of white matter microstructure, we also investigated whether these microstructural alterations are related to functional measures of the white matter during rest in migraine.

MATERIALS AND METHODS

Participants

We recruited 51 migraine patients in our study (18 MWA, 33 MwoA). The participants belonged to the same cohort, similar to our previous investigation (17), all of them were enlisted from the Headache Outpatients Clinic of the Department of Neurology, University of Szeged. Apart from migraine, participants had no other neurologic or psychiatric disorders. All patients suffered from episodic migraine. None of the patients reported migraineous attack at in the preceeding week of the scanning. Each participant filled out a questionnaire about the prevalence and traits of the headache, medication and other diseases. None of the patient reported diabetes, or any other major cardiovascular diseases. Only one patient with aura was on interval therapy (iprazochrome). Seven of the 33 MWoA patients received interval treatment (1 topiramate, 1 amytriptilline, 5 iprazochrome).

As control group, we recruited 32 healthy volunteers, age and sex matched to the patients. Demographic data is included in **Table 1**.

The local ethics committee of the University of Szeged approved the study (authority No.: 87/2009). All participants gave written informed consent in accordance with the Declaration of Helsinki.

Image Acquisition

MR imaging was performed on a 1.5 T GE Signa Excite HDxt MRI scanner. For every participant, we obtained high-resolution T1 weighted images (3D IR-FSPGR: TR/TE/TI: 10.3/4.2/450 ms, flip angle: 15°, ASSET: 2, FOV: 25*25 cm, matrix: 256*256, slice thickness: 1 mm,), a resting state fMRI protocol with echo-planar imaging technique (TE: 40 ms, TR: 3,000 ms, matrix: 64*64 cm, FOV: 30*30 cm, slice thickness: 6 mm, flip angle: 90°, NEX:

TABLE 1 | Demographic data of the participants.

	MWA	MWoA	Controls
n	18	33	32
Age (years; mean and SD)	32.1(8)	35.6(8.9)	35.2(11)
Gender (male)	3	3	2
Disease duration (years; mean and SD)	14.2(8.6)	13.7(9.1)	n.a.
Pain rated on visual analog scale	7.6(1.3)	8.7(1.2)	n.a.
Attack/year (days; mean and SD)	29(26)	55(45.6)	n.a.

1, ASSET: 2,0 Ph, Phases per Loc: 128, volumes: 200) and 60 directions diffusion-weighted images with 6 non-diffusion-weighted reference volume [TE: 93.8 ms; TR: 16.000 ms; matrix: 96 * 96; FOV: 23 * 23 cm; flip angle: 90°; in-plane resolution: 2.4 * 2.4 mm; slice thickness: 2.4 mm; b: 1,000 s/mm^2; number of excitations (NEX): 2; array spatial sensitivity encoding technique (ASSET) factor = 2]. Head motion was attenuated with foam pads.

Data Processing

We performed data pre-processing and statistical analyses with FSL (FMRIB's Software Library) toolkits. The Fourier transformation and statistical correlation calculation was performed by Matlab.

Pre-processing

We pre-processed resting state fMRI volumes using the FEAT toolbox, which included the removal of the first two non-steady-state volumes, removal of non-brain tissue via BET (34), motion correction (MCFLIRT), high pass filtering (cut-off sigma 100 s) and spatial smoothing with 6 mm FWHM. Because the motion parameters could alternate the BOLD signal, absolute and relative displacements were compared between groups. There were no significant differences in head movement. None of the subject's absolute displacement was larger then 0.8 mm.

All pre-processed fMRI images were registered to their own T1 images and to a standard structural image (MNI152, 2 mm isovoxel) with linear and non-linear registration respectively. To reduce calculation burden, we resampled all fMRI images to 4 mm isovoxel resolution. The pre-processed, standard space registered images were masked with a standard space white matter mask, thresholded at 0.99 probability.

We corrected diffusion data for eddy currents and movement artifacts by 12 degrees of freedom affine linear registration to the first non-diffusion-weighted reference image. Diffusion tensors at each voxel were fitted by FSL's FDT algorithm. Non-brain parts were removed with the brain extraction tool. We calculated fractional anisotropy (FA), mean diffusivity (MD), diffusivity axial (AD) and perpendicular (RD) to the principal diffusion direction for the whole brain, and aligned all subjects' FA images into a common space, using linear and non-linear registration. To match the resolution of functional volumes, we resampled the images to 4 mm isovoxel resolution.

Extraction of White Matter Resting State Networks

We identified group level, spatially independent resting state fMRI networks using independent component analysis as implemented in FSL's MELODIC (35). We used whole study population (patients and controls together) for networks' identification. Standard space white matter images entered the analysis flow after voxel wise demeaning and variance normalization. The individual participants' 4D fMRI data were concatenated into one dataset and decomposed into a set of matrices describing spatial and temporal domains, so that they showed maximally non-Gaussian distribution (fast ICA algorithm). We set the number of independent components to 30 and thresholded component spatial maps at $p < 0.5$. We selected components for further evaluation based on the following criteria: (I) no activation outside the brain or in the gray matter, (II) temporal fluctuation and power spectrum characteristics common to resting state gray matter networks (36, 37), (III) a spatial pattern similar to the previously described white matter networks (21).

Comparison of Networks and Power Spectrum Calculation

We used a dual regression approach for comparison between resting state white matter networks by using components' spatial maps as spatial regressors against the original subject-wise fMRI data, thus obtaining subject-specific versions of network time courses. We then regressed these time courses against the original fMRI data, which yielded individual spatial layouts for each network. To assess group differences in white matter network activity, we employed a standard GLM approach, with the group membership coded in the model. We used a non-parametric permutation test (5,000 permutations) for statistical inference, assessing cluster significance with the threshold-free cluster enhancement technique (38), and correcting for multiple comparisons via family wise error (FWE) correction (39).

To decompose network activity in the frequency domain, the time courses created in the first step underwent a Fast Fourier transform, generating a power spectrum for all individuals, for each network. We compared power spectra between groups by a two-sample *t*-test.

Relationship Between Resting State Fluctuation and Diffusion Parameters

Voxel-wise correlation was calculated between the diffusion parameters and the group difference functional activity of the white matter. The analysis was restricted to the voxels showing significant group difference of functional activity at a threshold of $p < 0.05$. We used a non-parametric permutation test (5,000 permutations) for statistical inference, assessing cluster significance with the threshold-free cluster enhancement technique (38), and correcting for multiple comparisons via family wise error (FWE) correction (39).

Correlation Between MRI Parameters and Clinical Data

Correlation was calculated between the diffusion parameters, functional activity of the white matter and clinical parameters. As dependent variable visual analog pain score (VAS), disease duration and attack frequency were used. MWA and MWoA groups were treated separately in our analysis. We used non-parametric permutation test for analysis and correcting for multiple comparisons via FWE.

RESULTS

Demographical Data

Age and gender showed no significant differences between the three groups. The disease duration did not differ between the two migraine subgroups. MwoA patients showed significantly higher

VAS of headache ($p < 0.01$) and attack frequency ($p < 0.03$) compared to MWA group.

White Matter Resting State Functional Networks

Eight white matter networks were identified, according to our inclusion criteria and publication revealed previously (21). The networks' spatial distribution are shown in the **Supplementary Figure S1**. Three white matter networks showed significant difference between patients and controls:

(I) IC2 included the genu (rostrum) of the corpus callosum, fiber bundles extending bilaterally into the frontal poles.
(II) IC7 contained bundles in the body of the corpus callosum, fibers extending bilaterally into the frontal and parietal lobes.
(III) IC17 contained the bilateral occipital white matter.

Different Expression of White Matter Functional Networks

MWA Compared to MWoA

The dual regression analysis identified higher expression in MWA compared to MWoA in all three networks.

For the network representing the genu of the corpus callosum (IC2), we found differences between MWA and MWoA in the right hemisphere and also in midline (**Figure 1A**).

For the network including the white matter fibers crossing in the body of the corpus callosum (IC7) differences appeared in the left frontal anterior area and right parietal white matter (**Figure 1B**).

For the network including the bilateral occipital bundles (IC17) differences were found next to the medial side of the occipital gray matter (**Figure 1C**).

All areas with connectivity differences showed increased amplitude of fluctuation in MWA compared to MWoA.

MWA Compared to Healthy Volunteers

IC2 showed changes in the bilateral frontal white matter (**Figure 2A**). IC17 revealed changes in the right occipital pathways (**Figure 2B**). In the area of significance, the amplitude of fluctuation was higher in MWA patients compared to healthy volunteers.

MWoA Compared to Healthy Volunteers

There were no significant differences between healthy volunteers and MWoA patients in any of the white matter resting state networks.

Connection Between Resting State Fluctuation and Underlying Microstructure

The resting state fMRI fluctuation of the network including the genu of the corpus callosum (IC2) was correlated with measures of the underlying microstructure. We found positive correlation with FA ($r = 0.61$, $p < 0.05$) and negative correlation with RD ($r = -0.55$; $p < 0.05$) in MWA patients (**Figure 3**).

No other functional network activity was associated with diffusion parameters.

Correlation Between MRI Parameters and Clinical Data

None of the resting state network, neither the diffusion parameters showed correlation with clinical parameters of the patients.

DISCUSSION

Our investigation showed that white matter functional networks similar to the gray matter resting state functional networks show alterations in migraine with aura. Three white matter networks showed stronger expression, primarily higher amplitude of activity fluctuation in MWA. Furthermore, alterations of resting state functional fluctuation showed a strong association with parameters of the underlying white matter microstructure, a feature that has not been reported before.

Conventional fMRI measures the BOLD signal in the gray matter. However, several studies found task dependent activation in the white matter as well (22, 40). A combined DTI and fMRI study found functional activation in a white matter tract connected to the cortex (41). Moreover, similar to the gray matter, the effect of anesthesia and hypercapnia is detectable in the BOLD response of the white matter (42, 43). There are, however, significant differences that separate WM activation from GM activation: for example, the power spectrum of the WM response is reduced (22), and the hemodynamic response function (HRF) also differs from that in the gray matter, as the WM response delayed and has a lower amplitude (44, 45). Furthermore, the WM HRF was more variable in separate tracts under functional loading (46). Although these previous studies used specialized fMRI sequences, it is widely accepted that the measured fMRI activation strongly depends on the HRF model. The different response may be attributed to lower vascular density or diameter (47, 48), or the lack of post synaptic potentiation in the white matter (49). Furthermore, the gray matter's relatively greater vascular volume, higher cerebral blood flow, metabolism and connected hemodynamic response (49, 50) results in a higher BOLD signal (41) compared to that of the WM.

It was also presented that BOLD activity fluctuation can be measured in the WM too. Resting state fMRI fluctuation in the WM showed a temporal profile similar to the GM, with a comparable power spectrum. There is a detectable connection between GM and WM tract activation in rest (22, 23, 37). Symmetrical white matter resting state networks can be identified, which show strong overlap with anatomical white matter tracts (21).

Previous electrophysiological and MRI studies found functional alterations in MWA patients compared to MWoA and healthy volunteers. Visual evoked potential studies registered increased response in MWA patients (5, 6). A TMS meta-analysis also found lower phosphene threshold in MWA, but not in MWoA (51). The background of such altered excitability might be the alteration of local neurotransmitter milieu. Lower GABA level an indicator of reduced inhibition (52), and higher glutamate/glutamine ratio was found in the MWA (53).

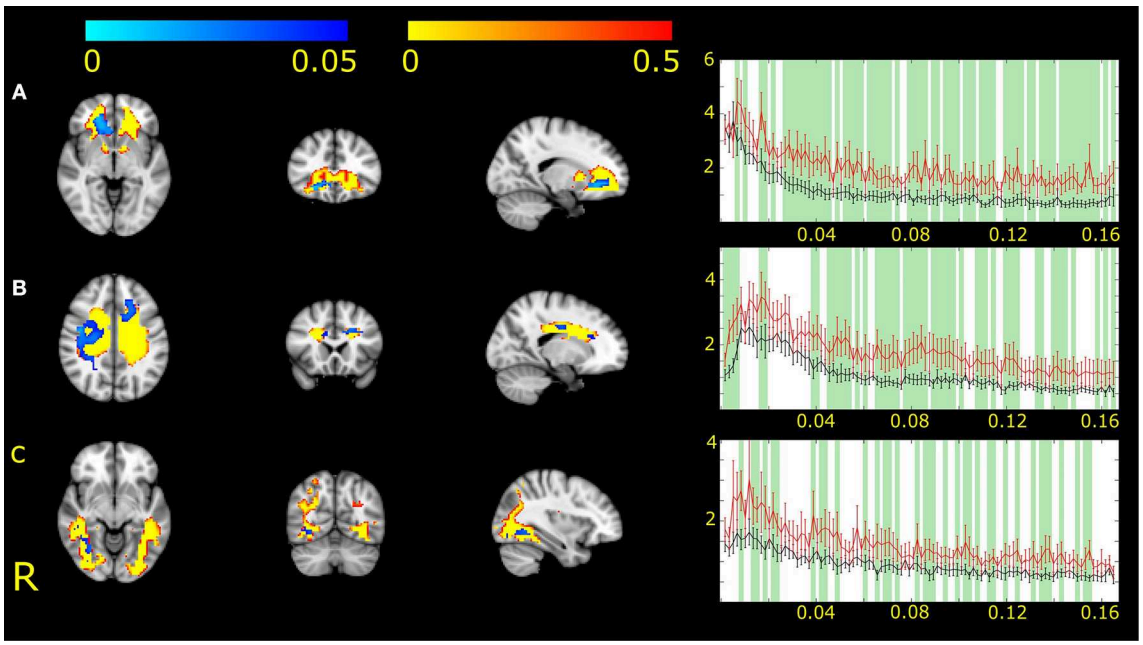


FIGURE 1 | Three white matter functional networks (IC2, **A**; IC7, **B** and IC17, **C**) had different expression in MWA and MWoA. Higher expression and amplitude was found in the case of MWA. The white matter functional networks are depicted in red-to-yellow thresholded to 0.5 probability. The group differences between MWA and MWoA is shown in blue-to-light blue thresholded at $p < 0.05$. The colorbar represents p-values. The group average Fourier spectrum presented next to the spatial maps. The red line represents MWA, the black MWoA. Green columns showed frequency values that different significantly between the two groups ($p < 0.05$).

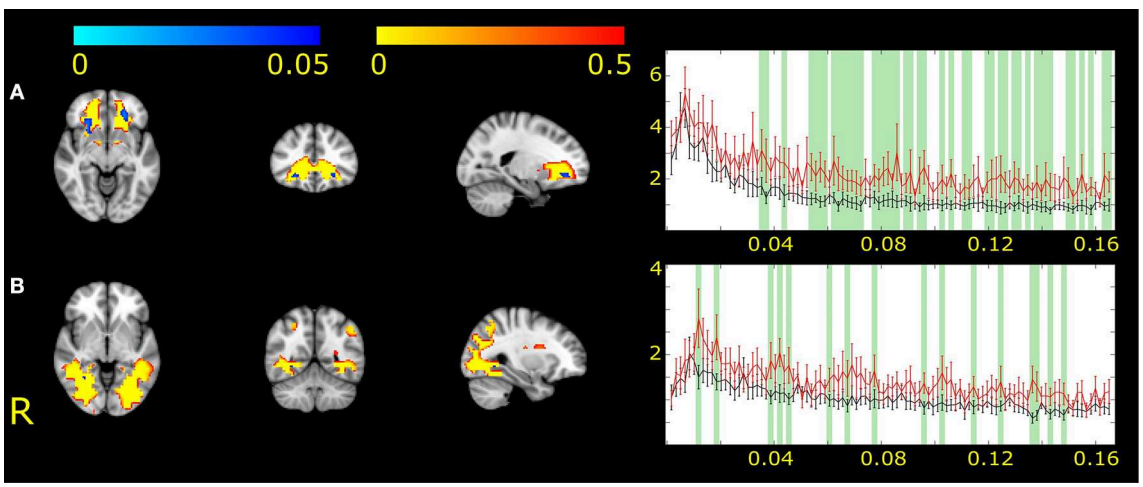


FIGURE 2 | The two white matter functional networks showing differences between MWA and healthy volunteers (IC2, **A** and IC17, **B**). The white matter functional networks are depicted in red-to-yellow and thresholded to 0.5 probability. The group differences are shown in blue-to-light blue thresholded at $p < 0.05$. The colorbar represents p-values. The group average Fourier spectrum presented next to the spatial maps. The red line represents MWA, the black controls. Green columns showed frequency values that different significantly between the two groups ($p < 0.05$).

As an indirect fMRI evidence of the altered excitability we found increased amplitude of resting BOLD fluctuation in large scale GM networks in MWA compared to MWoA (17, 52). Our analysis showed that this dysfunctions extends into the white matter, with increased connectivity and higher amplitude of BOLD fluctuation. In the background of the white matter functional alterations can stand from the connected axonal function or axonal loading transport changes, which are consequences of altered gray matter activity. The increased axonal usage generates higher energy demand that may affect the callosal much more (54). Higher activity in the occipital fibers might stem from the altered occipital neuronal activity connected

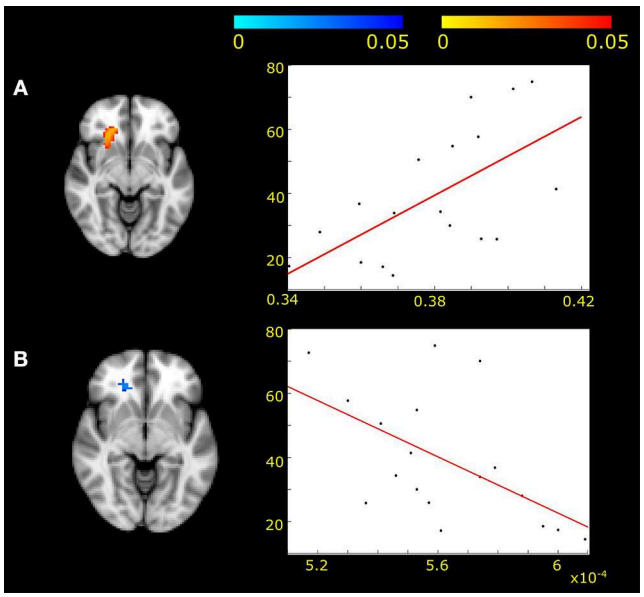


FIGURE 3 | Positive correlation was found between fractional anisotropy and frontal white matter activity fluctuations **(A)** ($p < 0.05$, corrected for multiple correlations) in MWA patients. Negative correlation was found between radial diffusivity and frontal white matter activity in the same area **(B)** ($p < 0.05$). The x axis represents the diffusion values of FA **(A)** and RD **(B)**. The y axis shows the z-scores under the specified area.

to CSD phenomenon (our MWA group of patients reported mostly visual aura).

In our earlier investigations we found white matter microstructural differences in migraine (27), mostly pronounced in MWA (28). Most importantly in the current study we found connection between microstructural and functional alterations. White matter resting state activity correlated strongly with FA and RD values of the corresponding white matter pathway, which are often interpreted as measures of myelin content and microstructural integrity (55). A recent review discusses a similar connection between fractional anisotropy and fMRI fluctuation (56), however, information about structure-function relationship in the white matter is scarce. A possible explanation for this connection is that increased myelin concentration requires an increased energy supply, which could translate to chronic BOLD fluctuation changes.

The signs of altered cortical excitability perceived not just in the gray, but also in the white matter in MWA. Being either the cause of or consequence, structural alterations can be found in migraine too, that is more pronounced in MWA. These results indicate fundamental differences in the two subtypes of the disease that needs attention in clinical care and also during development of therapeutic interventions.

Of course, out investigation is not without limitations. While the unequal size of the groups and the relatively small sample size are partially accounted for by the use of non-parametric statistical approaches these factors could potentially limit the generalisability of our findings. While theoretically one should account for multiple comparisons when investigating multiple ICs or functional networks, correction for multiple comparisons are potentially over-conservative and not frequently used in the literature.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committee of the University of Szeged (authority No.: 87/2009). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LV, ZK, NS, and PF planned the project and formulated the study hypothesis. ÁP, DS, and JT recruited the patients. ET, AK, BB, BK, DV, and KK organized and carried out the MRI measurements. BB, NS, and DV collected the clinical data. AK, PF, and DV analyzed the MRI data. DV, NS, ZK, PF, and JT formalized the discussion of the results. PF, ZK, NS, and AK wrote the manuscript.

FUNDING

The study was supported by: Neuroscience Research Group of the Hungarian Academy of Sciences and the University of Szeged, GINOP-2.3.2-15-2016-00034 grant, EFOP-3.6.1-16-2016-00008, NAP 2.0 (2017-1.2.1-NKP-2017-00002), National Brain Research Program (KTIA_13_NAP-A-II/20), UNKP-17-3 New National Excellence Program of the Ministry of Human Capacities, MTA-SZTE-Neuroscience Research Group and University of Szeged, Ministry of Human Capacities, Hungary grant (20391-3/2018/FEKUSSTRAT). BK is supported by the UNKP-18-3 New National Excellence Program of the Ministry of Human Capacities. Support was provided by the project CEITEC 2020 (LQ1601) from the Ministry of Education, Youth and Sports of the Czech Republic and from the National Center for Advancing Translational Sciences of the National Institutes of Health and European Union's Horizon 2020 research.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01039/full#supplementary-material

Supplementary Figure S1 | Spatial distibuion of the identified white matter networks.

REFERENCES

1. Lipton RB, Stewart WF, Von Korff M. Burden of migraine: societal costs and therapeutic opportunities. *Neurology.* (1997) 48:S4–9. doi: 10.1212/WNL.48.3_Suppl_3.4S
2. Pellegrino ABW, Davis-Martin RE, Houle TT, Turner DP, Smitherman TA. Perceived triggers of primary headache disorders: a meta-analysis. *Cephalalgia.* (2018) 38:1188–98. doi: 10.1177/0333102417727535
3. Charles AC, Baca SM. Cortical spreading depression and migraine. *Nat Rev Neurol.* (2013) 9:637–44. doi: 10.1038/nrneurol.2013.192
4. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annu Rev Physiol.* (2013) 75:365–91. doi: 10.1146/annurev-physiol-030212-183717
5. Sand T, Zhitniy N, White LR, Stovner LJ. Visual evoked potential latency, amplitude and habituation in migraine: a longitudinal study. *Clin Neurophysiol.* (2008) 119:1020–7. doi: 10.1016/j.clinph.2008.01.009
6. Coppola G, Bracaglia M, Di Lenola D, Di Lorenzo C, Serrao M, Parisi V, et al. Visual evoked potentials in subgroups of migraine with aura patients. *J Headache Pain.* (2015) 16:92. doi: 10.1186/s10194-015-0577-6
7. Antal A, Temme J, Nitsche MA, Varga ET, Lang N, Paulus W. Altered motion perception in migraineurs: evidence for interictal cortical hyperexcitability. *Cephalalgia.* (2005) 25:788–94. doi: 10.1111/j.1468-2982.2005.00949.x
8. Vincent M, Pedra E, Mourao-Miranda J, Bramati IE, Henrique AR, Moll J. Enhanced interictal responsiveness of the migraineous visual cortex to incongruent bar stimulation: a functional MRI visual activation study. *Cephalalgia.* (2003) 23:860–8. doi: 10.1046/j.1468-2982.2003.00609.x
9. Datta R, Aguirre GK, Hu SY, Detre JA, Cucchiara B. Interictal cortical hyperresponsiveness in migraine is directly related to the presence of aura. *Cephalalgia.* (2013) 33:365–74. doi: 10.1177/0333102412474503
10. Leao AA. Further observations on the spreading depression of activity in the cerebral cortex. *J Neurophysiol.* (1947) 10:409–14. doi: 10.1152/jn.1947.10.6.409
11. Ren J, Xiang J, Chen Y, Li F, Wu T, Shi J. Abnormal functional connectivity under somatosensory stimulation in migraine: a multi-frequency magnetoencephalography study. *J Headache Pain.* (2019) 20:3. doi: 10.1186/s10194-019-0958-3
12. Beese LC, Putzer D, Osada N, Evers S, Marziniak M. Contact heat evoked potentials and habituation measured interictally in migraineurs. *J Headache Pain.* (2015) 16:1. doi: 10.1186/1129-2377-16-1
13. Russo A, Esposito F, Conte F, Fratello M, Caiazzo G, Marcuccio L, et al. Functional interictal changes of pain processing in migraine with ictal cutaneous allodynia. *Cephalalgia.* (2017) 37:305–14. doi: 10.1177/0333102416644969
14. Kisler LB, Granovsky Y, Coghill RC, Sprecher E, Manor D, Yarnitsky D, et al. Do patients with interictal migraine modulate pain differently from healthy controls? A psychophysical and brain imaging study. *Pain.* (2018) 159:2667–77. doi: 10.1097/j.pain.0000000000001380
15. Tedeschi G, Russo A, Conte F, Corbo D, Caiazzo G, Giordano A, et al. Increased interictal visual network connectivity in patients with migraine with aura. *Cephalalgia.* (2016) 36:139–47. doi: 10.1177/0333102415584360
16. Niddam DM, Lai KL, Fuh JL, Chuang CYN, Chen WT, Wang SJ. Reduced functional connectivity between salience and visual networks in migraine with aura. *Cephalalgia.* (2016) 36:53–66. doi: 10.1177/0333102415583144
17. Farago P, Tuka B, Toth E, Szabo N, Kiraly A, Csete G, et al. Interictal brain activity differs in migraine with and without aura: resting state fMRI study. *J Headache Pain.* (2017) 18:8. doi: 10.1186/s10194-016-0716-8
18. Gawryluk JR, D'arcy RC, Mazerolle EL, Brewer KD, Beyea SD. Functional mapping in the corpus callosum: a 4T fMRI study of white matter. *Neuroimage.* (2011) 54:10–5. doi: 10.1016/j.neuroimage.2010.07.028
19. Gawryluk JR, Mazerolle EL, D'arcy RC. Does functional MRI detect activation in white matter? A review of emerging evidence, issues, and future directions. *Front Neurosci.* (2014) 8:239. doi: 10.3389/fnins.2014.00239
20. Marussich L, Lu KH, Wen HG, Liu ZM. Mapping white-matter functional organization at rest and during naturalistic visual perception. *Neuroimage.* (2017) 146:1128–41. doi: 10.1016/j.neuroimage.2016.10.005
21. Peer M, Nitzan M, Bick AS, Levin N, Arzyt S. Evidence for functional networks within the human brain's white matter. *J Neurosci.* (2017) 37:6394–407. doi: 10.1523/JNEUROSCI.3872-16.2017
22. Ding ZH, Huang YL, Bailey SK, Gao YR, Cutting LE, Rogers BP, et al. Detection of synchronous brain activity in white matter tracts at rest and under functional loading. *Proc Natl Acad Sci USA.* (2018) 115:595–600. doi: 10.1073/pnas.1711567115
23. Huang YL, Bailey SK, Wang PG, Cutting LE, Gore JC, Ding ZH. Voxel-wise detection of functional networks in white matter. *Neuroimage.* (2018) 183:544–52. doi: 10.1016/j.neuroimage.2018.08.049
24. Zhang Z, Liao M, Yao ZJ, Hu B, Xie YW, Zheng WH, et al. Frequency-specific functional connectivity density as an effective biomarker for adolescent generalized anxiety disorder. *Front Human Neurosci.* (2017) 11:549. doi: 10.3389/fnhum.2017.00549
25. Cocozza S, Pontillo G, Quarantelli M, Sacca F, Riccio E, Costabile T, et al. Default mode network modifications in Fabry disease: a resting-state fMRI study with structural correlations. *Hum Brain Mapp.* (2018) 39:1755–64. doi: 10.1002/hbm.23949
26. Jiang Y, Luo C, Li X, Li Y, Yang H, Li J, et al. White-matter functional networks changes in patients with schizophrenia. *Neuroimage.* (2018) 190:172–81. doi: 10.1016/j.neuroimage.2018.04.018
27. Szabo N, Kincses ZT, Pardutz A, Tajti J, Szok D, Tuka B, et al. White matter microstructural alterations in migraine: a diffusion-weighted MRI study. *Pain.* (2012) 153:651–6. doi: 10.1016/j.pain.2011.11.029
28. Szabo N, Farago P, Kiraly A, Vereb D, Csete G, Toth E, et al. Evidence for plastic processes in migraine with aura: a diffusion weighted MRI study. *Front Neuroanat.* (2017) 11:138. doi: 10.3389/fnana.2017.00138
29. Gohel SR, Biswal BB. Functional integration between brain regions at rest occurs in multiple-frequency bands. *Brain Connect.* (2015) 5:23–34. doi: 10.1089/brain.2013.0210
30. Zhang Z, Liao W, Chen H, Mantini D, Ding JR, Xu Q, et al. Altered functional-structural coupling of large-scale brain networks in idiopathic generalized epilepsy. *Brain.* (2011) 134:2912–28. doi: 10.1093/brain/awr223
31. Qi SL, Gao QJ, Shen J, Teng Y, Xie X, Sun YJ, et al. Multiple frequency bands analysis of large scale intrinsic brain networks and its application in schizotypal personality disorder. *Front Comput Neurosci.* (2018) 12:64. doi: 10.3389/fncom.2018.00064
32. Shen YT, Li JY, Yuan YS, Wang XX, Wang M, Wang JW, et al. Disrupted amplitude of low-frequency fluctuations and causal connectivity in Parkinson's disease with apathy. *Neurosci Lett.* (2018) 683:75–81. doi: 10.1016/j.neulet.2018.06.043
33. Xiao F, Wang T, Gao L, Fang J, Sun Z, Xu H, et al. Frequency-dependent changes of the resting BOLD signals predicts cognitive deficits in asymptomatic carotid artery stenosis. *Front Neurosci.* (2018) 12:416. doi: 10.3389/fnins.2018.00416
34. Smith SM. Fast robust automated brain extraction. *Human Brain Mapping.* (2002) 17:143–55. doi: 10.1002/hbm.10062
35. Beckmann CF, Deluca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. *Philos Transac R Soc B Biol Sci.* (2005) 360:1001–13. doi: 10.1098/rstb.2005.1634
36. Niazy RK, Xie JY, Miller K, Beckmann CF, Smith SM. Spectral characteristics of resting state networks. *Slow Brain Oscillations Sleep Resting State Vigilance.* (2011) 193:259–76. doi: 10.1016/B978-0-444-53839-0.00017-X
37. Ding ZH, Newton AT, Xu R, Anderson AW, Morgan VL, Gore JC. Spatio-temporal correlation tensors reveal functional structure in human brain. *PLoS ONE.* (2013) 8:82107. doi: 10.1371/journal.pone.0082107
38. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* (2009) 44:83–98. doi: 10.1016/j.neuroimage.2008.03.061
39. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp.* (2002) 15:1–25. doi: 10.1002/hbm.1058
40. Gawryluk JR, Mazerolle EL, Beyea SD, D'arcy RC. Functional MRI activation in white matter during the Symbol Digit Modalities Test. *Front Hum Neurosci.* (2014) 8:589. doi: 10.3389/fnhum.2014.00589
41. Mazerolle EL, Beyea SD, Gawryluk JR, Brewer KD, Bowen CV, D'arcy RCN. Confirming white matter fMRI activation in the corpus callosum: co-localization with DTI tractography. *Neuroimage.* (2010) 50:616–21. doi: 10.1016/j.neuroimage.2009.12.102

42. Rostrup E, Law I, Blinkenberg M, Larsson HBW, Born AP, Holm S, et al. Regional differences in the CBF and BOLD responses to hypercapnia: a combined PET and fMRI study. *Neuroimage.* (2000) 11:87–97. doi: 10.1006/nimg.1999.0526
43. Wu TL, Wang F, Anderson AW, Chen LM, Ding ZH, Gore JC. Effects of anesthesia on resting state BOLD signals in white matter of non-human primates. *Magnetic Resonance Imag.* (2016) 34:1235–41. doi: 10.1016/j.mri.2016.07.001
44. Fraser LM, Stevens MT, Beyea SD, D'arcy RCN. White versus gray matter: fMRI hemodynamic responses show similar characteristics, but differ in peak amplitude. *BMC Neurosci.* (2012) 13:91. doi: 10.1186/1471-2202-13-91
45. Courtemanche MJ, Sparrey CJ, Song XW, Mackay A, D'arcy RCN. Detecting white matter activity using conventional 3 Tesla fMRI: an evaluation of standard field strength and hemodynamic response function. *Neuroimage.* (2018) 169:145–50. doi: 10.1016/j.neuroimage.2017.12.008
46. Li MW, Newton AT, Anderson AW, Ding ZH, Gore JC. Characterization of the hemodynamic response function in white matter tracts for event-related fMRI. *Nat Commun.* (2019) 10:1140. doi: 10.1038/s41467-019-09076-2
47. Nonaka H, Akima M, Hatori T, Nagayama T, Zhang Z, Ihara F. Microvasculature of the human cerebral white matter: arteries of the deep white matter. *Neuropathology.* (2003) 23:111–8. doi: 10.1046/j.1440-1789.2003.00486.x
48. Mozumder M, Pozo JM, Coelho S, Costantini M, Simpson J, Highley JR, et al. Quantitative histomorphometry of capillary microstructure in deep white matter. *Neuroimage Clin.* (2019) 23:101839. doi: 10.1016/j.nicl.2019.101839
49. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature.* (2001) 412:150–7. doi: 10.1038/35084005
50. Helenius J, Perkio J, Soinne L, Ostergaard L, Carano RA, Salonen O, et al. Cerebral hemodynamics in a healthy population measured by dynamic susceptibility contrast MR imaging. *Acta Radiol.* (2003) 44:538–46. doi: 10.1034/j.1600-0455.2003.00104.x
51. Brigo F, Storti M, Tezzon F, Manganotti P, Nardone R. Primary visual cortex excitability in migraine: a systematic review with meta-analysis. *Neurol Sci.* (2013) 34:819–30. doi: 10.1007/s10072-012-1274-8
52. Bridge H, Stagg CJ, Near J, Lau CI, Zisner A, Cader MZ. Altered neurochemical coupling in the occipital cortex in migraine with visual aura. *Cephalalgia.* (2015) 35:1025–30. doi: 10.1177/0333102414566860
53. Gonzalez De La Aleja J, Ramos A, Mato-Abad V, Martinez-Salio A, Hernandez-Tamames JA, Molina JA, et al. Higher glutamate to glutamine ratios in occipital regions in women with migraine during the interictal state. *Headache.* (2013) 53:365–75. doi: 10.1111/head.12030
54. Tracey I. Imaging pain. *Br J Anaesth.* (2008) 101:32–9. doi: 10.1093/bja/aen102
55. Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage.* (2005) 26:132–40. doi: 10.1016/j.neuroimage.2005.01.028
56. Warbrick T, Rosenberg J, Shah NJ. The relationship between BOLD fMRI response and the underlying white matter as measured by fractional anisotropy (FA): a systematic review. *Neuroimage.* (2017) 153:369–81. doi: 10.1016/j.neuroimage.2016.12.075

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 02 October 2019
doi: 10.3389/fneur.2019.00982

Are Migraine With and Without Aura Really Different Entities?

Zsigmond Tamás Kincses[1,2†], Dániel Veréb[1†], Péter Faragó[1], Eszter Tóth[1], Krisztián Kocsis[1], Bálint Kincses[1], András Király[1,3], Bence Bozsik[1], Árpád Párdutz[1], Délia Szok[1], János Tajti[1], László Vécsei[1,4], Bernadett Tuka[1,4] and Nikoletta Szabó[1,3]*

[1] Department of Neurology, Faculty of Medicine, Interdisciplinary Excellent Centre, University of Szeged, Szeged, Hungary, [2] Department of Radiology, University of Szeged, Szeged, Hungary, [3] Brain and Mind Research, Central European Institute of Technology, Brno, Czechia, [4] MTA-SZTE, Neuroscience Research Group, Szeged, Hungary

Background: Migraine research is booming with the rapidly developing neuroimaging tools. Structural and functional alterations of the migrainous brain were detected with MRI. The outcome of a research study largely depends on the working hypothesis, on the chosen measurement approach and also on the subject selection. Against all evidence from the literature that migraine subtypes are different, most of the studies handle migraine with and without aura as one disease.

Methods: Publications from PubMed database were searched for terms of "migraine with aura," "migraine without aura," "interictal," "MRI," "diffusion weighted MRI," "functional MRI," "compared to," "atrophy" alone and in combination.

Conclusion: Only a few imaging studies compared the two subforms of the disease, migraine with aura, and without aura, directly. Functional imaging investigations largely agree that there is an increased activity/activation of the brain in migraine with aura as compared to migraine without aura. We propose that this might be the signature of cortical hyperexcitability. However, structural investigations are not equivocal. We propose that variable contribution of parallel, competing mechanisms of maladaptive plasticity and neurodegeneration might be the reason behind the variable results.

Keywords: DTI, functional MRI, microstructure, migraine with and without aura, pathomechanism

OPEN ACCESS

Edited by:
Massimo Filippi, Vita-Salute San Raffaele University, Italy

Reviewed by:
Claudia Altamura, Campus Bio-Medico University, Italy
Marco Carotenuto, University of Campania Luigi Vanvitelli, Italy

****Correspondence:***
Zsigmond Tamás Kincses
kincses.zsigmond.tamas@med.u-szeged.hu

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *30 June 2019*
Accepted: *28 August 2019*
Published: *02 October 2019*

Citation:
Kincses ZT, Veréb D, Faragó P, Tóth E, Kocsis K, Kincses B, Király A, Bozsik B, Párdutz Á, Szok D, Tajti J, Vécsei L, Tuka B and Szabó N (2019) Are Migraine With and Without Aura Really Different Entities? Front. Neurol. 10:982. doi: 10.3389/fneur.2019.00982

INTRODUCTION

Migraine is a heterogeneous disease affecting cca 10–20% of the population worldwide. It is associated with significant disability, reduced quality of life, and consequently poses an enormous financial burden to society (1). Since migraine ranks among the top disorders causing disability (2). It is in the focus of neuroimaging, molecular, and pharmaceutical research. In 20% of the cases, migraine headache is preceded or accompanied by reversible focal neurological symptoms, such as visual, motor, sensory, or speech disturbances (3). The ICHD-3 classification (4) bases the diagnosis of migraine on the patient's medical history and physical examination. Accordingly, migraine can be categorized into migraine with aura (MWA) and without aura (MWoA) as subtypes of the disease (among other categories). Besides the similarities in the epidemiology, clinical presentation, and the genetic evidence that MWA and MWoA largely overlap (5), the question has been raised a few years ago: are MWA and MWoA separate entities (6–8) or rather the two ends of a spectrum? Nevertheless, studying mixed groups of migraine patients should be

avoided in further investigations if critical differences exist. Nevertheless, studying mixed groups of migraine patients should be avoided in further investigations if critical differences exist.

Since magnetic resonance imaging (MRI) makes it possible to investigate the structure and function of the brain *in vivo*, hundreds of papers were published in the last 20 years that describe the migrainous brain using neuroimaging methodology. The majority of these studies examined mixed patient groups or compared only one subtype to healthy individuals.

This review article summarizes the most significant neuroimaging results from studies comparing MWA patients to MWoA. To identify relevant articles, we searched the PubMed database for terms of "migraine with aura," "migraine without aura," "interictal," "MRI," "diffusion weighted MRI" (DWI), "functional MRI" (fMRI), "compared to," "atrophy" alone and in combination up to June 2019.

RESULTS FROM FUNCTIONAL NEUROIMAGING

Brain activity during rest and task performance can be described non-invasively by measuring the blood oxygen level dependent (BOLD) signal with functional MRI. Traditional fMRI studies compare signal differences in various phases of a task, but recently, there has also been a growing interest in studying brain activity patterns during rest. Interestingly, remote areas show synchronous activity, which renders resting state activity into functional networks (9, 10). Although fMRI parameters remain basically the same, we are witnessing a rapid development in the statistical analysis of fMRI scans.

Two publications confirmed brain activation differences between MWA and MWoA in the interictal phase (11, 12). Datta et al. (11) described higher BOLD response in migraine in response to visual stimuli in a BOLD fMRI study. This higher BOLD response was more robust in MWA than in MWoA patients. Interestingly the resting perfusion parameters of the two groups was not different, hence the authors discussed their finding in the light of the existing evidences that it relates to hyperresponsiveness of the visual cortex in MWA. On the contrary, resting brain perfusion did not differ between patients and controls or between MWA and MWoA patients (11). In a considerably larger cohort Cucchiara et al. found similarly greater BOLD amplitude in the visual cortex in MWA that positively correlated with visual discomfort score. No such correlation was found in MWoA (12).

Limited data are available on resting brain activity. Increased expression of the visual resting functional network was found in MWA compared to MWoA and controls (13). In our earlier investigation we found higher amplitude of resting state activity fluctuation in all identified resting state networks in the 0.08–0.04 Hz frequency range in MWA as compared to MWoA (14). On the contrary, lower amplitudes were found in the default mode network in MWoA compared to controls.

Reduced connectivity between the occipital lobe and anterior insula was found in MWA but not in MWoA, and the connectivity strength correlated with migraine severity in MWA (15). Increased connectivity was found in the default mode network in the pre-central gyrus, post-central gyrus, insular cortex, angular gyrus, supramarginal gyrus in MWA compared to MWoA (16).

RESULTS FROM STRUCTURAL NEUROIMAGING

Cortical Thickness

Several investigations have shown that there are gray matter alterations in migraine: the gray matter density of several pain related cortical regions is reduced compared to healthy individuals (17). It should be noted that similar brain structural alterations were found in other chronic pain conditions. Importantly, only a few investigations concentrated on comparing the two subgroups of migraine.

Granziera et al. found increased cortical thickness and altered microstructure in migraineurs in the white matter beneath motion processing areas, namely motion processing visual areas and V3A area, but there were no differences between MWA and MWoA patients (18). In a similar cohort, voxel-based morphometry (VBM) did not detect any differences between the two patient groups (13). In a multicentre study involving a considerably larger migraine population, MWoA patients exhibited thinner cortex in the left central sulcus, in the left occipito-temporal gyrus, in the right cuneus and the superior parietal gyrus bilaterally. In some of these regions, the cortical thickness correlated with the frequency of migraine attacks and disease duration (19). Interestingly, a few of these regions were not only thinner in MWoA as compared to controls, but also when compared to MWA.

Diffusion Tensor Imaging

Among the structural abnormalities, white matter microstructure changes, as described by DWI, are receiving more and more attention. DWI is sensitive to the diffusion of water molecules, which in the brain is largely restricted by the membranes of cellular and sub-cellular elements. By fitting a diffusion tensor model it is possible to estimate diffusion parameters that reflect the microscopic organization of the measured volume (20).

White matter microstructural changes in MWA were reported, but studies are not congruent in calculated diffusion parameters and results. DaSilva et al. presented lower fractional anisotropy (FA) in the ventral trigemino-thalamic pathway in MWA and lower FA was detected in the ventrolateral periaqueductal gray matter (PAG) in MWoA (21). No correlation was found with clinical parameters. While migraineurs showed reduced FA subjacent to visual motion processing areas, no differences in diffusion parameters were found between MWA and MWoA (18). Similarly, tract-based-spatial statistics (TBSS) and a pre-defined region-of-interest analysis from fMRI results did not reveal microstructural white matter alterations between the two subtypes (13, 22). On the other hand, we found extensive white matter regions showing higher FA in MWA in a whole brain TBSS analysis (8). Also, we found that clinical parameters, such as disease duration and estimated lifetime attack number were associated with lower axial diffusivity (AD) in the left

superior longitudinal fascicle, the left corticospinal tract and with the right superior longitudinal fascicle of MWA patients (8).

DISCUSSION

There are only few neurological disorders that were investigated so extensively and the hypotheses for its pathophysiology went through such evolution like migraine. In spite of this enormous body of research, the "migraine puzzle" is still incomplete. While migraine was thought to be a functional disease of the brain, recent studies have shown that brain structure and microstructure also exhibit profound alterations. Independent MRI studies observed functional and structural differences between MWA and MWoA in the interictal period. In summary, it can be pointed out that studies concur in finding higher brain activity/activation in MWA, but structural differences between the two subtypes of the disease are not so well-established, and results are ambiguous in the literature (**Table 1**).

In MWA, during the transient visual, sensory or language symptoms a slow depolarization wave called cortical spreading depression (CSD) spreads through the cortex (23). During visual aura, BOLD signal changes develop in the occipital cortex and progress slowly, reflecting underlying depolarization waves (24). Apart from being the putative cause of the aura symptoms, CSD has been associated with neuroinflammation, possibly contributing further to the headache by activating the meningeal nociceptors and the neurons in the spinal trigeminal nucleus and trigeminal nucleus caudalis (25, 26). Neurophysiological investigations showed that the two subtypes of the disease differ considerably. The amplitudes of visual evoked potentials (VEP) were higher in migraineurs (27–30). Recent reports showed that hyperexcitability, as measured via VEP is predominantly true for MWA (31, 32). The threshold of transcranial magnetic stimulation (TMS) evoked phosphenes is also lower in migraineurs and the prevalence of phosphenes is higher (33). Interestingly, a recent metaanalysis pointed out that, similarly to the VEP results, this kind of TMS measured hyperexcitability is only true for patients experiencing aura (34). Moreover, the perception of cross-modal interaction that depends highly on cortical hyperexcitability differs between healthy volunteers and migraineurs (35). The effect is more pronounced in MWA. A possible background mechanism behind this hyperexcitability might be the altered neurochemical milieu, the imbalance of the excitatory and inhibitory neurotransmitter levels in migraineurs as detected by MR spectroscopy or other neurochemical approaches [e.g., glutamate and GABA, see (36, 37) for a review]. However, no study investigated the differences between MWA and MWoA. The above-mentioned functional imaging studies also demonstrated higher activation/activity in MWA. Considering that hyperexcitability comes along with increased firing frequency (38) that has a higher energy demand, it easily follows that BOLD fMRI studies find increased amplitude of response or resting activity fluctuation. In consequence to this increased activity, especially if it is regionally specific, interregional connections might strengthen, that could be measured as increased functional connectivity.

TABLE 1 | Structural and functional MRI studies comparing migraine without to migraine with aura.

Method	Subjects	Main findings
BOLD fMRI; resting ASL Datta et al. (11)	25 MWA, 25 MwoA, 25 controls	Robust visual pathway activation was in MWA. ASL showed no difference.
BOLD fMRI Cucchiara et al. (12)	51 MWA, 45 MwoA, 45 controls	Greater visual cortex activation and correlation with light sensitivity in MWA.
RSN fMRI; DTI Tedeschi et al. (13)	20 MWA, 20 MwoA, 20 controls	Increased component activity was in lingual gyrus from visual network in MWA. Structural analysis showed no differences.
RSN fMRI; T1 Niddam et al. (15)	26 MWA, 26 MwoA, 26 controls	Reduced connectivity was between visual cortex and insula in MWA. The right parahippocampal region was decreased in MWA.
RSN fMRI Lo Buono (16)	14 MWA, 14 MwoA, 14 controls	Increased functional connectivity was in angular gyrus, supramarginal gyrus, pre-central gyrus, post-central gyrus, insular cortex in MWA.
RSN fMRI Faragó et al. (14)	18 MWA, 33 MwoA, 32 controls	Amplitude of RSN fluctuation is higher in MWA: cingulate cortex, superior parietal lobule, cerebellum and bilateral frontal regions.
DTI Tessitore et al. (22)	20 MWA, 20 MwoA, 20 controls	TBSS and VBM analyses detected no differences.
DTI, T1 DaSilva et al. (21)	12 MWA, 12 MwoA, 12 controls	Trigeminothalamic tract and periaqueductal gray area showed difference in FA.
DTI Granziera et al. (18)	12 MWA, 12 MwoA, 15 controls	White matter analysis and cortical thickening showed no differences.
T1 Magon et al. (19)	38 MWA, 93 MwoA, 115 controls	MWoA showed thinner cortex: left central sulcus, left occipito-temporal gyrus, right cuneus, bilateral superior parietal gyrus; MWoA showed thicker cortex: inferior temporal gyrus.
DTI Szabó et al. (8)	18 MWA, 25 MwoA, 28 controls	FA was higher in left parieto-occipital white matter in MWA. Clinical parameters correlated with white matter integrity in MWA.

Nevertheless, one should not forget that fMRI is measuring the indirect vascular response to neuronal activity/activation. Since migraine is a neurovascular disease the identified differences in any fMRI study might be due to the filtering effect of the altered hemodynamic response function. In fact, altered vasomotor reactivity was identified in MWA (39).

The results of structural investigations are far less equivocal about the differences between the two subtypes of the disease.

A prominent reason behind the differences in the outcome of the structural studies might be the pathomechanism itself. Structural alterations could either be a (1) consequence or the (2) cause of the disease. In case of the former, one might consider two alternatives:

(a) The recurring painful attacks and hyperexcitability could lead to maladaptive plasticity. Use-dependent plasticity induced morphological changes are well-known in the gray

and white matter (40–42). Repeated pain stimuli can also increase gray matter density in pain processing regions including the cingulate and the contralateral somatosensory cortex (43). One might hypothesize that the increased firing frequency due to hyperexcitability may induce similar use-dependent plastic changes. And finally, plastic changes were reported in animals after induction of CSD (44, 45). These processes presumably appear in the form of increased FA and thickened cortex (40–42).

(b) The underlying pathology might also cause degenerative processes in migraine. CSD might well-contribute to the noxious process (46), as it induces neuroinflammation and cellular damage (47–49). The recurring painful attacks and the cortical hyperexcitability might lead to excessive glutamate release (50), which is also known to induce excitotoxicity and cell death (51). CSD causes upregulation of matrix-metalloproteases (MMP) (52) and increased MMP activity was described in human migraineurs (53). This can lead to the leakage of the blood-brain barrier and inflammatory response and neuronal damage (54). In line with these hypotheses, increased ictal levels of S100B (a marker of glial damage) and neuron specific enolase (a marker of neuronal damage) were detected in migraineurs (55). These degenerative processes could presumably appear in the form of white matter disintegration (reduction of FA) and cortical atrophy.

We propose that these parallel, competing mechanisms coexist, but their relative contribution is different in MWA and MWoA. However, one might see the two sub-forms of the disease a spectrum, rather than two distinct entities and hence homogenous patient groups cannot be reproducibly formed.

An alternative explanation for the structural alterations might well-be that they are not consequential but rather causal factors of the disease. Accordingly, the genetic background is different between the two subtypes. Pisanu et al. demonstrated that genetic risk factors calculated on migraine-associated single nucleotide polymorphism differ between subgroups suggesting MWA and MWoA have different genetic backgrounds that contribute to the pathogenesis (56). Even so, we cannot exclude the possibility that co-morbidities and epigenetics have an influence on migraine pathogenesis (57, 58).

A number of findings showed that the clinical expression of migraine is consistent with perivascular trigeminal activation and release of neuropeptides [calcitonin gene-related peptide (CGRP), substance P and pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38)] (59–66). It was also shown that CSD is tightly connected to CGRP release (67). Several aspects of the CGRP-related trigemino-vascular functions are also abnormal in FHM1-mutant mice showing an overall hyperexcitability phenotype (68). We showed that interictal PACAP-38 concentrations were lower in migraineurs, which approached normal levels during headache (69) and this altered interictal PACAP-38 serum level correlated with the microstructural integrity of pain related brain structures (70). Whether neuropeptide concentrations are different in MWA and MWoA is still to be investigated.

Whether CSD is the initiator of all the events of migraine attack (activation of distinct brain stem nuclei, neuropeptide release at the periphery, activation, and sensitization at the level of trigeminal nociceptors) remains controversial: although that there is evidence that CSD can induce activation trigeminal nociception in animals (71), but migrainous aura can occur without headache and the pain can start during the aura onset, moreover most of the migraineurs do not experience aura phenomenon at all, which suggests that CSD alone is insufficient and non-essential for the attack. If the latter is true CSD is not the cause, but the consequence or a part of the disease (72).

Importantly, several other reasons could be pointed out behind the variable results of structural studies. For example, the headache frequency is different in MWA and MWoA (73), which means the studies should be strictly matched for clinical parameters. The time since the last and until the next headache should also be strictly monitored. Unfortunately, none of the above mentioned studies are controlled for these factors.

Importantly, we have not considered white matter hyperintensities in our review in details, but it has to be pointed out that the prevalence of these lesions are also different in the two subtypes of the diseases (74, 75). The etiology of these lesions is not entirely clear yet, but thought to be microinfarction with a numerous factors contributing to it. Neurogenic inflammation, endothelial changes, thrombocyte aggregation may play a role, and the induced oligaemia might be deepened by the CSD (76).

CONCLUSION

Among primary headache disorders, migraine is a heterogeneous disease with two major subtypes. Functional imaging studies repeatedly confirmed various metrics of hyperexcitability. The results of structural imaging studies are far from being equivocal. We propose that variable contribution of parallel, competing mechanisms of maladaptive plasticity and neurodegeneration might be the reason behind the variable results. Therefore, in further research projects MWA and MWoA should be handled separately and groups should be strictly matched for clinical parameters if the two subtypes are directly compared.

AUTHOR CONTRIBUTIONS

ZK, DV, LV, and NS formulated the review hypothesis. NS, ZK, KK, ET, BB, BK, PF, DS, ÁP, BT, AK, JT, and DV went through on literature, collected the articles. NS, DV, and ZK wrote the manuscript.

FUNDING

This study was supported by Neuroscience Research Group of the Hungarian Academy of Sciences and the University of Szeged, GINOP-2.3.2-15-2016-00034 grant, EFOP-3.6.1-16-2016-00008, NAP 2.0 (2017-1.2.1-NKP-2017-00002), National Brain Research Program (KTIA_13_NAP-A-II/20), UNKP-17-3 New National Excellence Program of the Ministry of Human Capacities, also University of Szeged, Ministry of Human Capacities, Hungary grant (20391-3/2018/FEKUSSTRAT). BK was supported by the

UNKP-18-3 New National Excellence Program of the Ministry of Human Capacities. Support was provided by the project CEITEC 2020 (LQ1601) from the Ministry of Education, Youth and Sports of the Czech Republic and from the National Center for Advancing Translational Sciences of the National Institutes of Health and European Union's Horizon 2020 research.

REFERENCES

1. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. *Headache*. (2005) 45(Suppl. 1):S3–13. doi: 10.1111/j.1526-4610.2005.4501001.x
2. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. (2016) 388:1545–602. doi: 10.1016/S0140-6736(16)31678-6
3. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain*. (1994) 117:199–210. doi: 10.1093/brain/117.1.199
4. Headache classification committee of the International Headache Society (IHS) the International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202
5. Zhao H, Eising E, de Vries B, Vijfhuizen LS, International Headache Genetics C, Anttila V, et al. Gene-based pleiotropy across migraine with aura and migraine without aura patient groups. *Cephalalgia*. (2016) 36:648–57. doi: 10.1177/0333102415591497
6. Ranson R, Igarashi H, MacGregor EA, Wilkinson M. The similarities and differences of migraine with aura and migraine without aura: a preliminary study. *Cephalalgia*. (1991) 11:189–92. doi: 10.1046/j.1468-2982.1991.1104189.x
7. Manzoni GC, Torelli P. Migraine with and without aura: a single entity? *Neurol Sci.* (2008) 29(Suppl 1):S40–3. doi: 10.1007/s10072-008-0884-7
8. Szabó N, Farago P, Kiraly A, Vereb D, Csete G, Toth E, et al. Evidence for plastic processes in migraine with aura: a diffusion weighted MRI study. *Front Neuroanat*. (2017) 11:138. doi: 10.3389/fnana.2017.00138
9. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci*. (2005) 360:1001–13. doi: 10.1098/rstb.2005.1634
10. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M. Electrophysiological signatures of resting state networks in the human brain. *Proc Natl Acad Sci USA*. (2007) 104:13170–5. doi: 10.1073/pnas.0700668104
11. Datta R, Aguirre GK, Hu S, Detre JA, Cucchiara B. Interictal cortical hyperresponsiveness in migraine is directly related to the presence of aura. *Cephalalgia*. (2013) 33:365–74. doi: 10.1177/0333102412474503
12. Cucchiara B, Datta R, Aguirre GK, Idoko KE, Detre J. Measurement of visual sensitivity in migraine: validation of two scales and correlation with visual cortex activation. *Cephalalgia*. (2015) 35:585–92. doi: 10.1177/0333102414547782
13. Tedeschi G, Russo A, Conte F, Corbo D, Caiazzo G, Giordano A, et al. Increased interictal visual network connectivity in patients with migraine with aura. *Cephalalgia*. (2016) 36:139–47. doi: 10.1177/0333102415584360
14. Farago P, Tuka B, Toth E, Szabo N, Kiraly A, Csete G, et al. Interictal brain activity differs in migraine with and without aura: resting state fMRI study. *J Headache Pain*. (2017) 18:8. doi: 10.1186/s10194-016-0716-8
15. Niddam DM, Lai KL, Fuh JL, Chuang CY, Chen WT, Wang SJ. Reduced functional connectivity between salience and visual networks in migraine with aura. *Cephalalgia*. (2016) 36:53–66. doi: 10.1177/0333102415583144
16. Lo Buono V, Bonanno L, Corallo F, Pisani LR, Lo Presti R, Grugno R, et al. Functional connectivity and cognitive impairment in migraine with and without aura. *J Headache Pain*. (2017) 18:72. doi: 10.1186/s10194-017-0782-6
17. May A. Pearls and pitfalls: neuroimaging in headache. *Cephalalgia*. (2013) 33:554–65. doi: 10.1177/0333102412467513
18. Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. *PLoS Med*. (2006) 3:e402. doi: 10.1371/journal.pmed.0030402
19. Magon S, May A, Stankewitz A, Goadsby PJ, Schankin C, Ashina M, et al. Cortical abnormalities in episodic migraine: a multi-center 3T MRI study. *Cephalalgia*. (2019) 39:665–73. doi: 10.1177/0333102418795163
20. Beaulieu C. The basis of anisotropic water diffusion in the nervous system–a technical review. *NMR Biomed*. (2002) 15:435–55. doi: 10.1002/nbm.782
21. DaSilva AF, Granziera C, Tuch DS, Snyder J, Vincent M, Hadjikhani N. Interictal alterations of the trigeminal somatosensory pathway and periaqueductal gray matter in migraine. *Neuroreport*. (2007) 18:301–5. doi: 10.1097/WNR.0b013e32801776bb
22. Tessitore A, Russo A, Conte F, Giordano A, De Stefano M, Lavorgna L, et al. Abnormal connectivity within executive resting-state network in migraine with aura. *Headache*. (2015). 55:794–805. doi: 10.1111/head.12587
23. Leao A. Spreading depression of activity in the cerebral cortex. *J Neurophysiol*. (1944) 7:359–90. doi: 10.1152/jn.1944.7.6.359
24. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA*. (2001) 98:4687–92. doi: 10.1073/pnas.071582498
25. Moskowitz MA, Macfarlane R. Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev*. (1993) 5:159–77.
26. Moskowitz MA, Nozaki K, Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. *J Neurosci*. (1993) 13:1167–77. doi: 10.1523/JNEUROSCI.13-03-01167.1993
27. Connolly JF, Gawel M, Rose FC. Migraine patients exhibit abnormalities in the visual evoked potential. *J Neurol Neurosurg Psychiatry*. (1982) 45:464–7. doi: 10.1136/jnnp.45.5.464
28. Gawel M, Connolly JF, Rose FC. Migraine patients exhibit abnormalities in the visual evoked potential. *Headache*. (1983) 23:49–52. doi: 10.1111/j.1526-4610.1983.hed2302049.x
29. Diener HC, Scholz E, Dichgans J, Gerber WD, Jack A, Bille A, et al. Central effects of drugs used in migraine prophylaxis evaluated by visual evoked potentials. *Ann Neurol*. (1989) 25:125–30. doi: 10.1002/ana.410250204
30. Oelkers R, Grosser K, Lang E, Geisslinger G, Kobal G, Brune K, et al. Visual evoked potentials in migraine patients: alterations depend on pattern spatial frequency. *Brain*. (1999) 122:1147–55. doi: 10.1093/brain/122.6.1147
31. Sand T, Zhitniy N, White LR, Stovner LJ. Visual evoked potential latency, amplitude and habituation in migraine: a longitudinal study. *Clin Neurophysiol*. (2008) 119:1020–7. doi: 10.1016/j.clinph.2008.01.009
32. Coppola G, Bracaglia M, Di Lenola D, Di Lorenzo C, Serrao M, Parisi V, et al. Visual evoked potentials in subgroups of migraine with aura patients. *J Headache Pain*. (2015) 16:92. doi: 10.1186/s10194-015-0577-6
33. Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P, Ramadan NM. Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. *Neurology*. (1998) 50:1111–4. doi: 10.1212/WNL.50.4.1111
34. Brigo F, Storti M, Tezzon F, Manganotti P, Nardone R. Primary visual cortex excitability in migraine: a systematic review with meta-analysis. *Neurol Sci*. (2013) 34:819–30. doi: 10.1007/s10072-012-1274-8
35. Brighina F, Bolognini N, Cosentino G, Maccora S, Paladino P, Baschi R, et al. Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions. *Neurology*. (2015) 84:2057–61. doi: 10.1212/WNL.0000000000001584
36. Younis S, Hougaard A, Vestergaard MB, Larsson HBW, Ashina M. Migraine and magnetic resonance spectroscopy: a systematic review. *Curr Opin Neurol*. (2017) 30:246–62. doi: 10.1097/WCO.0000000000000436
37. Tajti J, Szok D, Nagy-Grocz G, Tuka B, Petrovics-Balog A, Toldi J, et al. Kynurenines and PACAP in migraine: medicinal chemistry and pathogenetic aspects. *Curr Med Chem*. (2017) 24:1332–49. doi: 10.2174/0929867324666170227115019
38. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J Physiol*. (1964) 172:369–82. doi: 10.1113/jphysiol.1964.sp007425
39. Wolf ME, Jäger T, Bäzner H, Hennerici M. Changes in functional vasomotor reactivity in migraine with aura. *Cephalalgia*. (2009) 29:1156–64. doi: 10.1111/j.1468-2982.2009.01843.x

40. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. *Nature*. (2004) 427:311–2. doi: 10.1038/427311a
41. Boyke J, Driemeyer J, Gaser C, Buchel C, May A. Training-induced brain structure changes in the elderly. *J Neurosci*. (2008) 28:7031–5. doi: 10.1523/JNEUROSCI.0742-08.2008
42. Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white-matter architecture. *Nat Neurosci*. (2009) 12:1370–1. doi: 10.1038/nn.2412
43. Teutsch S, Herken W, Bingel U, Schoell E, May A. Changes in brain gray matter due to repetitive painful stimulation. *Neuroimage*. (2008) 42:845–9. doi: 10.1016/j.neuroimage.2008.05.044
44. Dehbandi S, Speckmann EJ, Pape HC, Gorji A. Cortical spreading depression modulates synaptic transmission of the rat lateral amygdala. *Eur J Neurosci*. (2008) 27:2057–65. doi: 10.1111/j.1460-9568.2008.06188.x
45. Haghir H, Kovac S, Speckmann EJ, Zilles K, Gorji A. Patterns of neurotransmitter receptor distributions following cortical spreading depression. *Neuroscience*. (2009) 163:1340–52. doi: 10.1016/j.neuroscience.2009.07.067
46. Moskowitz MA. Pathophysiology of headache–past and present. *Headache*. (2007) 47(Suppl 1):S58–63. doi: 10.1111/j.1526-4610.2007.00678.x
47. Arnold G, Reuter U, Kinze S, Wolf T, Einhaupl KM. Migraine with aura shows gadolinium enhancement which is reversed following prophylactic treatment. *Cephalalgia*. (1998) 18:644–6. doi: 10.1046/j.1468-2982.1998.1809644.x
48. Knotkova H, Pappagallo M. Imaging intracranial plasma extravasation in a migraine patient: a case report. *Pain Med*. (2007) 8:383–7. doi: 10.1111/j.1526-4637.2006.00197.x
49. Cui Y, Takashima T, Takashima-Hirano M, Wada Y, Shukuri M, Tamura Y, et al. 11C-PK11195 PET for the *in vivo* evaluation of neuroinflammation in the rat brain after cortical spreading depression. *J Nucl Med*. (2009) 50:1904–11. doi: 10.2967/jnumed.109.066498
50. D'Andrea G, Cananzi AR, Joseph R, Morra M, Zamberlan F, Ferro Milone F, et al. Platelet glycine, glutamate and aspartate in primary headache. *Cephalalgia*. (1991) 11:197–200. doi: 10.1046/j.1468-2982.1991.1104197.x
51. Longoni M, Ferrarese C. Inflammation and excitotoxicity: role in migraine pathogenesis. *Neurol Sci. (*2006) 27(Suppl 2):S107–10. doi: 10.1007/s10072-006-0582-2
52. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bermpohl D, Jin H, et al. Cortical spreading depression activates and upregulates MMP-9. *J Clin Invest*. (2004) 113:1447–55. doi: 10.1172/JCI200421227
53. Bernecker C, Pailer S, Kieslinger P, Horejsi R, Moller R, Lechner A, et al. Increased matrix metalloproteinase activity is associated with migraine and migraine-related metabolic dysfunctions. *Eur J Neurol*. (2010) 18:571–6. doi: 10.1111/j.1468-1331.2010.03205.x
54. Gupta VK. CSD, BBB and MMP-9 elevations: animal experiments versus clinical phenomena in migraine. *Expert Rev Neurother*. (2009) 9:1595–614. doi: 10.1586/ern.09.103
55. Yilmaz N, Karaali K, Ozdem S, Turkay M, Unal A, Dora B. Elevated S100B and neuron specific enolase levels in patients with migraine-without aura: evidence for neurodegeneration? *Cell Mol Neurobiol*. (2011) 31:579–85. doi: 10.1007/s10571-011-9651-z
56. Pisanu C, Preisig M, Castelao E, Glaus J, Pistis G, Squassina A, et al. A genetic risk score is differentially associated with migraine with and without aura. *Hum Genet*. (2017) 136:999–1008. doi: 10.1007/s00439-017-1816-5
57. Yang MH, Yang FY, Oyang YJ. Application of density estimation algorithms in analyzing co-morbidities of migraine. *Netw Model Anal Health Inform Bioinform*. (2013) 2:95–107. doi: 10.1007/s13721-013-0028-8
58. Roos-Araujo D, Stuart S, Lea RA, Haupt LM, Griffiths LR. Epigenetics and migraine; complex mitochondrial interactions contributing to disease susceptibility. *Gene*. (2014) 543:1–7. doi: 10.1016/j.gene.2014.04.001
59. Knyihar-Csillik E, Tajti J, Mohtasham S, Sari G, Vecsei L. Electrical stimulation of the Gasserian ganglion induces structural alterations of calcitonin gene-related peptide-immunoreactive perivascular sensory nerve terminals in the rat cerebral dura mater: a possible model of migraine headache. *Neurosci Lett*. (1995) 184:189–92. doi: 10.1016/0304-3940(94)11203-U
60. Knyihar-Csillik E, Tajti J, Chadaide Z, Csillik B, Vecsei L. Functional immunohistochemistry of neuropeptides and nitric oxide synthase in the nerve fibers of the supratentorial dura mater in an experimental migraine model. *Microsc Res Tech*. (2001) 53:193–211. doi: 10.1002/jemt.1084
61. Knyihar-Csillik E, Chadaide Z, Okuno E, Krisztin-Peva B, Toldi J, Varga C, et al. Kynurenine aminotransferase in the supratentorial dura mater of the rat: effect of stimulation of the trigeminal ganglion. *Exp Neurol*. (2004) 186:242–7. doi: 10.1016/j.expneurol.2003.12.001
62. Villalon CM, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. *Pharmacol Ther*. (2009) 124:309–23. doi: 10.1016/j.pharmthera.2009.09.003
63. Olesen J. Calcitonin gene-related peptide. (CGRP) in migraine. *Cephalalgia*. (2010). doi: 10.1177/0333102410388438
64. Tajti J, Pardutz A, Vamos E, Tuka B, Kuris A, Bohar Z, et al. Migraine is a neuronal disease. *J Neural Transm*. (2010) 118:511–24. doi: 10.1007/s00702-010-0515-3
65. Tuka B, Helyes Z, Markovics A, Bagoly T, Nemeth J, Mark L, et al. Peripheral and central alterations of pituitary adenylate cyclase activating polypeptide-like immunoreactivity in the rat in response to activation of the trigeminovascular system. *Peptides*. (2012) 33:307–16. doi: 10.1016/j.peptides.2011.12.019
66. Akerman S, Goadsby PJ. Neuronal PAC1 receptors mediate delayed activation and sensitization of trigeminocervical neurons: Relevance to migraine. *Sci Transl Med*. (2015) 7:308ra157. doi: 10.1126/scitranslmed.aaa7557
67. Tozzi A, de Iure A, Di Filippo M, Costa C, Caproni S, Pisani A, et al. Critical role of calcitonin gene-related peptide receptors in cortical spreading depression. *Proc Natl Acad Sci USA*. (2012) 109:18985–90. doi: 10.1073/pnas.1215435109
68. Chan KY, Labastida-Ramirez A, Ramirez-Rosas MB, Labruijere S, Garrelds IM, Danser AH, et al. Trigeminovascular calcitonin gene-related peptide function in Cacna1a R192Q-mutated knock-in mice. *J Cereb Blood Flow Metab*. (2017) 39:718–29. doi: 10.1177/0271678X17725673
69. Tuka B, Helyes Z, Markovics A, Bagoly T, Szolcsanyi J, Szabo N, et al. Alterations in PACAP-38-like immunoreactivity in the plasma during ictal and interictal periods of migraine patients. *Cephalalgia*. (2013) 33:1085–95. doi: 10.1177/0333102413483931
70. Vereb D, Szabo N, Tuka B, Tajti J, Kiraly A, Farago P, et al. Correlation of neurochemical and imaging markers in migraine: PACAP38 and DTI measures. *Neurology*. (2018) 91:e1166–74. doi: 10.1212/WNL.0000000000006201
71. Dalkara T, Zervas NT, Moskowitz MA. From spreading depression to the trigeminovascular system. *Neurol Sci*. (2006) 27(Suppl 2):S86–90. doi: 10.1007/s10072-006-0577-z
72. Charles A. Migraine: a brain state. *Curr Opin Neurol*. (2013) 26:235–9. doi: 10.1097/WCO.0b013e32836085f4
73. Jürgens TP, Schulte LH, May A. Migraine trait symptoms in migraine with and without aura. *Neurology*. (2014) 82:1416–24. doi: 10.1212/WNL.0000000000000337
74. Fazekas F, Koch M, Schmidt R, Offenbacher H, Payer F, Freidl W, et al. The prevalence of cerebral damage varies with migraine type: a MRI study. *Headache*. (1992) 32:287–91. doi: 10.1111/j.1526-4610.1992.hed3206287.x
75. Pavese N, Canapicchi R, Nuti A, Bibbiani F, Lucetti C, Collavoli P, et al. White matter MRI hyperintensities in a hundred and twenty-nine consecutive migraine patients. *Cephalalgia*. (1994) 14:342–5. doi: 10.1046/j.1468-2982.1994.1405342.x
76. Porter A, Gladstone JP, Dodick DW. Migraine and white matter hyperintensities. *Curr Pain Headache Rep*. (2005) 9:289–93. doi: 10.1007/s11916-005-0039-y

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 October 2019
doi: 10.3389/fneur.2019.01112

Application of the Migraine Aura Complexity Score (MACS): Clinical and Neuroimaging Study

Igor Petrusic[1]*, *Michele Viana*[2,3], *Marko Dakovic*[1] and *Jasna Zidverc-Trajkovic*[4,5]

[1] Laboratory for Advanced Analysis of Neuroimages, Faculty of Physical Chemistry, University of Belgrade, Belgrade, Serbia, [2] Headache Center, Institute of the Neurocenter of Southern Switzerland (NSI), Regional Hospital Lugano, Lugano, Switzerland, [3] Headache Group, Department of Basic and Clinical Neurosciences, King's College London, London, United Kingdom, [4] Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [5] Center for Headaches, Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia

Background: Manifestations of typical migraine aura can be numerous. Investigation of its pathophysiological mechanisms can be challenging if a stratification of phenotypes is not performed. In this context, the Migraine Aura Complexity Score (MACS), recently developed, may help. Here we aimed to categorize migraine patients into homogenous groups using MACS and to compare those groups with respect to patients' characteristics and neuroimaging findings.

Methods: Participants who have a migraine with aura (MwA) were interviewed after each attack in order to obtain the characteristics of migraine aura. Thereafter, we scored the complexity of their auras by MACS. The MACS was used to categorize patients into three groups: MwA-S (with simple aura), MwA-MC (with moderately complex aura), and MwA-C (with complex aura). The patient characteristics and estimated cortical thickness of regions of interest, which are potentially linked to the symptoms that develop during the aura, were used to compare these groups.

Results: In total, 338 MwA attacks were recorded in analyzed groups. Scotoma was the most frequently reported symptom in the groups, followed by somatosensory aura in the MwA-C group and zig-zag lines in the MwA-MC and MwA-S groups. Patients in the MwA-C and MwA-MC groups had a thicker cortex in the left primary visual cortex with respect to MwA-S group. In addition, patients in the MwA-C group had a thicker cortex in several visual and somatosensory cortical regions relative to the MwA-S group.

Conclusions: Our results show that the newly developed MACS can be used for the stratification of MwA patients, herewith allowing the better investigation of changes in migraineurs' brains.

Keywords: migraine with aura, higher cortical dysfunction, dysphasia, cortical thickness, magnetic resonance imaging

OPEN ACCESS

Edited by:
Roberta Messina, Vita-Salute San Raffaele University, Italy

Reviewed by:
Marco Carotenuto, University of Campania Luigi Vanvitelli, Italy
Marcelo M. Valença, Federal University of Pernambuco, Brazil

***Correspondence:**
Igor Petrusic
ip7med@yahoo.com

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *24 May 2019*
Accepted: *04 October 2019*
Published: *18 October 2019*

Citation:
Petrusic I, Viana M, Dakovic M and Zidverc-Trajkovic J (2019) Application of the Migraine Aura Complexity Score (MACS): Clinical and Neuroimaging Study. Front. Neurol. 10:1112. doi: 10.3389/fneur.2019.01112

INTRODUCTION

Migraine with aura (MwA) strikes nearly 3.6% of the world population (1–3). In typical migraine aura (MA), visual symptoms are the most common, followed by somatosensory, and then dysphasic auras (4). Manifestations of visual auras can be numerous, including positive and negative symptoms, as well as disturbances of visual perception (5). Somatosensory symptoms can be

manifested as tingling or numbness, which can lead to dyspraxia. Different forms of dysphasia and other higher cortical dysfunctions (HCDs), such as disturbances of memory, were noted during the MA (6). MwA becomes particularly important when the duration of neurological symptoms and the modality of their appearance may constitute a cause of severe anxiety and distress in patients (7).

MA is thought to be caused by cortical spreading depolarization followed by cortical spreading depression (CSD) (8). It is possible that propagation of CSD results in a variety of symptoms correspond to the affected cortical region (9). The widely accepted approaches to explore mechanisms of MA are different modalities of advanced neuroimaging (10–12). However, the main methodological issue of the majority of the studies lies in the lack of inappropriate homogenization of patients with respect to aura phenotype (13).

Recently, we developed a scoring system for evaluating the complexity of MA (Migraine Aura Complexity Score—MACS) with an aim to provide better stratification of MA patients who participate in neuroimaging studies or clinical trials (14). The range of MACS is 0–9. Higher values indicate more complex aura. We demonstrated that this score positively correlates with cortical thickness of some regions, which are potentially linked, from a functional point of view, to the symptoms that develop during the aura. Moreover, we found that MACS allows detecting patients who have a complex aura with a sensitivity of 86% and specificity of 100% if their median MACS after 10 recordings is $\geq$4.5 points. However, some of the issues relatives to the use of this scoring system have remained to be elucidated. In fact, categorization of patients whose median MACS is $<$4.5 points due to the fact that the majority of their auras are simple, but they also have few attacks with the score that denote them as patients with complex aura, is not determined. We hypothesize that these patients could have a different phenotype from those who experience mostly complex auras or those who have never experienced a complex aura. Furthermore, categorizing patients using MACS can be used to investigate patient characteristics in order to determine their phenotypes.

The aim of this study was to use MACS and three distinctive manifestations of typical aura (visual, somatosensory and dysphasic symptoms) to categorize migraine patients into homogenous groups and to compare them in terms of patients' characteristics, thus to investigate the clinical phenotype of patients who are stratified in the same group. Also, we aimed to explore the application of MACS in magnetic resonance imaging (MRI) studies that investigate the thickness of the cerebral cortex.

Abbreviations: CSD, Cortical spreading depression; GLM, General linear model; MA, migraine aura; MACS, Migraine Aura Complexity Score; MRI, magnetic resonance imaging; MwA, migraine with aura; MwA-C groups, patients who have a migraine with complex aura; MwA-MC group, patients who have a migraine with moderately complex aura; MwA-S group, patients who have a migraine with simple aura; MwA-A group, patients who have only visual symptoms; MwA-SS group, patients who have visual and somatosensory symptoms; MwA-D group, patients who have visual, somatosensory, and dysphasic symptoms.

TABLE 1 | Study questionnaire.

During the aura of your migraine attack, have you noticed:
1. Flashes of bright light in the visual field?
2. Blurred spot in the visual field?
3. Scotoma (a partial loss of vision)?
4. Twinkling zig-zag lines in the visual field?
5. Tunnel vision (narrowing of the visual field)?
6. Deformed or deformed images, unrelated to the disturbance of vision?
7. Difficulties in recognizing faces, unrelated to the disturbance of vision?
8. Objects becomes biger or smaller?
9. Tingling or numbness in hand, leg, and face (head)?
10. Difficulties in recognizing objects by touch?
11. Difficulties in activities requiring coordination and movement of extremities?
12. Unawareness of one part of your body?
13. Difficulties in recalling names?
14. Difficulties in recalling or remembering events from the past?
15. Difficulties in speaking even when you knew what you wanted to say?
16. Difficulties in understanding people who were talking to you?
17. Difficulties in reading comprehension, unrelated to visual disorders?
18. Difficulties in writing that were not caused by the disturbance of vision?
19. Difficulties in calculating and/or memorizing numbers?
If you expirienced symptoms of visual aura please report the level of involvement of the visual field (a quarter, half or the whole of the visual field):
How did your visual aura symptoms last for?
If you expirienced symptoms of somatosensory aura please report the number of body regions that were involved (upper limb, head and/or trunk/lower limb):
How did your somatosensory aura symptoms last for?
If you expirienced symptoms of dysphasic aura please report the duration:
How long was the duration of a headache?
Please rate head pain intensity on the scale from 1 to 10:

MATERIALS AND METHODS

Participants

Migraine patients included in the study were from the cohort of patients that were enrolled in previous migraine neuroimaging studies (13, 15), including patients that participated in developing the MACS (14).

All participants had an episodic migraine with aura according to the International Classification of Headache Disorders criteria (3rd edition) (4). The inclusion criteria were: (a) individuals with episodic migraine, (b) 21–60 years of age, (c) acceptance of participation in the study, (d) absence of migraine preventive therapy, and (e) no pathological findings on participants' MRI scans. Exclusion criteria included a presence of other neurological or cardiovascular diseases and motor aura symptoms.

Selected participants were instructed to complete the specific questionnaire about the quality of aura symptoms after each attack of a MA (**Table 1**). Patients who had experienced visual disturbances also reported the level of involvement of the visual field (a quarter, half or the whole of the visual field), while patients who had experienced somatosensory symptoms also

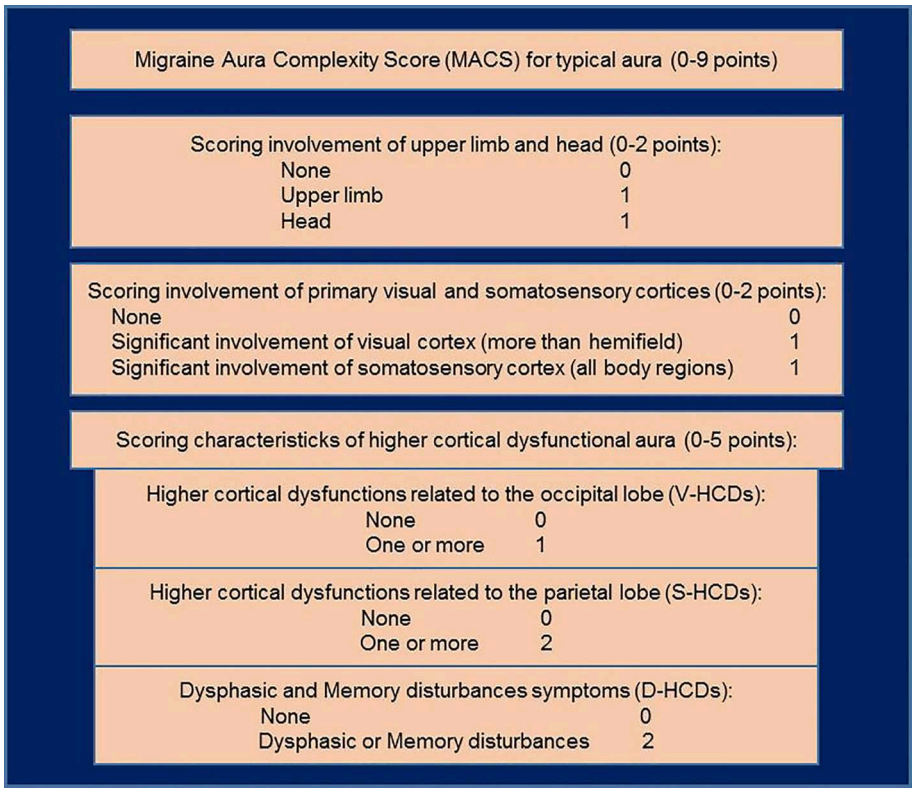


FIGURE 1 | Schema of the Migraine Aura Complexity Score (MACS). Higher cortical dysfunctions of occipital cortex (V-HCDs): micropsia, macropsia, dysmorphia, fractured vision, and prosopagnosia; higher cortical dysfunctions of parietal cortex (S-HCDs): astereognosis, dyspraxia, and unawareness of one's own body parts; dysphasic and memory disturbances symptoms (D-HCDs): (Broca's dysphasia, Wernicke's dysphasia, dysnomia, dyslexia, difficulties in remembering or recalling events, recalling names, and calculating and/or memorizing numbers). Adapted from our previous research paper (14).

reported the number of body regions that were involved. Body regions were divided into three areas: (a) upper limb, (b) head, and (c) trunk/lower limb. Also, patients reported the duration of the aura and their subforms, duration of the headache, and pain intensity. The questionnaire was used to score the MACS (**Figure 1**) and to collect the characteristics of MA and headache. The questionnaire was filled out within 2 days after the attack to minimize a possible bias of failing to recall symptoms during attacks. The patients were monitored and data were collected during a period of 12 months (December 23rd 2017–December 24th 2018). In order to complete the study patients needed to record at least 6 MwA attacks during the monitored period allowing us to more accurately assess the overall MACS in each patient.

The MACS was used to categorize patients into three categories: (1) patients who have simple auras (MACS $\leq$ 1 point), (2) patients who have moderately complex auras (MACS between $>$1 and $<$4.5), and (3) patients who have complex auras (MACS $\geq$4.5 points), making MwA-S, MwA-MC, and MwA-C groups, respectively. Also, patients were stratified into visual (patients who have only visual symptoms), somatosensory (patients who have visual and somatosensory symptoms) and dysphasic (patients who have visual, somatosensory and dysphasic symptoms) groups, making MwA-V, MwA,-SS, and MwA-D groups, respectively. The patient characteristics and neuroimaging measures of cortical thickness were used to compare these groups.

MRI Data Acquisition

MR examinations of patients were performed using a 1.5 T MR scanner with an eight-channel head coil (Signa, General Electric Healthcare, Milwaukee, WI, USA). The imaging protocol consisted of T2 weighted spin echo (T2W) in an axial plane [Echo time (TE) = 105.8 ms, repetition time (TR) = 5,700 ms, flip angle (FA) = 90°, 24 slices with 0.47 × 1 × 5 mm^3 voxels, slice thickness = 5 mm, acquisition matrix 512 × 512) and three-dimensional T1 weighted fast spoiled gradient-echo (T1-3D-FSPGR) series (TE = 3.60 ms, TR = 8.12 ms, FA = 15°, 248 contiguous slices with 0.47 × 0.47 × 1.4 mm^3 voxels, slice thickness = 1.4 mm, acquisition matrix 512 × 512, FOV = 256 × 256 mm^2). T2W images were only used to exclude the presence of brain lesions.

Freesurfer (version 5.3.0) analysis was performed on an HP 350 server (Intel Xeon 1,800 Mhz, eight cores, 16 GB RAM) using a recon-all script for automatic cortical reconstruction and segmentation of brain structures. Average run time (with the parallelization option used) was 6 h. Details about Freesurfer and its routines can be found elsewhere (16, 17). For this study, we

TABLE 2 | Characteristics of patients.

Variable	Patients ($n = 39$)
Female, %	29 (74.4%)
Age, mean ± SD (range), in years	38.38 ± 9.8 (24–59)
Age at onset of migraine with aura, mean ± SD (range)	20.49 ± 8.2 (7–38)
Frequency of migraine with aura, mean ± SD (range)	8.67 ± 5.6 (2–28)
Duration of the aura, mean ± SD (range), in minutes	47.82 ± 36.1 (10–180)
Co-occurrence of migraine without aura, %	11 (28.2%)
Familiar history of migraine with aura[a], %	16 (41.0%)

[a] *First and second-degree relatives have been considered.*

TABLE 3 | Frequency of occurrence of symptoms during migraine with aura attacks.

Type of symptoms	Patients[a] ($n = 39$), %	Auras ($n = 338$), %
Scotoma	38 (100)	326 (96)
Zig-zag lines	25 (64)	203 (60)
Tunnel vision	8 (21)	42 (12)
Somatosensory aura affecting hand	24 (62)	156 (46)
Somatosensory aura affecting head	21 (54)	141 (42)
Somatosensory aura affecting leg	7 (18)	38 (11)
Visual higher cortical dysfunctions	3 (8)	21 (6)
Somatosensory higher cortical dysfunctions	11 (28)	75 (22)
Dysphasic and/or memory disturbances	18 (46)	103 (30)

[a] *The described characteristics occurred in the patient at least in one of migraine with aura attacks.*

used cortical thickness measures of predefined cortical regions of interest (Primary visual cortex (V1), secondary visual cortex (V2), visual area V5/MT and somatosensory cortex (Brodmann areas: BA1, BA2, BA3a, and BA3b), which are available as an automated output of Freesurfer analysis.

Statistical Analysis

Subject demographics and MwA characteristics were reported using descriptive statistics. Kruskal–Wallis and Mann–Whitney *U*-test were used to compare the data between the groups. The mean cortical thickness of mapped cortical regions was extracted from surface-based morphometry results and exported into the R statistics program. We used GLM and *post-hoc* Tukey tests for comparing the groups in terms of cortical thickness, controlled for the effect of age and sex to avoid spurious results.

RESULTS

The study included 39 patients with an episodic migraine with typical aura. The characteristics of the patients are reported in **Table 2**. Overall, 338 MwA attacks were recorded (**Table 3**) with estimated average aura duration of 47.82 ± 36.1 min [visual aura = 33.72 ± 23.3 (range 10–150); somatosensory aura = 42.62 ± 44.8 (range 10–180); and dysphasic aura = 40.31 ± 41.6 (range 5–180)], headache duration of 7.82 ± 10.7 h (range 1–48) and pain intensity of 6.77 ± 2.1 on the scale from 1 to 10.

Seven patients had <6 MwA attacks during the monitored period and therefore they were not included in the group analysis. Comparisons of the groups relative to the patients' characteristics and their MwA features, as well as frequencies of symptoms, are shown in **Tables 4**, **5**, respectively. Scotoma was the most frequently reported symptom in the groups, followed by somatosensory aura in the MwA-C group and zig-zag lines in the MwA-MC and MwA-S groups.

Comparisons of regions of interest in the visual and somatosensory cortex, as well as cortex involved in a speech, between groups derived from MACS, were shown in **Table 6**. Patients in the MwA-C and MwA-MC groups have had thicker cortex relative to MwA-S group in the left primary visual cortex ($p = 0.006$; $p = 0.010$), respectively. In addition, patients in the MwA-C group have had thicker cortex relative to MwA-S group in the left secondary visual cortex ($p = 0.001$), right secondary visual cortex ($p = 0.002$), left visual area V5 ($p = 0.011$), right visual area V5 ($p = 0.013$), right somatosensory BA3a cortex ($p = 0.009$), and left somatosensory BA3b cortex ($p = 0.017$).

Stratification of the patients according to the distinctive manifestations in typical aura yielded 10 patients in MwA-V, 6 patients in MwA-SS and 16 patients in MwA-D group. Comparisons of regions of interest in the visual and somatosensory cortex, as well as cortex involved in a speech, between groups derived according to the distinctive manifestations of typical aura, were shown in **Table 7**. Patients in the MwA-D and MwA-SS groups have had thicker cortex relative to MwA-V group in the left primary visual cortex ($p = 0.018$; $p = 0.025$), respectively. In addition, patients in the MwA-D group have had thicker cortex relative to MwA-A group in the left secondary visual cortex ($p = 0.004$), right secondary visual cortex ($p = 0.001$), left visual area V5 ($p = 0.011$) and right visual area V5 ($p = 0.005$).

DISCUSSION

In the present study, we recorded the frequency of MA symptoms in our population of MwA patients and explored a possible difference of patients' characteristics and thickness of cerebral cortex between stratified patients using a Migraine Aura Complexity Score system. The main finding was that patients in the MwA-C and MwA-MC groups had thicker left primary visual cortex relative to the patients from the MwA-S group. In addition, patients in the MwA-C group had thicker cortex in several visual and somatosensory cortical regions with respect to the MwA-S group. Also, stratification into groups using MACS pointed to more cortical regions that should be of interest in further research than stratification into groups according to the distinctive manifestations in the typical aura.

MA usually affects mostly one sensory area of the cerebral cortex producing in the majority of cases only visual symptoms (4, 5). All examined patients in our cohort had visual aura symptoms. MwA can be also manifested as very complex phenomenon including disturbances of multisensory systems in

TABLE 4 | Comparison of patients' characteristics and their migraine with aura (MwA) features between three groups categorized by MACS.

Type of symptoms	MwA-S $n = 14$	MwA-MC $n = 9$	MwA-C $n = 9$	Statistics
Female, *n* (%)	9 (64.3)	8 (88.9)	8 (88.9)	$P = 0.248$
Age, mean ± SD (range), in years	36.71 ± 7.7	42.56 ± 9.2	34.22 ± 10.1	$P = 0.142$
Age at onset of migraine with aura, mean ± SD (range)	22.07 ± 7.0	20.67 ± 8.1	16.22 ± 9.9	$P = 0.256$
Frequency of migraine with aura, mean ± SD (range)	9.21 ± 5.7	12.44 ± 7.0	8.11 ± 2.6	$P = 0.226$
Duration of the aura, mean ± SD (range), in minutes	30.00 ± 11.8	59.44 ± 44.9	61.11 ± 49.1	$P = 0.076$
Duration of the headache, mean ± SD (range), in hours	10.57 ± 11.4	7.78 ± 15.2	5.89 ± 7.6	$P = 0.639$
Pain intensity (scale 1–10), mean ± SD	6.21 ± 1.6	6.44 ± 2.1	7.89 ± 2.0	$P = 0.117$
Co-occurrence of migraine without aura	3 (21.4)	4 (44.4)	4 (44.4)	$P = 0.397$
Familiar history of migraine with aura[a]	6 (42.9)	3 (33.3)	4 (44.4)	$P = 0.872$
Scotoma[b], *n* (%)	14 (100)	9 (100)	8 (88.9)	$P = 0.267$
Zig-zag lines[b], *n* (%)	11 (78.6)	7 (77.8)	3 (33.3)	$P = 0.055$
Tunnel vision[b]	1 (7.1)	3 (33.3)	3 (33.3)	$P = 0.206$
Somatosensory aura affecting hand[b], *n* (%)	4 (28.6)	9 (100)	9 (100)	$P < 0.001$ (MwA-S vs. MwA-MC, $p < 0.001$; MwA-S vs. MwA-C, $p < 0.001$)
Somatosensory aura affecting head[b], *n* (%)	2 (14.3)	7 (77.8)	9 (100)	$P < 0.001$ (MwA-S vs. MwA-MC, $p = 0.002$; MwA-S vs. MwA-C, $p < 0.001$; MwA-MC vs. MwA-C, $p = 0.031$)
Somatosensory aura affecting leg[b], *n* (%)	1 (7.1)	3 (33.3)	2 (22.2)	$P = 0.277$
Visual higher cortical dysfunctions[b], *n* (%)	0 (0)	0 (0)	3 (33.3)	$P = 0.015$ (MwA-S vs. MwA-C, $p < 0.001$; MwA-MC vs. MwA-C, $p < 0.001$)
Somatosensory higher cortical dysfunctions[b], *n* (%)	0 (0)	4 (44.4)	6 (66.7)	$P = 0.002$ (MwA-S vs. MwA-C, $p = 0.007$)
Dysphasic higher cortical dysfunctions[b], *n* (%)	1 (7.1)	6 (66.7)	9 (100)	$P < 0.001$ (MwA-S vs. MwA-MC, $p < 0.001$; MwA-S vs. MwA-C, $p < 0.001$; MwA-MC vs. MwA-C, $p < 0.001$)
MACS (≥4.5 points), *n* (%)	0 (0)	6 (66.7)	9 (100)	$P < 0.001$ (MwA-S vs. MwA-MC, $p < 0.001$; MwA-S vs. MwA-C, $p < 0.001$; MwA-MC vs. MwA-C, $p < 0.001$)

MACS, Migraine Aura Complexity Score; MwA-S, patients who have simple auras; MwA-MC, patients who have moderately complex auras; MwA-C, patients who have complex auras.
[a] *First and second-degree relatives have been considered.*
[b] *The described characteristic occurred in the patient at least in one of MwA attacks.*

the brain (6) with somatosensory aura symptoms and higher cortical disturbances, which is noted in the MwA-MC and MwA-C groups. Moreover, symptoms during an aura can be very heterogeneous, not just among patients but also in the same patient (5, 18). In our study of 338 MwA attacks that were recorded, the most reported visual symptom was scotoma, followed by zig-zag lines, and tunnel vision, which is also noted in other studies (19). Somatosensory aura was also reported by some patients, mostly affecting the hand and head. Dysphasic symptoms were the most frequent among symptoms of HCDs reported by 46% of patients. These results suggest that patients who have HCDs during the aura are not a small part and such symptoms deserve the attention of physicians who investigates MwA. Recently proposed migraine aura scoring system (14), could help in better categorizing those groups of patients, leading to a phenotype stratification of patients in MwA studies. According to the MACS, patients can be denoted as ones who experience mostly simple auras and those who have mostly complex auras. We believe it is useful to include a third category for those who have a moderately complex aura (i.e., those who suffer from both simple and complex auras). In that way, patients can be stratified more homogeneously in terms of their clinical phenotype.

We used MACS to categorize patients into three groups: MwA-S, MwA-MC, and MwA-C. We, therefore, were able to test our hypothesis that these three groups have different phenotypes and MRI findings. Our opinion is supported by the fact that patients who once experienced complex MA have the potential to experience it again, regardless of whether they have had more frequently reported migraine with a simple aura. Therefore, they should not be labeled as patients whose overall aura is presumed as simple aura, as we implied in our previous study (14). Indeed, in comparison with MwA-C, MwA-MC group reported the similar duration of the aura, the occurrence of the tunnel vision

TABLE 5 | Comparison of frequency of MwA symptoms between three groups categorized by the MACS.

Type of symptoms	MwA-S ($n = 129$ auras)	MwA-MC ($n = 112$ auras)	MwA-C ($n = 73$ auras)	Statistics
Scotoma, *n* (%)	125 (96.9)	112 (100)	73 (100)	$P = 0.608$
Zig-zag lines, *n* (%)	74 (57.4)	94 (83.9)	22 (30.1)	$P = 0.101$
Tunnel vision, *n* (%)	6 (4.7)	18 (16.1)	16 (22.0)	$P = 0.252$
Somatosensory aura affecting hand, *n* (%)	6 (4.6)	79 (70.5)	70 (95.9)	$P < 0.001$ (MwA-S vs. MwA-MC, $p < 0.001$; MwA-S vs. MwA-C, $p < 0.001$)
Somatosensory aura affecting head, *n* (%)	3 (2.3)	64 (57.1)	70 (95.9)	$P < 0.001$ (MwA-S vs. MwA-MC, $p = 0.002$; MwA-S vs. MwA-C, $p < 0.001$)
Somatosensory aura affecting leg, *n* (%)	1 (0.7)	21 (18.7)	16 (22.0)	$P = 0.250$
Visual higher cortical dysfunctions, *n* (%)	0 (0)	0 (0)	21 (28.8)	$P = 0.017$
Somatosensory higher cortical dysfunctions, *n* (%)	0 (0)	23 (20.5)	52 (72.1)	$P = 0.001$ (MwA-S vs. MwA-C, $p = 0.007$)
Dysphasic higher cortical dysfunctions, *n* (%)	2 (1.6)	29 (25.9)	72 (98.6)	$P < 0.001$ (MwA-S vs. MwA-MC, $p = 0.013$; MwA-S vs. MwA-C, $p < 0.001$; MwA-MC vs. MwA-C, $p = 0.004$)
MACS (≥4.5 points), *n* (%)	0 (0)	19 (18.2)	67 (85.0)	$P < 0.001$ (MwA-S vs. MwA-MC, $p < 0.001$; MwA-S vs. MwA-C, $p < 0.001$; MwA-MC vs. MwA-C, $p < 0.001$)

MACS, Migraine Aura Complexity Score; MwA-S, patients who have migraine with simple auras; MwA-MC, patients who have migraine with moderately complex auras; MwA-C, patients who have migraine with complex auras.

TABLE 6 | Comparison of cortical thickness of the regions of interest in the visual, somatosensory and language cortex between three groups categorized by the MACS.

Cortical region of interest	MwA-S (mean ± SD)	MwA-MC (mean ± SD)	MwA-C (mean ± SD)	Statistics
Left primary visual cortex	1.397 ± 0.072	1.489 ± 0.066	1.495 ± 0.063	$P = 0.003$ (MwA-S vs. MwA-MC, $p = 0.010$; MwA-S vs. MwA-C, $p = 0.006$)
Right primary visual cortex	1.481 ± 0.106	1.605 ± 0.141	1.590 ± 0.111	$P = 0.089$
Left secondary visual cortex	1.754 ± 0.066	1.828 ± 0.073	1.887 ± 0.095	$P = 0.005$ (MwA-S vs. MwA-C, $p = 0.001$)
Right secondary visual cortex	1.798 ± 0.056	1.889 ± 0.098	1.943 ± 0.115	$P = 0.002$ (MwA-S vs. MwA-C, $p = 0.002$)
Left visual area V5	2.332 ± 0.122	2.450 ± 0.141	2.513 ± 0.152	$P = 0.008$ (MwA-S vs. MwA-C, $p = 0.011$)
Right visual area V5	2.234 ± 0.115	2.331 ± 0.123	2.424 ± 0.201	$P = 0.010$ (MwA-S vs. MwA-C, $p = 0.013$)
Left somatosensory cortex BA1	2.015 ± 0.143	2.040 ± 0.105	2.070 ± 0.207	$P = 0.477$
Right somatosensory cortex BA1	2.104 ± 0.149	2.190 ± 0.159	2.136 ± 0.178	$P = 0.436$
Left somatosensory cortex BA2	2.111 ± 0.107	2.140 ± 0.163	2.217 ± 0.135	$P = 0.357$
Right somatosensory cortex BA2	2.015 ± 0.123	2.104 ± 0.128	2.064 ± 0.126	$P = 0.209$
Left somatosensory cortex BA3a	1.622 ± 0.098	1.649 ± 0.077	1.734 ± 0.115	$P = 0.081$
Right somatosensory cortex BA3a	1.654 ± 0.090	1.704 ± 0.100	1.745 ± 0.082	$P = 0.040$ (MwA-S vs. MwA-C, $p = 0.009$)
Left somatosensory cortex BA3b	1.725 ± 0.116	1.814 ± 0.055	1.859 ± 0.129	$P = 0.014$ (MwA-S vs. MwA-C, $p = 0.017$)
Right somatosensory cortex BA3b	1.583 ± 0.116	1.605 ± 0.106	1.613 ± 0.134	$P = 0.663$
Left BA44	2.558 ± 0.137	2.628 ± 0.105	2.659 ± 0.129	$P = 0.190$
Right BA44	2.502 ± 0.105	2.555 ± 0.076	2.615 ± 0.153	$P = 0.117$
Left BA45	2.409 ± 0.088	2.451 ± 0.165	2.512 ± 0.148	$P = 0.246$
Right BA45	2.440 ± 0.139	2.522 ± 0.132	2.548 ± 0.165	$P = 0.135$

MACS, Migraine Aura Complexity Score; BA, Brodmann area; MwA-S, patients who have migraine with simple auras; MwA-MC, patients who have migraine with moderately complex auras; MwA-C, patients who have migraine with complex auras.

and characteristics of somatosensory aura. However, according to the MACS criteria for complex aura (14), MwA-MC expressed a small percentage of MwA attacks with complex aura. We can only speculate that these results suggest differences in migraineurs brains, which lead patients in MwA-C and MwA-MC groups to express complex manifestation of the aura contrary to patients from MwA-S group. Results also suggest the presence of some inhibitory mechanism in patients from MwA-MC group that prevents the complex manifestation of the MA in most of their attacks, which differentiate them from the MwA-C group.

Furthermore, MACS was used to compare the cortical thickness of regions of interest, which have been linked to MA,

TABLE 7 | Comparison of cortical thickness of the regions of interest in the visual, somatosensory and language cortex between three groups categorized by the manifestations of typical aura.

Cortical region of interest	MwA-V (mean ± SD)	MwA-SS (mean ± SD)	MwA-D (mean ± SD)	Statistics
Left primary visual cortex	1.397 ± 0.077	1.487 ± 0.082	1.470 ± 0.071	$P = 0.026$ (MwA-V vs. MwA-SS, $p = 0.025$; MwA-V vs. MwA-D, $p = 0.018$)
Right primary visual cortex	1.498 ± 0.123	1.614 ± 0.190	1.552 ± 0.099	$P = 0.056$
Left secondary visual cortex	1.751 ± 0.068	1.806 ± 0.076	1.853 ± 0.096	$P = 0.012$ (MwA-V vs. MwA-D, $p = 0.004$)
Right secondary visual cortex	1.783 ± 0.058	1.853 ± 0.093	1.919 ± 0.102	$P = 0.004$ (MwA-V vs. MwA-D, $p = 0.001$)
Left visual area V5	2.313 ± 0.135	2.427 ± 0.072	2.476 ± 0.158	$P = 0.033$ (MwA-V vs. MwA-D, $p = 0.011$)
Right visual area V5	2.200 ± 0.101	2.310 ± 0.109	2.388 ± 0.172	$P = 0.018$ (MwA-V vs. MwA-D, $p = 0.005$)
Left somatosensory cortex BA1	2.018 ± 0.148	1.957 ± 0.133	2.080 ± 0.155	$P = 0.290$
Right somatosensory cortex BA1	2.102 ± 0.167	2.120 ± 0.196	2.166 ± 0.145	$P = 0.621$
Left somatosensory cortex BA2	2.131 ± 0.120	2.073 ± 0.037	2.189 ± 0.157	$P = 0.478$
Right somatosensory cortex BA2	1.988 ± 0.117	2.079 ± 0.126	2.085 ± 0.126	$P = 0.141$
Left somatosensory cortex BA3a	1.637 ± 0.101	1.614 ± 0.085	1.694 ± 0.110	$P = 0.413$
Right somatosensory cortex BA3a	1.643 ± 0.101	1.744 ± 0.096	1.706 ± 0.083	$P = 0.112$
Left somatosensory cortex BA3b	1.728 ± 0.137	1.772 ± 0.066	1.830 ± 0.110	$P = 0.097$
Right somatosensory cortex BA3b	1.578 ± 0.132	1.605 ± 0.123	1.608 ± 0.108	$P = 0.729$
Left BA44	2.541 ± 0.147	2.613 ± 0.082	2.644 ± 0.124	$P = 0.143$
Right BA44	2.488 ± 0.111	2.524 ± 0.081	2.596 ± 0.124	$P = 0.086$
Left BA45	2.394 ± 0.092	2.382 ± 0.040	2.510 ± 0.154	$P = 0.094$
Right BA45	2.423 ± 0.149	2.469 ± 0.092	2.547 ± 0.151	$P = 0.153$

BA, Brodmann area; MwA-A, patients who have only visual symptoms; MwA-SS, patients who have visual and somatosensory symptoms; MwA-D, patients who have visual, somatosensory and dysphasic symptoms.

in investigated groups. The analysis identified differences in the primary visual cortex, where the cortex was thicker in the MwA-C and MwA-MC groups with respect to the MwA-S. Also, patients in the MwA-C group had thicker cortex relative to MwA-S group in several visual and secondary somatosensory cortical regions, suggesting that MA could be associated with different ways of aberrant brain functional organization (20). These differences were not observed between the MwA-C and MwA-MC groups, which could explain the overlap of the clinical characteristics of these two groups. However, this finding should be further investigated with a larger cohort of patients and with multimodal neuroimaging techniques to strengthen the interpretation of changes in the migraineurs brain. Moreover, previous neuroimaging studies of MwA implicate different brain regions as biomarkers for MwA (13, 21–23), which could be explained by the lack of adequate stratification of patients in which MACS may help. Also, these heterogeneous neuroimaging findings could represent specific brain networks for subtypes of MA (24). This can be further strengthened by the finding that stratification of patients according to the distinctive manifestations in typical aura pointed to the same results, which challenges the point of view that patients who have only visual symptoms and someone who has visual and somatosensory or dysphasic aura should be equally weighted and placed in the same group. Moreover, stratifications using MACS point to more cortical regions, allocated to the somatosensory cortex, that could be involved in a different experience of aura in MwA patients. Of course, strong similarities between the investigated two modalities of stratification of MwA patients and an additional contribution of MACS model in neuroimaging studies should be confirmed by other independent investigators. Anyhow, the neuroimaging findings from our study suggest that MACS can be successfully used for the stratification of patients in studies investigating the difference in cortical thickness among distinct phenotypes of MwA patients. Moreover, the fact that selected patients regularly completed questionnaire after each MwA attack and no one withdrew from the study, suggest that the MACS can be properly implemented and fulfill its intended use.

Altogether, if we would try to describe phenotypes of patients from those three groups, the results suggest that the patients from the MwA-S group have a shorter duration of the whole aura, longer duration of the headache, rare occurrence of the tunnel vision, somatosensory aura and symptoms of HCDs, as well as thinner cerebral cortex in general, with respect to the MwA-MC and MwA-C groups. Shorter duration of the aura in patients who did not experience HCDs was previously noticed (6). This finding supports the idea that the duration of the aura may depend on the site in which the CSD originates (9) and the adaptive capacity of affected regions which can abort CSD through other cortical regions, thus avoiding symptoms of somatosensory aura and HCDs. On the other hand, patients from the MwA-C group started to experience MwA at a younger age, have less frequent MwA attacks although more severe headaches, rare occurrence of the zig-zag lines in their visual field but more frequent occurrence of the HCDs, as well as thicker cerebral cortex in general, when compared to the MwA-MC and MwA-S groups. This demonstrates that cerebral cortex is a hallmark for the investigation of the pathophysiology of a complex MA

and require further sub-phenotypes investigation in order to link HCDs and changes in cortical thickness. Patients from the MwA-MC group are prone to more frequent MwA attacks and more common occurrence of the zig-zag lines with respect to the MwA-C and MwA-S groups. Also, they have more similarity to the MwA-C group in terms of duration of the aura and occurrence of the tunnel vision. Anyhow, studies including a higher number of patients per group should provide a more detailed profile of such identified phenotypes.

A limitation of the study is that the sample size of three subgroups is relatively small for definitive conclusions. However, the strength of the study is that participants were carefully divided into homogenous groups according to their clinical phenotypes and that neuroimaging results were strongly comparable with findings from investigation of groups stratified according to the distinctive manifestations in the typical aura. Moreover, our patients did not present any comorbidity and did not use migraine preventive therapy that could have influenced the investigation. Also, we based our discussion on the results that were not corrected for multiple comparisons. Although this could lead to false-positive findings, correction for multiple comparisons increases the risk of generating false-negative findings (25), which could underestimate subtle differences in the investigated groups. Because of that, we think that is important to show and discuss uncorrected data for multiple comparisons to achieve better methodological solutions which will allow using a better strategy for investigation of MA pathophysiology and new targets for treating it. Finally, the results of this study should be confirmed using a new and independent cohort of subjects.

Our results show that the newly developed MACS can be used for the stratification of MwA patients and identifying their phenotypes, herewith allowing the better investigation of changes in migraineurs' brains. Further efforts toward a better system for stratification of MwA patients are needed to provide new knowledge about complex pathological mechanisms of MA and their influence on the brain plasticity. Thus, the MACS may help in revealing new therapeutic targets and evaluation of the efficiency of MA treatment.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of the Neurology Clinic, Clinical Center of Serbia, and was conducted in accordance with the Declaration of Helsinki. Informed consent forms were completed by all the participants after receiving an explanation of the study.

AUTHOR CONTRIBUTIONS

IP contributed to the study aim, design, acquisition, analysis, interpretation, and drafting of the manuscript. MV contributed to the interpretation and drafting of the manuscript. MD contributed to acquisition and analysis. JZ-T contributed to interpretation and critically revised manuscript. All authors read and approved the final manuscript.

FUNDING

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: IP and MD received research grant support from the Ministry of Education and Science, Republic of Serbia (project no. III 41005), and JZ-T received research grant support from the Ministry of Education and Science, Republic of Serbia (project no. 175022).

REFERENCES

1. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. (2018) 17:954–76. doi: 10.1016/S1474-4422(18)30322-3
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *J Headache Pain*. (2018) 19:17. doi: 10.1186/s10194-018-0846-2
3. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia*. (1992) 12:221–8. doi: 10.1046/j.1468-2982.1992.1204221.x
4. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202
5. Viana M, Sances G, Linde M, Ghiotto N, Guaschino E, Allena M, et al. Clinical features of migraine aura: results from a prospective diary-aided study. *Cephalalgia*. (2017) 37:979–89. doi: 10.1177/0333102416657147
6. Petrusic I, Zidverc-Trajkovic J, Podgorac A, Sternic N. Underestimated phenomena: higher cortical dysfunctions during migraine aura. *Cephalalgia*. (2013) 33:861–7. doi: 10.1177/0333102413476373
7. Swanson SA, Zeng Y, Weeks M, Colman I. The contribution of stress to the comorbidity of migraine and major depression: results from a prospective cohort study. *BMJ Open*. (2013) 3:e002057. doi: 10.1136/bmjopen-2012-002057
8. Hadjikhani N, Sanchez del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA*. (2001) 98:4687–92. doi: 10.1073/pnas.071582498
9. Petrusic I, Zidverc-Trajkovic J. Cortical spreading depression: origins and paths as inferred from the sequence of events during migraine aura. *Funct Neurol*. (2014) 29:207–12. doi: 10.11138/FNeur/2014.29.3.207
10. Chong CD, Schwedt TJ, Dodick DW. Migraine: what Imaging Reveals. *Curr Neurol Neurosci Rep*. (2016) 16:64. doi: 10.1007/s11910-016-0662-5
11. Yang H, Zhang J, Liu Q, Wang Y. Multimodal MRI-based classification of migraine: using deep learning convolutional neural network. *Biomed Eng Online*. (2018) 17:138. doi: 10.1186/s12938-018-0587-0
12. Szabó N, Faragó P, Király A, Veréb D, Csete G, Tóth E, et al. Evidence for plastic processes in migraine with aura: a diffusion weighted MRI study. *Front Neuroanat*. (2018) 11:138. doi: 10.3389/fnana.2017.00138
13. Petrusic I, Dakovic M, Kacar K, Zidverc-Trajkovic J. Migraine with aura: surface-based analysis of the cerebral cortex with magnetic resonance imaging. *Korean J Radiol*. (2018) 19:e86. doi: 10.3348/kjr.2018.19.4.767
14. Petrusic I, Viana M, Dakovic M, Goadsby PJ, Zidverc-Trajkovic J. Proposal for a migraine aura complexity score. *Cephalalgia*. (2018) 39:732–41. doi: 10.1177/0333102418815487

15. Petrušić I, Daković M, Kačar K, Mićić O, Zidverc-Trajković J. Migraine with aura and white matter tract changes. *Acta Neurol Belg.* (2018) 118:485–91. doi: 10.1007/s13760-018-0984-y
16. Dale AM, Fischl B, Sereno MI. Cortical surface based analysis I: segmentation and surface reconstruction. *Neuroimage*. (1999) 9:179–94. doi: 10.1006/nimg.1998.0395
17. Fischl B. FreeSurfer. *Neuroimage*. (2012) 62:774–81. doi: 10.1016/j.neuroimage.2012.01.021
18. Hansen JM, Goadsby PJ, Charles AC. Variability of clinical features in attacks of migraine with aura. *Cephalalgia*. (2016) 36:216–24. doi: 10.1177/0333102415584601
19. Queiroz LP, Friedman DI, Rapoport AM, Purdy RA. Characteristics of migraine visual aura in Southern Brazil and Northern USA. *Cephalalgia*. (2011) 31:1652–8. doi: 10.1177/0333102411430263
20. Schwedt TJ, Chong CD. Functional imaging and migraine: new connections? *Curr Opin Neurol.* (2015) 28:265–70. doi: 10.1097/WCO.0000000000000194
21. DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. *Neurology*. (2007) 69:1990–5. doi: 10.1212/01.wnl.0000291618.32247.2d
22. Messina R, Rocca MA, Colombo B, Valsasina P, Horsfield MA, Copetti M, et al. Cortical abnormalities in patients with migraine: a surface-based analysis. *Radiology*. (2013) 268:170–80. doi: 10.1148/radiol.13122004
23. Gaist D, Hougaard A, Garde E, Reislev NL, Wiwie R, Iversen P, et al. Migraine with visual aura associated with thicker visual cortex. *Brain*. (2018) 141:776–85. doi: 10.1093/brain/awx382
24. Chong CD, Gaw N, Fu Y, Li J, Wu T, Schwedt TJ. Migraine classification using magnetic resonance imaging resting-state functional connectivity data. *Cephalalgia*. (2017) 37:828–44. doi: 10.1177/0333102416652091
25. Sangseok L, Dong KL. What is the proper way to apply the multiple comparison test? *Korean J Anesthesiol.* (2018) 71:353–60. doi: 10.4097/kja.d.18.00242

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 13 December 2019
doi: 10.3389/fneur.2019.01325

Imaging the Visual Network in the Migraine Spectrum

Francesca Puledda [1,2], Dominic Ffytche [3], Owen O'Daly [4] and Peter J. Goadsby [1,2]*

[1] Headache Group, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [2] NIHR-Wellcome Trust King's Clinical Research Facility, SLaM NIHR Biomedical Research Centre, King's College Hospital, London, United Kingdom, [3] Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [4] Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

The involvement of the visual network in migraine pathophysiology has been well-known for more than a century. Not only is the aura phenomenon linked to cortical alterations primarily localized in the visual cortex; but also migraine without aura has shown distinct dysfunction of visual processing in several studies in the past. Further, the study of photophobia, a hallmark migraine symptom, has allowed unraveling of distinct connections that link retinal pathways to the trigeminovascular system. Finally, visual snow, a recently recognized neurological disorder characterized by a continuous visual disturbance, is highly comorbid with migraine and possibly shares with it some common pathophysiological mechanisms. Here, we review the most relevant neuroimaging literature to date, considering studies that have either attempted to investigate the visual network or have indirectly shown visual processing dysfunctions in migraine. We do this by taking into account the broader spectrum of migrainous biology, thus analyzing migraine both with and without aura, focusing on light sensitivity as the most relevant visual symptom in migraine, and finally analyzing the visual snow syndrome. We also present possible hypotheses on the underlying pathophysiology of visual snow, for which very little is currently known.

Keywords: migraine, migraine spectrum, neuroimaging, visual snow, visual network, aura, photophobia

OPEN ACCESS

Edited by:
Tim P. Jürgens,
University Hospital Rostock, Germany

Reviewed by:
Marco Carotenuto,
University of Campania Luigi Vanvitelli, Italy
Gianluca Coppola,
Sapienza University of Rome, Italy

****Correspondence:***
Francesca Puledda
francesca.puledda@kcl.ac.uk

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *23 September 2019*
Accepted: *29 November 2019*
Published: *13 December 2019*

Citation:
Puledda F, Ffytche D, O'Daly O and Goadsby PJ (2019) Imaging the Visual Network in the Migraine Spectrum. Front. Neurol. 10:1325. doi: 10.3389/fneur.2019.01325

KEY CONCEPTS

- A key feature of migraine, during and between attacks, is represented by altered visual cortex excitability. Multiple functional and structural neuroimaging studies have shown alterations in several areas of the visual network in migraine both with and without aura compared to controls, particularly of the motion processing network.
- Visual symptoms are the most common clinical manifestation of the aura phenomenon. The neurophysiological correlate of visual aura is likely represented by cortical spreading depression, starting in the extrastriate area V3A. Neuroimaging has shown in various forms that migraine with aura is characterized by lower and higher visual processing impairment, both ictally and interictally.
- Photophobia is an important aspect of migraine biology, present during, before and after the headache attacks. Migrainous photophobia is most likely linked to abnormal sensory processing in thalamic structures, particularly the pulvinar.

- Visual snow is a neurological disorder, commonly comorbid with migraine, characterized by a continuous visual disturbance that takes the form of uncountable tiny flickering dots covering the entire visual field. Its underlying pathophysiology is possibly characterized by a combination of peripheral, subcortical, and cortical dysfunctions causing an increased perception of normally subthreshold visual stimuli.

INTRODUCTION

In the last decades, imaging has gained considerable interest in the field of neuroscience and has allowed researchers to begin to unravel important mechanisms in the biology of complex neurological disorders. Several conventional and more advanced neuroimaging techniques have been implemented over the years and have proven to be important tools in the understanding of normal and pathological brain biology.

In the field of primary headaches, and migraine in particular, a growing body of neuroimaging work has served the purpose of dissecting important structural and functional alterations that characterize the disorder. One of the main aspects that has emerged from these studies is the confirmation, previously shown through animal models, that migraine does not represent a primary vascular disorder, rather a complex brain dysfunction involving several cortical and subcortical networks (1, 2).

The visual network has been one of the most studied systems in the migraine brain for several reasons. The most obvious explanation is certainly linked to the intriguing phenomenon of aura, a fully reversible neurological dysfunction which occurs in about a third of migraine cases and is represented chiefly by positive or negative visual symptoms (3, 4).

Another reason for the rising interest in studying visual function has been photophobia, a clinical hallmark of migraine both during attacks and in the interictal phase (5, 6). Recent evidence has led to better insight on the link between light inputs and pain, through the discovery of a pathway where photic signals from the retina converge on thalamic trigeminovascular neurons (7).

Finally, the notion that visual function is abnormal in migraineurs even in between attacks has lead researchers in the past to carry out extensive neurophysiological investigation of the visual network in migraine (8, 9). This uncovered important pathophysiological mechanisms now known to be typical of the migrainous brain, such as lack of habituation (10, 11). This particular form of altered excitability has been found interictally (12), although it typically fluctuates through the migraine cycle and can revert with disease chronification (13).

The visual brain is an extremely complex system consisting of multiple, hierarchical nodes which specialize in different functions at different times. These separate systems—which are incredibly uniform at a cytoarchitectonic level within the human cortex—work in parallel synchrony and autonomously from each other, resulting in the final conscious percept of vision (14). The complex integration between different areas of the visual network is made possible by existing connections between different cortical and subcortical areas specializing in different aspects of vision, and also between other cortical sensory, attentional, and cognitive processing networks (15, 16). The visual motion network is a perfect example of such integration and hierarchical sub-specialization, and it is particularly relevant in migraine biology, as this review will highlight. The motion network is composed chiefly of visual area V5, which specifically responds to motion stimuli, of sub-compartments within V1/V2, of area V3/V3A in the cuneus and finally of Brodmann area (BA) 7 in the precuneus (17).

In this review, we focus on neuroimaging findings that have shown direct involvement of the visual network in migraine. We will review studies broadly considered as being in the "migraine spectrum," thus focusing on migraine both with and without aura, photophobia, and finally visual snow.

Visual snow (VS) is a common comorbidity of migraine, with which it may share some pathophysiological mechanisms (18, 19). In addition to describing the limited neuroimaging literature available for VS, we will proceed to present distinct hypotheses for putative pathophysiological mechanisms underlying visual snow, hoping to elucidate the neurobiology of the disorder and provide insight for future studies attempting its investigation.

METHODS

For the purpose of this narrative review, we performed a literature search using PubMed database in April 2019, with the following key words: "migraine," "aura," "migraine with aura," "migraine without aura," "visual snow," "prolonged aura," "visual," "visual network" combined with "imaging," "neuroimaging," "BOLD," "functional MRI," "fMRI," "VBM," "PET," "spectroscopy." Articles were chosen based on their relevance to the topic. The reference lists of most publications and any other relevant papers known to the authors were further reviewed.

THE VISUAL NETWORK IN MIGRAINE BIOLOGY

In the last decades, we have learnt much about migraine pathophysiology by studying the visual system of migraineurs, particularly in, but not limited to, the context of aura and light hypersensitivity. Both structural and functional neuroimaging techniques have been used for this purpose. The majority of studies have focused on the interictal migraine phase, as this is generally more practical, however, an increasing number of recent studies have also successfully investigated the ictal phase. This has been achieved either by imaging attacks of spontaneous onset (20) or by triggering headache through different forms of pharmacological provocation (21).

Functional imaging approaches are particularly suitable for a disorder characterized by pathological network dysfunction such as migraine. Positron emission tomography (PET) - using different radiotracers to investigate brain metabolism— and functional magnetic resonance imaging (fMRI), either with visual stimuli to capture the blood-oxygen-level-dependent (BOLD) responses or scanning during the resting state to study brain connectivity, are commonly used techniques in this context. These powerful approaches have uncovered important

information regarding brain function and network configuration between attacks and at their initiation.

Structural techniques, such as voxel and surface-based morphometry (SBM) or DTI, on the other hand, provide insights on the morphological characteristics of key gray and white matter structures that are implicated in the biology of the migrainous brain.

Finally, magnetic resonance spectroscopy (MRS) allows to investigate brain metabolism directly.

Functional Neuroimaging in Migraine

Several functional neuroimaging studies have shown a dysfunction of the visual network in migraine, both with (MwA) and without aura (MwoA). A summary of these is provided in **Table 1**.

Visual stimulation is capable of triggering migraine attacks, and this has shown to involve brainstem structures, in particular the red nucleus and substantia nigra (23). Furthermore, MwoA and MwA have been repeatedly associated with increased BOLD response in the primary visual cortex and higher-order visual areas, both during the interictal period (24, 25) and during visually triggered attacks (23).

Migraineurs, both with and without aura, show a more extensive photoresponsive area in the visual cortex in response to light (26) as well as a general increased response to visual stimuli (28). These patients also display a lack of interictal habituation for repetitive visual stimulation (29) in event-related fMRI studies in between attacks.

Spontaneous migraine attacks have also been associated with increased activity in the visual cortex with $H_2^{15}O$ PET (27) in response to increasing intensities of light stimulation used to induce photophobia.

In an fMRI study investigating the same MwoA patient daily over the course of 30 days, a bilateral visual cortex activation (specifically Brodmann areas 17 and 18) was found in the 24 hours prior to attack onset, as well as in response to trigeminal nociceptive stimulation during the postictal phase. Interestingly, the same area showed significant deactivation during attacks compared with the interictal phase. These results indicate either an increased visual and nociceptive integration in the build-up of the migraine attack, which in turn reverts during the actual attack, or an increased activation of the visual cortex at baseline in migraineurs, whom therefore lack a normal occipital response during pain (45).

Functional connectivity (fc) is also altered within the visual network in MwoA. In a resting-state fMRI study using PACAP38 to induce attacks, decreased fc was found between the sensorimotor network and the left visual cortex, while conversely, increased connectivity was found between the default mode network (DMN) and the visual cortices bilaterally (36). It is possible that part of these BOLD signal changes were due to PACAP38 itself, given that it is a potent vasodilator, however, its effect on intracerebral arteries seems limited (46).

Another study found interictal fc reduction between the DMN and the visuo-spatial system in episodic migraineurs without aura in-between spontaneous attacks (37), whereas a more recent connectivity analysis in migraineurs without aura showed increased functional anti-correlation between the right temporo-parietal junction and the bilateral visual cortex (42).

Finally, a combined visual evoked potentials (VEPs) and [^{18}F]-FDG PET study in interictal migraineurs without aura showed significantly reduced glucose uptake in the left BAs 19, 18, and 7, in patients. This results was present when regressing for the VEP area under the curve, thus suggesting an activity-induced rupture of cerebral metabolic homeostasis in migraine (41).

Structural Alterations of the Visual Network

Several imaging studies have shown changes in cerebral gray matter (GM) and white matter (WM) volume in patients with migraine (**Table 2**).

A cortical thickness and DTI study in 12 MwA and an equal number of MwoA patients showed an increase in the thickness of motion-processing areas V5 and V3A area in migraineurs respect to controls, accompanied by reduced fractional anisotropy in the WM subjacent to V3A as well as the lateral geniculate nucleus (LGN) (47). Another DTI study showed tractography alterations in the optic radiations of seven migraineurs with visual auras compared to healthy controls and migraineurs without visual aura (48).

Zhang et al. combined voxel-based morphometry (VBM), SBM, and DTI to investigate structural alterations in 32 MwoA patients compared to healthy controls. They found that migraineurs had increased GM volume in an area encompassing the lingual, fusiform, and parahippocampal gyri. Further, cortical thickness in the lateral occipital cortex and gyrification index in the right lateral occipital cortex were significantly increased in migraineurs. No changes in white matter microstructure using DTI were found in this study (49).

Slightly contradicting these results, Coppola et al. analyzed 20 patients with chronic MwoA and found decreased GM volume in the left primary occipital cortex and visual association areas (corresponding to Brodmann areas 17 and 18) with respect to healthy volunteers. It should be noted that these results only survived cluster-wise multiple comparisons correction at a more lenient cluster-forming threshold than normally adopted (50).

A larger study on 84 migraineurs both with ($n = 52$) and without ($n = 32$) aura showed a decrease in GM volume of visual areas V3 and V5 (Brodmann area 19) in patients, compared to controls. A *post-hoc* analysis showed that changes in V5 were more pronounced in migraineurs with an "active" disease (51).

In an elegant study comparing females with MwA to their unaffected twins and unrelated controls, Gaist et al. assessed the cortical thickness of V1, V2, V3A, and V5 areas, finding an increased thickness of areas V2 and V3A in the patient group (52). This alteration was not associated with clinical parameters such as disease activity or aura attack frequency, leading the authors to hypothesize that the morphometric changes represented an inherent trait of migraine with visual aura.

A recent study combining VBM and VEP by Lisicki et al. found no global differences in gray matter volume of migraine patients respect to controls. There was, however, a significant correlation in migraineurs between VEP amplitude and GM volume within the visual cortex, among other regions (53).

TABLE 1 | Main functional neuroimaging studies investigating the visual network in migraine with (MwA) and without aura (MwoA).

References	Patient cohort	Migraine phase and attack type	Methodology	Main results
Hadjikhani et al. (22)	2 MwA	Ictal and during aura; 2 spontaneous and 3 induced attacks with physical exercise	Event-related fMRI with visual stimulus (checkerboard on/off pattern every 16 s)	Focal increase followed by a decrease in BOLD signal, starting in area V3A of extrastriate cortex (lingual gyrus), and progressing congruently with retinotopic representation of visual aura percept
Cao et al. (23)	10 MwA 2 MwoA	Ictal and during aura (in 4 MwA patients); induced attacks with visual stimulation	Event-related fMRI with visual stimulus (checkerboard on/off pattern every 14 s)	Visual stimulus can trigger migraine attacks (with and without aura) through the activation of brainstem structures (red nucleus and substantia nigra)
Vincent et al. (24)	5 MwA	Interictal	Event-related fMRI with visual stimulus (alternating lines simulating zigzags of aura)	Increased activation of extrastriate cortex respect to controls
Boulloche et al. (6)	4 MwA, 3 MwoA, episodic	Interictal	$H_2^{15}O$ PET with visual stimulus (luminous stimulation at three intensities) with and without noxious trigeminal heat stimulation	Light stimulation caused increased striate and extrastriate visual cortex activation (cuneus, lingual gyrus, and posterior cingulate cortex) in migraineurs respect to controls
Antal et al. (25)	12 MwA 12 MwoA	Interictal	Event-related fMRI with visual motion stimulus (moving dots alternated with static dots)	Decreased activation of inferior-posterior V5 complex (middle temporal area) and increased activation of superior-anterior V5 complex in migraineurs respect to controls, showing that higher-order visual areas are affected in migraine
Martin et al. (26)	7 MwA 12 MwoA	Interictal	Event-related fMRI with visual stimulus (luminous stimulations at four intensities)	Wider photoresponsive area in the visual cortex in response to light, as well as hyperexcitability of the visual cortex respect to controls
Denuelle et al. (27)	8 MwoA, episodic	Ictal, post-ictal, and post treatment; spontaneous attacks	$H_2^{15}O$ PET with visual stimulus (luminous stimulations at increasing intensities to induce photophobia)	Increased activation in the visual cortex of migraineurs respect to controls, both during migraine attacks with photophobia and following headache relief with sumatriptan. Hyperexcitability was not present in the interictal phase
Huang et al. (28)	7 MwA, 4 MwoA episodic	Interictal	Event-related fMRI with visual stimulus (striped patterns)	Increased activation in visual cortex of migraineurs respect to controls
Descamps et al. (29)	21 MwoA episodic	Interictal	Event-related fMRI with visual stimulus (faces, short interstimulus intervals)	Repetitive visual stimuli in migraine showed an altered hemodynamic refractory response respect to controls, possibly confirming lack of interictal habituation
Datta et al. (30)	25 MwA, 25 MwoA	Interictal	Event-related fMRI with visual stimulus (checkerboard on/off pattern every 15 s)	Increased BOLD response to visual stimulation in V1 and LGN in MwA patients compared to both MwoA and controls
Hougaard et al. (31)	20 MwA episodic	Interictal	Event-related fMRI with visual stimulus (dartboard on/off pattern every 18 s)	Increased BOLD response to visual stimulation in downstream visual network areas (inferior frontal gyrus, superior parietal lobule, intraparietal sulcus, and inferior parietal lobule) of symptomatic aura hemispheres compared to controls
Griebe et al. (32)	18 MwA episodic	Interictal	Event-related fMRI with visual stimulus (optokinetic drum with colored figures)	Increased activation in visual motion perception areas (bilateral V5 complex and left area V3) as well as cuneus and precuneus
Maniyar et al. (33)	10 MwoA episodic	Ictal premonitory phase; induced attacks with GTN	$H_2^{15}O$ PET	Increased activation of cuneus (BA18, part of the extrastriate visual cortex) and right precentral gyrus (BA4) in patients with photophobia in the premonitory phase vs. baseline phase, respect to patients without photophobia
Niddam et al. (34)	26 MwA, 26 MwoA	Interictal	Resting-state fMRI (seed based; ROIs in salience network and dorsal attention network)	Decreased connectivity between the anterior insula and extrastriate areas (including V3A) in MwA compared to both MwoA and controls. The reduced connectivity correlated with headache severity

(Continued)

TABLE 1 | Continued

References	Patient cohort	Migraine phase and attack type	Methodology	Main results
Tedeschi et al. (35)	20 MwA, 20 MwoA	Interictal	Resting-state fMRI (ICA)	Increased functional connectivity in the right lingual gyrus (within the resting-state visual network) in migraine aura patients, respect to migraine without aura and controls
Amin et al. (36)	16 MwoA	Interictal and ictal; induced attacks with PACAP38	Resting-state fMRI (seed based; ROIs in salience network, default mode network, and sensorimotor network)	Decreased connectivity in the sensorimotor network with the left visual cortex. Increased connectivity in the DMN with the visual cortices
Coppola et al. (37)	18 MwoA	Interictal	Resting-state fMRI (ICA)	Decreased connectivity between the default mode network and the visuospatial system
Hougaard et al. (38)	16 MwA	Interictal, ictal during aura	Resting-state fMRI (ICA + seed based; ROIs in cortical visual areas and areas of pain)	Increased functional connectivity between V5 and the ipsilateral middle frontal gyrus of the hemisphere contralateral to the perceived visual aura symptoms, following visual aura attack
Faragó et al. (39)	18 MwA, 35 MwoA	Interictal	Resting-state fMRI (ICA)	Increased amplitude of resting activity fluctuation in the lateral visual network in MwA patients respect to MwoA and controls
Arngrim et al. (40)	5 MwA	Interictal, ictal during aura; induced attacks with hypoxia, sham hypoxia, or physical exercise	Event-related fMRI with visual stimulus (dartboard on/off pattern every 18 s)	Reduced BOLD response in patients reporting scotoma and increased response in patients with positive aura symptoms. Bi-hemispherical BOLD changes in patients with bilateral visual symptoms
Lisicki et al. (41)	20 MwoA	Interictal	[18F]-FDG PET (with VEPs)	Increased neuronal activation-to-resting glucose uptake ratio in the visual cortex in patients
Lisicki et al. (42)	19 MwoA	Interictal	Resting-state fMRI (seed based)	Increased functional anti-correlations between the right temporo-parietal junction and the visual cortex in patients
Russo et al. (43)	17 MwA, 18 MwoA	Interictal	Event-related fMRI with noxious trigeminal heat stimulation	Increased activation of visual network (lingual gyrus, inferior parietal lobule, inferior frontal gyrus, and medial frontal gyrus) and midline-inferior cerebellum in patients with MwA compared to healthy controls and MwoA
Arngrim et al. (44)	15 MwA	Interictal, during hypoxia	Event-related fMRI with visual stimulus (dartboard on/off pattern every 18 s)	Greater hypoxia-induced decrease in BOLD following visual stimulation in visual areas V1, V2, V3, V4

The opposing findings of increased and decreased gray matter volumes within the motion network in migraineurs are difficult to interpret. Variations within technical acquisition or image processing could be a relevant cause. Another important element could be the differences among study populations. Some authors investigated predominantly episodic (47, 49) while others exclusively chronic (50) migraine; others did not distinguish between the two (51, 52). Given that volumetric differences in area V5 and the cerebellum were associated with attack frequency (51) and acute medication intake, respectively (50), this is an aspect that certainly needs to be taken into account in the planning of future studies.

Spectroscopy Investigations

The use of MRS has increased the already expanding knowledge on visual cortex activation in migraine, by studying *in-vivo* neuronal metabolism. ^{1}H-magnetic resonance in particular allows to measure concentration of N-acetylaspartate (NAA), creatinine (Cr), glutamate (Glx), GABA, and lactate. Several studies performed with this technique in migraineurs—mostly with visual aura—have shown alterations of the visual system.

One paper investigating visual cortex metabolism in MwA, MwoA, and controls subject to visual stimuli, showed that photic stimulation caused a more sustained decrease of NAA and concomitant increase in lactate in MwA patients respects to the other groups, which the authors argue could highlighting potential abnormal mitochondrial function in aura subjects (54). This dysfunction was confirmed by Sandor et al., who studied visual cortex lactate changes in MwA following prolonged visual stimulation, and found that compared to controls or subjects with sensory or motor aura, patients with visual aura displayed abnormally elevated lactate levels, even at rest (55).

With simultaneous transcranial direct current stimulation (tDCS), VEP recording and spectroscopy in MwA patients, Siniatchkin et al. were able to show that occipital areas in migraineurs are characterized by altered homeostasis and cortical information processing (56). In the healthy controls of the study, excitatory and inhibitory baseline tDCS, respectively, triggered either an increase or decrease in Glx/Cr ratio, which could be reversed by photic stimulation. Migraineurs, however, showed decreased Glx/Cr ratio in response to both types of tDCS

TABLE 2 | Main structural neuroimaging studies showing alterations of the visual network in migraine with (MwA) and without aura (MwoA).

References	Patient cohort	Methodology	Main results
Granziera et al. (47)	12 MwA 12 MwoA	DTI, cortical thickness	Increased cortical thickness in V3A and V5 in migraineurs respect to controls. Reduced fractional anisotropy in V3A and LGN in migraineurs
Rocca et al. (48)	7 MwA 8 MwoA	DTI	Altered tractography in optic radiations of migraineurs with visual aura respect to controls and patients without aura
Zhang et al. (49)	32 MwoA	VBM, DTI, SBM	Increased GM volume in the lingual gyrus, fusiform gyrus, and parahippocampal gyrus in patients respect to controls. Increased cortical thickness and gyrification index in lateral occipital cortex in patients
Coppola et al. (50)	20 MwoA, chronic	VBM	Decreased GM volume in left V1/V2 in patients respect to controls
Palm-Meinders et al. (51)	52 MwA 32 MwoA	VBM	Decreased GM volume in V3 and V5 in migraineurs respect to controls. V5 changes correlated with disease activity
Gaist et al. (52)	166 MwA	Cortical thickness	Increased cortical thickness in areas V2 and V3A in migraineurs with visual aura
Lisicki et al. (53)	20 MwoA	VBM	No differences in GM volume in patients respect to controls; positive correlation between GM volume in BA 17 and mean VEP amplitude

stimulation, and importantly this did not to return to baseline in response to visual stimulus.

Another study in migraine with visual aura patients showed a 10% reduction in occipital cortex GABA concentrations respect to controls, as well as significant correlations between glutamate levels and BOLD response to visual stimulation that was not seen in controls. This suggested an altered excitation-inhibition coupling in MwA patients (57). Finally, a recent paper assessed the levels of visual cortex glutamate in both MwA and MwoA, finding higher Glx levels in migraineurs without aura compared to controls (58).

Overall, these studies suggest abnormal cortical processing of visual information and lack of habituation in between attacks in migraineurs, possibly due to an underlying metabolic dysfunction.

The picture that emerges from imaging across different modalities, is that of multiple functional, structural, and metabolic abnormalities affecting the visual network of migraineurs. The motion network in particular seems to be most significantly affected. This is true both for the extensive functional alterations found in the primary visual processing areas of V1/V2, which have specific sub-compartments involved in motion detection, as well as for the structural differences that multiple studies have uncovered in areas V3A and V5.

MIGRAINE WITH AURA

By far the most common clinical manifestation of aura is represented by visual symptoms that are prototypically characterized by an arc-shaped scintillating scotoma (59), although a high variability in symptomatology across and within patients has been recorded (60). The phenomenon of migraine aura has interested clinicians and researchers since its earliest descriptions. In recent decades, the mechanism of aura has become better understood, particularly thanks to seminal neuroimaging studies (61).

The most likely electrophysiological event underlying aura is cortical spreading depression (CSD), first described by Leão in the 1940s (62) and characterized by a wave of neuronal hyperexcitation followed by a sustained depression, traveling at a rate of 2–6 mm/min.

The most prominent evidence linking aura to CSD has come from a study involving the near-continuous recording of a patient with two aura attacks through the use of functional MRI (22). This showed that retinotopic progression of visual aura symptoms was congruently linked to an increase and successive decrease of BOLD signal, starting in cortical area V3A of the extrastriate cortex and progressing contiguously over the occipital cortex. Area V3A is linked to both motion processing and luminance contrast; it further has a retinotopic representation of the opposite hemifield (63). A more recent study in five MwA patients confirmed this link between BOLD changes and aura symptoms, and even showed that clinical heterogeneity in aura—such as prominence of positive or negative symptoms—corresponds to differences in BOLD signaling in the visual cortex. This paper in fact showed that the typical scotoma is associated with a reduced BOLD response likely caused by the depression in neural activity linked to CSD, whereas positive symptoms are linked to an increase in BOLD (40).

One debate regarding migraine aura has centered on the question of whether it represents a separate entity with respect to MwoA, and whether migraine pain can actually be caused by CSD itself.

A theory linking migraine pathogenesis to "silent CSD attacks" largely relies on animal studies showing that CSD can activate trigeminovascular neurons (64). The study by Cao et al. failed to find evidence in support of this hypothesis however, showing rather that activation of substantia nigra and red nucleus anticipates occipital cortex changes in spontaneous and visually triggered migraine with aura attacks (23). A more recent study demonstrated that, following visual aura attacks, there is increased connectivity between the pons and the somatosensory

cortex and between V5 and the ipsilateral lower middle frontal gyrus; however, it found no differences in connectivity between visual cortex and pain areas (38).

Taken together, these studies seem to suggest that brainstem mechanisms contributed to the generation of pain attacks in both MwA and MwoA, and that involvement of the cortex in aura is a subsequent, parallel phenomenon.

Altered excitability of the visual pathways certainly plays a prominent role in the pathophysiology of MwA. Several neuroimaging studies have shown hyperexcitability of both primary and secondary visual cortices, even outside of the attacks.

Vincent et al. first showed that, following visual activation simulating the typical "zigzag lines" percept of aura, patients showed enhanced interictal reactivity of the extrastriate cortex respect to healthy subjects (24). MwA patients also show a stronger BOLD activation in the primary visual cortex and lateral geniculate nuclei compared to both healthy volunteers and MwoA patients, even when matched for levels of visual discomfort (30). Further, in the affected hemisphere of migraineurs with aura, response to visual pattern stimulation has shown to be increased in several downstream areas of the visual network involved in perception of motion, oculomotor control, visual attention and spatial memory (31). This is also seen following more complex forms of optokinetic stimulation (32). Finally, in response to an hypoxia challenge, patients with aura exhibit a greater decrease in BOLD signaling following visual stimulation, possibly due to higher blood oxygen extraction secondary to increased cortical excitability or to an abnormal vascular response (44).

Neuroimaging studies have also shown altered functional connectivity in MwA. Niddam et al. showed that MwA, compared to MwoA, had weaker fc between anterior insula and V3A, suggesting abnormal connections between the limbic and visual systems in aura (34). Faragó et al. found that MwA subjects present resting-state alterations within the lateral visual network respect to controls and MWoA, with increased amplitudes of resting BOLD fluctuations in the cingulate cortex, superior parietal lobule, cerebellum and bilateral frontal regions (39). Tedeschi et al. compared resting-state connectivity in the ictal phase of MwA vs. MwoA and controls, finding stronger fc within the visual network, particularly the extrastriate regions within the lingual gyrus (35). Interestingly, this resting-brain alteration was not limited to the aura phenomenon and was not correlated with clinical parameters or morphological differences, leading the authors to hypothesize that increased extrastriate cortical connectivity could represent a functional biomarker of MwA, differentiating it from MwoA and the non-migrainous brain. The same group has also recently demonstrated an abnormal response to trigeminal nociceptive stimulation in the lingual gyrus, inferior parietal lobule and cerebellum of MwA patients. This confirms the involvement of areas of higher visual processing in MwA, and possibly shows that functional integration between visual and trigeminal pain networks could represent a key pathophysiological mechanisms underlying migraine with aura (43).

Overall, these studies show that both lower and higher visual processing is impaired in aura patients, ictally and interictally. The visual cortices generally present hyperexcitability in response to visual stimulus in migraine with aura. Further, functional connectivity seems to be increased within the visual network and conversely decreased between the visual network and other key brain structures in MwA. Even if these characteristic are not limited to MwA, they certainly seem to be more prominent in this subpopulation.

PHOTOPHOBIA

Typically, light can either exacerbate ongoing migraine pain (photic allodynia), or it can be perceived as very bright or uncomfortable (photic hypersensitivity). Photophobia and migraine pain are directly correlated, with light stimuli causing lower thresholds to pain in trigeminal innervated locations in migraineurs (65, 66), and painful trigeminal stimulation leading to decreased visual discomfort thresholds (5). Importantly, photophobia prevalence appears to be independent of migraine aura (65). Nonetheless photic sensitivity is a key aspect of migraine biology, representing not only a prominent feature of the attack (67), but commonly present in the premonitory (68) and interictal phases also (69).

Photophobia is also frequently experienced as part of the visual snow syndrome (19), underlying the important pathophysiological link between these two conditions.

Several studies have investigated the mechanism of photophobia in migraine, with one prominent paper that identified a pathway through which photic signals from the retina converge on nociceptive pathways mediating migraine pain (70), likely explaining the exacerbation of headache by light.

In a $H_2^{15}O$ PET study, Boulloche et al. showed that in response to light stimulation migraineurs had increased activation of visual network areas—specifically the cuneus, lingual gyrus and posterior cingulate cortex—respect to controls (6). Furthermore, this increased activation was potentiated by trigeminal pain, demonstrating a close interrelation between light perception and the trigeminal nociceptive pathway. The same group then directly investigated ictal photophobia in spontaneous attacks of MwoA, finding that light sensitivity was linked to an increased activation in the visual cortex present during the attack, involving the areas of the lingual gyrus and the cuneus (27). With the same technique, Maniyar et al. studied photic sensitivity in premonitory phase of glyceryl trinitrate (GTN) induced attacks of MwoA and found that premonitory photic hypersensitivity is linked to activation of extrastriate visual cortex, specifically Brodmann areas 18 and 4 (33).

In a functional MRI study on interictal chronic migraineurs, authors found an altered connectivity between the anterior insula and pulvinar of patients with migraine, which could explain, at least in part, the abnormal perception of visual stimuli as painful (71). The pulvinar is relevant in selecting salient visual stimuli (72) and has a direct role in the integration between trigeminal pain and visual inputs (70) through a pathway involving the optic nerves and dura-sensitive spinal trigeminal nucleus neurons (73).

These studies suggest that migrainous photophobia is characterized by diffuse associative visual cortex abnormalities,

and that these are possibly linked to abnormal sensory processing in thalamic structures, particularly the pulvinar.

VISUAL SNOW

Visual snow is a neurological disorder characterized by a continuous visual disturbance that takes the form of uncountable tiny flickering dots covering the whole visual field (74). This static disturbance is often referred to as "snow;" it is typically black and white but can also be colored, flashing, or transparent. In the more complex visual snow syndrome, patients experience several other visual symptoms, that can be of neurological origin—such as palinopsia, photophobia, and nyctalopia—or originate directly from the optic apparatus. The latter are called "entoptic phenomena" and manifest in the syndrome with various combinations of blue field entoptic phenomenon (BFEP), floaters, self-light of the eye, and/or spontaneous photopsia (19).

Even if visual snow represents an entity distinct from both migraine without aura and typical migraine aura, comorbid migraine is present in up to 80% of visual snow cases, significantly complicating its phenotype (75–77). In particular, VS patients who have comorbid migraine present an increased chance of having non-entoptic visual symptoms. Further, some cases of VS has been reported to start with an aura episode (18).

To date there has been only one neuroimaging investigation on VS syndrome, and this was an [^{18}F]-FDG PET study performed on 17 patients (75). This study demonstrated that patients with VS exhibit increased brain metabolism in the area of the right lingual gyrus compared to healthy volunteers. The distribution of hypermetabolism was very similar to the area also shown to be directly linked to ictal photophobia in migraine (27), further supporting the hypothesis of a pathophysiological overlap between the conditions.

Toward a Model for Visual Snow

The lack of recognition of the visual snow condition, which was only characterized very recently, has posed a challenge to understanding the biology underlying this disorder. The consistency of the clinical description offered by affected patients allows to hypothesize a common, general, pathophysiological mechanism, although it is also possible for different aspects to be more relevant in-between subjects.

We here outline possible theories on the visual snow pathogenesis, proceeding anatomically from the periphery onto higher areas of visual processing, and hypothesizing on a common biology underlying the condition by analyzing the different features that characterize it.

The first, most obvious, explanation for VS is that it is directly or indirectly triggered by an eye disease. Several ophthalmologic cases can present with clinical features of "static" similar to visual snow. The authors themselves (FP/PJG) received an unpublished report of VS in a subject diagnosed with X-linked Retinitis Pigmentosa. Indeed a de-afferentation syndrome, in which even a temporary alteration in retinal firing causes a dissociation between peripheral sensory input and central visual perception, would explain the similarity of visual snow to tinnitus, a highly common comorbidity (74) and in some respects the auditory counterpart of visual snow. A similar mechanism is also present in the classic hallucinatory condition of Charles-Bonnet syndrome (CBS), where progressive loss of visual function causes hypo-connectivity from the visual periphery to the brain and gives rise to hallucinations (78). It is also tempting to explain the associated entoptic phenomena of VS syndrome as something arising plainly from the eye, as they are indeed typically described in ophthalmic disorders (79) and can even be present in healthy individuals as a consequence of floating strands of vitreous or white blood cells within the microvasculature stimulating retinal neurons (80–82).

The main counter-argument to interpreting VS as a purely eye phenomenon however, lies primarily in the absence of ophthalmic disorders, a required criterion for the diagnosis of VS (19), and also in the normality of basic eye electrophysiology, such as ERG or VEPs, reported in VS cohorts (74, 76). This does not exclude that perhaps some cases of visual snow might be caused by eye disorders. In this respect it is interesting to recall that in certain examples, CBS hallucinations are characterized by simple flashes, dots of light, or palinopsia, an important feature of VS syndrome (83). More case studies are clearly needed to further elucidate the interaction of eye disorders and visual snow-like phenomena.

A second theory on VS pathophysiology involves a direct thalamic dysfunction. In a process known as thalamo-cortical dysrhythmia, a dissociation exists between sensory inputs from the thalamus and its projections to the cortex. This mechanism was first described by Llinas in tinnitus (84), and is characterized by an increase in unusual, large-scale and coherent thalamo-cortical low-frequency oscillations. These delta and theta oscillations are likely caused by a switch from tonic to high-frequency thalamic bursting—due to protracted cell hyperpolarization—and ultimately determine a disintegration of sensory perception at the cortical level. It is certainly possible to hypothesize a role for thalamo-cortical dysrhythmia in visual snow. Potentially, an underlying homeostatic imbalance of visual pathways, either from altered retinal activity or genetic predisposition, could cause a disinhibition of projections from the posterior thalamus to primary and secondary visual cortices and parietal cortex as well—explaining palinopsia and a continuous perception of movement—thus affecting normal visual perception (76).

Interestingly, the thalamo-cortical dysrhythmia hypothesis also seems to be relevant for migraine pathophysiology (85), where a functional disconnection of the thalamus is thought to be contributing to the abnormal habituation deficit repeatedly observed (86).

In a more simplistic view, the thalamus could be responsible for VS symptoms through a localized increase in activity of the LGN or the pulvinar. The pulvinar is part of the "thalamic matrix" and projects diffusely to the cortex, playing a significant role in cognition and attentive stimulus processing (87). Recent studies have confirmed that the pulvinar can facilitate attention-related communication across widespread neuronal networks including higher-order sensory cortices (88) and, as mentioned before, it has a clear role in photophobia. In the future, neuroimaging studies focused on these nuclei will help clear the role of thalamic dysfunction in visual snow.

A third option could be to hypothesize VS as a purely cortical phenomenon. In visual hallucinatory syndromes, the percept of hallucinations has been shown to correspond to a dysfunction in the cortical area where that particular perception is represented (89). If the "cortical dysfunction theory" were true, we should therefore expect altered brain structure, compensatory neuroplasticity or functional activity to be constrained to visual association/motion areas. It is known that topological visual disorders caused by hyper-function in V1/V2 areas can present with hallucinations similar to visual snow (90). Further, a recent case of sporadic Creutzfeldt-Jakob disease presenting with features of visual snow has been reported in the literature (91). These cases are, however, exceptional and they would certainly not explain most cases of VS in which no gross central nervous system abnormalities are found.

A more complex explanation of the role of the cortex could involve a widespread dysfunction of higher-order visual processing areas, particularly the extrastriate cortex. Certainly the cited PET study, showing increased metabolic activity in the lingual gyrus, points to this (75). There have also been important neurophysiological (92–94) and behavioral (95) studies demonstrating an altered processing and dishabituation in the visual network of the VS brain.

The dorsal visual network, involved in processing visual motion, is likely to play a role in a condition characterized by the perception of constantly moving objects. The motion network is part of what has now been renamed as the "how-pathway" (96) and spreads from V1 dorsally to the parietal lobe, involving visual motion area V5 located in the temporo-parietal-occipital junction (97).

Finally, an altered connection between visual networks and other brain networks involved in salience, cognition and interoception is possible in a disorder like VS. Vision is a dynamic, active process in which top-down influences are seen at all stages of the visual hierarchy—with the exception of the retina—and control various functional properties of vision, particularly attention (98). We can hypothesize that visual snow may be characterized by a general altered excitability and connectivity of the visual network with either the salience and/or DMNs, which typically exert top-down influence on the visual cortex, = or the dorsal and ventral attentional networks, which have been abundantly implicated in theories of visual hallucinations (99, 100).

The final, overarching framework that we propose for visual snow encompasses the three aforementioned hypotheses. If a combination of peripheral, subcortical and cortical dysfunctions were all at play, either in different subjects or in different moments of the natural disease history, this would explain not only the main symptom of the snow common to all patients, but also the variety of symptoms characterizing the VS syndrome. Similarly to a model that has been used to explain tinnitus and is potentially involved in chronic pain as well (101), we could imagine that subcortical spontaneous activity normally

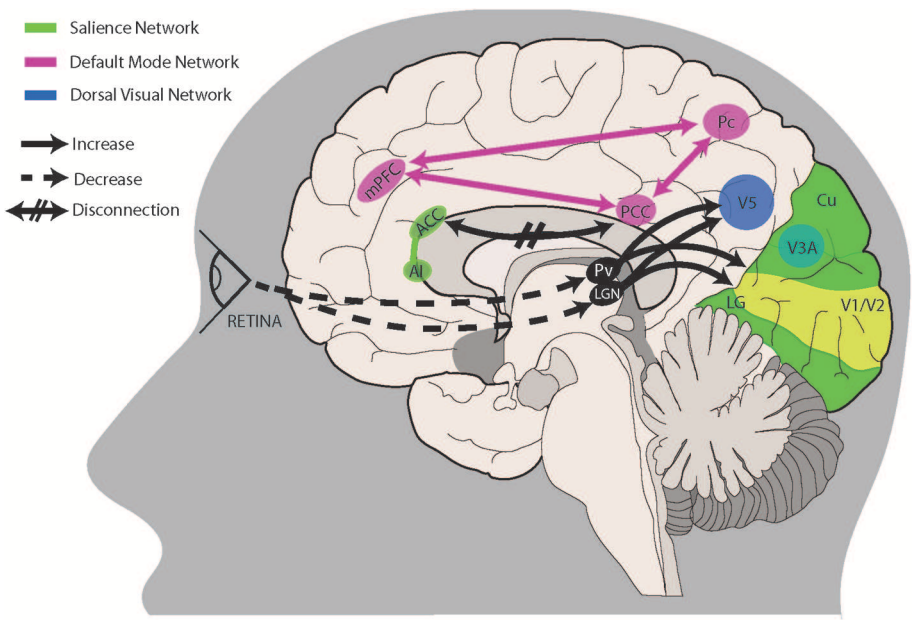


FIGURE 1 | A proposed model for visual snow pathophysiology. Altered peripheral visual stimulation or a form of genetic predisposition could induce dysrhythmic connections between thalamic structures and cortical visual areas. The lateral geniculate nucleus (LGN) and pulvinar (Pv) in particular are directly connected to motion area V5 and the lingual gyrus (LG). Relevant to visual snow biology is the motion processing network, which is composed of areas within the primary visual cortex (V1/V2), area V3A within the cuneus (Cu), area V5 located ventrolaterally among the lateral occipital sulcus and inferior temporal sulcus, and Brodmann area 7 in the precuneus (Pc). Structures pertaining to the default mode network (PCC, posterior cingulate cortex; Pc; mPFC, middle prefrontal cortex) and/or the salience network (AI, anterior insula; ACC, anterior cingulate cortex) are involved in salience and interoception. Disruption of these networks, possibly through altered connectivity between cortical areas, could also play a role in visual snow pathophysiology. See main text for a more in-depth explanation.

ignored and considered as erroneous by the brain in normal conditions, might for various reasons increase in salience and be considered as the default visual perception, particularly if the hierarchical sensory processing networks in the brain do not correct this faulty perception. This model would certainly explain the continuous background perception of the simple static or snow, but also the more complex phenomena typical of the syndrome: palinopsia, entoptic phenomena, photophobia and even nyctalopia, which could in fact simply represent an increased perception of the "noise" when no other stimulus is present. **Figure 1** summarizes the salient aspects of this theory, showing the most important brain structures and connections likely involved in visual snow pathophysiology. Neuroimaging studies will be particularly useful in the future to determine the strength of this reasoning, as well as the role of the different mechanisms in VS biology.

A continuous dysfunction of large-scale visual processing networks, in particular of the motion network, through this or other mechanisms in visual snow possibly constitutes a link to its "cousin" condition of migraine, in which manifestations of altered visual processing, although not predominant, constitute an important aspect of a disease characterized by generalized alterations of sensory processing.

CONCLUSIONS

In summary, modern neuroimaging has allowed to detect several functional, structural and metabolic changes affecting multiple elements of the visual network in migraineurs, both with and without aura. These abnormalities help explain some of the key features of the condition, such as abnormal sensory processing, photophobia and the aura phenomenon, and further link it to the growingly recognized neurological syndrome of visual snow. In this condition, which is likely on a similar pathophysiological spectrum as migraine, multiple elements (i.e., cortical hypermetabolism, thalamo-cortical dysrhythmia, brain network dysfunctions) could be at play in the generation of a persistent visual illusion.

AUTHOR CONTRIBUTIONS

FP wrote the first draft of the manuscript. DF and OO'D revised the initial drafts and gave scientific contribution. PG edited the final version of the manuscript.

FUNDING

FP was funded by the Visual Snow Initiative and the NIHR-Wellcome Trust King's Clinical Research Facility and the National Institute for Health Research (NIHR) Biomedical Research Center at South London and Maudsley NHS Foundation Trust and King's College London for their support. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

REFERENCES

1. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine- A disorder of sensory processing. *Physiol Rev.* (2017) 97:553–622. doi: 10.1152/physrev.00034.2015
2. Chong CD, Schwedt TJ, Hougaard A. Brain functional connectivity in headache disorders: a narrative review of MRI investigations. *J Cereb Blood Flow Metab.* (2019) 39:650–69. doi: 10.1177/0271678X17740794
3. Charles A, Hansen JM. Migraine aura: new ideas about cause, classification, and clinical significance. *Curr Opin Neurol.* (2015) 28:255–60. doi: 10.1097/WCO.0000000000000193
4. Viana M, Sances G, Linde M, Ghiotto N, Guaschino E, Allena M, et al. Clinical features of migraine aura: results from a prospective diary-aided study. *Cephalalgia.* (2017) 37:979–89. doi: 10.1177/0333102416657147
5. Drummond PD, Woodhouse A. Painful stimulation of the forehead increases photophobia in migraine sufferers. *Cephalalgia.* (1993) 13:321–4. doi: 10.1046/j.1468-2982.1993.1305321.x
6. Boulloche N, Denuelle M, Payoux P, Fabre N, Trotter Y, Geraud G. Photophobia in migraine: an interictal PET study of cortical hyperexcitability and its modulation by pain. *J Neurol Neurosurg Psychiatry.* (2010) 81:978–84. doi: 10.1136/jnnp.2009.190223
7. Noseda R, Burstein R. Advances in understanding the mechanisms of migraine-type photophobia. *Curr Opin Neurol.* (2011) 24:197–202. doi: 10.1097/WCO.0b013e3283466c8e
8. Schoenen J, Wang W, Albert A, Delwaide PJ. Potentiation instead of habituation characterizes visual evoked potentials in migraine patients between attacks. *Eur J Neurol.* (1995) 2:115–22. doi: 10.1111/j.1468-1331.1995.tb00103.x
9. Afra J, Cecchini AP, De Pasqua V, Albert A, Schoenen J. Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. *Brain.* (1998) 121 (Pt 2):233–41. doi: 10.1093/brain/121.2.233
10. Schoenen J. Neurophysiological features of the migrainous brain. *Neurol Sci.* (2006) 27 (Suppl. 2):S77–81. doi: 10.1007/s10072-006-0575-1
11. Coppola G, Pierelli F, Schoenen J. Is the cerebral cortex hyperexcitable or hyperresponsive in migraine? *Cephalalgia.* (2007) 27:1427–39. doi: 10.1111/j.1468-2982.2007.01500.x
12. Ambrosini A, Schoenen J. The electrophysiology of migraine. *Curr Opin Neurol.* (2003) 16:327–31. doi: 10.1097/01.wco.0000073945.19076.1f
13. Coppola G, Schoenen J. Cortical excitability in chronic migraine. *Curr Pain Headache Rep.* (2012) 16:93–100. doi: 10.1007/s11916-011-0231-1
14. Zeki S. Localization and globalization in conscious vision. *Annu Rev Neurosci.* (2001) 24:57–86. doi: 10.1146/annurev.neuro.24.1.57
15. Cohen AL, Fair DA, Dosenbach NU, Miezin FM, Dierker D, Van Essen DC, et al. Defining functional areas in individual human brains using resting functional connectivity MRI. *Neuroimage.* (2008) 41:45–57. doi: 10.1016/j.neuroimage.2008.01.066
16. Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. *Trends Cogn Sci.* (2008) 12:99–105. doi: 10.1016/j.tics.2008.01.001
17. Watson JD, Myers R, Frackowiak RS, Hajnal JV, Woods RP, Mazziotta JC, et al. Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex.* (1993) 3:79–94. doi: 10.1093/cercor/3.2.79
18. Schankin CJ, Goadsby PJ. Visual snow–persistent positive visual phenomenon distinct from migraine aura. *Curr Pain Headache Rep.* (2015) 19:23. doi: 10.1007/s11916-015-0497-9
19. Puledda F, Schankin C, Digre K, Goadsby PJ. Visual Snow syndrome: what we know so far. *Curr Opin Neurol.* (2017) 31:52–8. doi: 10.1097/WCO.0000000000000523
20. Schulte LH, May A. Functional neuroimaging in migraine: chances and challenges. *Headache.* (2016) 56:1474–81. doi: 10.1111/head.12944

21. Ashina M, Hansen JM, Olesen J. Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience. *Cephalalgia.* (2013) 33:540–53. doi: 10.1177/0333102412475234
22. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA.* (2001) 98:4687–92. doi: 10.1073/pnas.071582498
23. Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM. Functional MRI-BOLD of brainstem structures during visually triggered migraine. *Neurology.* (2002) 59:72–8. doi: 10.1212/WNL.59.1.72
24. Vincent M, Pedra E, Mourão-Miranda J, Bramati I, Henrique A, Moll J. Enhanced interictal responsiveness of the migraineous visual cortex to incongruent bar stimulation: a functional MRI visual activation study. *Cephalalgia.* (2003) 23:860–8. doi: 10.1046/j.1468-2982.2003.00609.x
25. Antal A, Polania R, Saller K, Morawetz C, Schmidt-Samoa C, Baudewig J, et al. Differential activation of the middle-temporal complex to visual stimulation in migraineurs. *Cephalalgia.* (2011) 31:338–45. doi: 10.1177/0333102410379889
26. Martin H, Sanchez del Rio M, de Silanes CL, Alvarez-Linera J, Hernandez JA, Pareja JA. Photoreactivity of the occipital cortex measured by functional magnetic resonance imaging-blood oxygenation level dependent in migraine patients and healthy volunteers: pathophysiological implications. *Headache.* (2011) 51:1520–8. doi: 10.1111/j.1526-4610.2011.02013.x
27. Denuelle M, Boulloche N, Payoux P, Fabre N, Trotter Y, Geraud G. A PET study of photophobia during spontaneous migraine attacks. *Neurology.* (2011) 76:213–8. doi: 10.1212/WNL.0b013e3182074a57
28. Huang J, Zong X, Wilkins A, Jenkins B, Bozoki A, Cao Y. fMRI evidence that precision ophthalmic tints reduce cortical hyperactivation in migraine. *Cephalalgia.* (2011) 31:925–36. doi: 10.1177/0333102411409076
29. Descamps B, Vandemaele P, Reyngoudt H, Deblaere K, Leybaert L, Paemeleire K, et al. Absence of haemodynamic refractory effects in patients with migraine without aura – an interictal fMRI study. *Cephalalgia.* (2011) 31:1220–31. doi: 10.1177/0333102411415881
30. Datta R, Aguirre GK, Hu S, Detre JA, Cucchiara B. Interictal cortical hyperresponsiveness in migraine is directly related to the presence of aura. *Cephalalgia.* (2013) 33:365–74. doi: 10.1177/0333102412474503
31. Hougaard A, Amin FM, Hoffmann MB, Rostrup E, Larsson HB, Asghar MS, et al. Interhemispheric differences of fMRI responses to visual stimuli in patients with side-fixed migraine aura. *Hum Brain Mapp.* (2014) 35:2714–23. doi: 10.1002/hbm.22361
32. Griebe M, Flux F, Wolf ME, Hennerici MG, Szabo K. Multimodal assessment of optokinetic visual stimulation response in migraine with aura. *Headache.* (2014) 54:131–41. doi: 10.1111/head.12194
33. Maniyar FH, Sprenger T, Schankin C, Goadsby PJ. Photic hypersensitivity in the premonitory phase of migraine–a positron emission tomography study. *Eur J Neurol.* (2014) 21:1178–83. doi: 10.1111/ene.12451
34. Niddam DM, Lai KL, Fuh JL, Chuang CY, Chen WT, Wang SJ. Reduced functional connectivity between salience and visual networks in migraine with aura. *Cephalalgia.* (2016) 36:53–66. doi: 10.1177/0333102415583144
35. Tedeschi G, Russo A, Conte F, Corbo D, Caiazzo G, Giordano A, et al. Increased interictal visual network connectivity in patients with migraine with aura. *Cephalalgia.* (2016) 36:139–47. doi: 10.1177/0333102415584360
36. Amin FM, Hougaard A, Magon S, Asghar MS, Ahmad NN, Rostrup E, et al. Change in brain network connectivity during PACAP38-induced migraine attacks: a resting-state functional MRI study. *Neurology.* (2016) 86:180–7. doi: 10.1212/WNL.0000000000002261
37. Coppola G, Di Renzo A, Tinelli E, Lepre C, Di Lorenzo C, Di Lorenzo G, et al. Thalamo-cortical network activity between migraine attacks: insights from MRI-based microstructural and functional resting-state network correlation analysis. *J Headache Pain.* (2016) 17:100. doi: 10.1186/s10194-016-0693-y
38. Hougaard A, Amin FM, Larsson HB, Rostrup E, Ashina M. Increased intrinsic brain connectivity between pons and somatosensory cortex during attacks of migraine with aura. *Hum Brain Mapp.* (2017) 38:2635–42. doi: 10.1002/hbm.23548
39. Faragó P, Tuka B, Tóth E, Szabó N, Király A, Csete G, et al. Interictal brain activity differs in migraine with and without aura: resting state fMRI study. *J Headache Pain.* (2017) 18:8. doi: 10.1186/s10194-016-0716-8
40. Arngrim N, Hougaard A, Ahmadi K, Vestergaard MB, Schytz HW, Amin FM, et al. Heterogenous migraine aura symptoms correlate with visual cortex functional magnetic resonance imaging responses. *Ann Neurol.* (2017) 82:925–39. doi: 10.1002/ana.25096
41. Lisicki M, D'Ostilio K, Coppola G, Scholtes F, Maertens de Noordhout A, Parisi V, et al. Evidence of an increased neuronal activation-to-resting glucose uptake ratio in the visual cortex of migraine patients: a study comparing (18)FDG-PET and visual evoked potentials. *J Headache Pain.* (2018) 19:49. doi: 10.1186/s10194-018-0877-8
42. Lisicki M, D'Ostilio K, Coppola G, de Noordhout AM, Parisi V, Schoenen J, et al. Increased functional connectivity between the right temporo-parietal junction and the temporal poles in migraine without aura. *Cephalalgia Rep.* (2018) 1:2515816318804823. doi: 10.1177/2515816318804823
43. Russo A, Tessitore A, Silvestro M, Di Nardo F, Trojsi F, Del Santo T, et al. Advanced visual network and cerebellar hyperresponsiveness to trigeminal nociception in migraine with aura. *J Headache Pain.* (2019) 20:46. doi: 10.1186/s10194-019-1002-3
44. Arngrim N, Hougaard A, Schytz HW, Vestergaard MB, Britze J, Amin FM, et al. Effect of hypoxia on BOLD fMRI response and total cerebral blood flow in migraine with aura patients. *J Cereb Blood Flow Metab.* (2019) 39:680–9. doi: 10.1177/0271678X17719430
45. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain.* (2016) 139:1987–93. doi: 10.1093/brain/aww097
46. Amin FM, Hougaard A, Schytz HW, Asghar MS, Lundholm E, Parvaiz AI, et al. Investigation of the pathophysiological mechanisms of migraine attacks induced by pituitary adenylate cyclase-activating polypeptide-38. *Brain.* (2014) 137:779–94. doi: 10.1093/brain/awt369
47. Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. *PLoS Med.* (2006) 3:e402. doi: 10.1371/journal.pmed.0030402
48. Rocca MA, Pagani E, Colombo B, Tortorella P, Falini A, Comi G, et al. Selective diffusion changes of the visual pathways in patients with migraine: a 3-T tractography study. *Cephalalgia.* (2008) 28:1061–8. doi: 10.1111/j.1468-2982.2008.01655.x
49. Zhang J, Wu YL, Su J, Yao Q, Wang M, Li GF, et al. Assessment of gray and white matter structural alterations in migraineurs without aura. *J Headache Pain.* (2017) 18:74. doi: 10.1186/s10194-017-0783-5
50. Coppola G, Petolicchio B, Di Renzo A, Tinelli E, Di Lorenzo C, Parisi V, et al. Cerebral gray matter volume in patients with chronic migraine: correlations with clinical features. *J Headache Pain.* (2017) 18:115. doi: 10.1186/s10194-017-0825-z
51. Palm-Meinders IH, Arkink EB, Koppen H, Amlal S, Terwindt GM, Launer LJ, et al. Volumetric brain changes in migraineurs from the general population. *Neurology.* (2017) 89:2066–74. doi: 10.1212/WNL.0000000000004640
52. Gaist D, Hougaard A, Garde E, Reislev NL, Wiwie R, Iversen P, et al. Migraine with visual aura associated with thicker visual cortex. *Brain.* (2018) 141:776–85. doi: 10.1093/brain/awx382
53. Lisicki M, D'Ostilio K, Coppola G, Maertens de Noordhout A, Parisi V, Schoenen J, et al. Brain correlates of single trial visual evoked potentials in migraine: more than meets the eye. *Front Neurol.* (2018) 9:393. doi: 10.3389/fneur.2018.00393
54. Sarchielli P, Tarducci R, Presciutti O, Gobbi G, Pelliccioli GP, Stipa G, et al. Functional 1H-MRS findings in migraine patients with and without aura assessed interictally. *Neuroimage.* (2005) 24:1025–31. doi: 10.1016/j.neuroimage.2004.11.005
55. Sandor PS, Dydak U, Schoenen J, Kollias SS, Hess K, Boesiger P, et al. MR-spectroscopic imaging during visual stimulation in subgroups of migraine with aura. *Cephalalgia.* (2005) 25:507–18. doi: 10.1111/j.1468-2982.2005.00900.x
56. Siniatchkin M, Sendacki M, Moeller F, Wolff S, Jansen O, Siebner H, et al. Abnormal changes of synaptic excitability in migraine with aura. *Cereb Cortex.* (2011) 22:2207–16. doi: 10.1093/cercor/bhr248
57. Bridge H, Stagg CJ, Near J, Lau CI, Zisner A, Cader MZ. Altered neurochemical coupling in the occipital cortex in migraine with visual aura. *Cephalalgia.* (2015) 35:1025–30. doi: 10.1177/0333102414566860

58. Zielman R, Wijnen JP, Webb A, Onderwater GLJ, Ronen I, Ferrari MD, et al. Cortical glutamate in migraine. *Brain.* (2017) 140:1859–71. doi: 10.1093/brain/awx130
59. Hansen JM, Baca SM, Vanvalkenburgh P, Charles A. Distinctive anatomical and physiological features of migraine aura revealed by 18 years of recording. *Brain.* (2013) 136:3589–95. doi: 10.1093/brain/awt309
60. Hansen JM, Goadsby PJ, Charles AC. Variability of clinical features in attacks of migraine with aura. *Cephalalgia.* (2016) 36:216–24. doi: 10.1177/0333102415584601
61. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. *Ann Neurol.* (1981) 9:344–52. doi: 10.1002/ana.410090406
62. Leão AAP. Spreading depression of activity in the cerebral cortex. *J Neurophysiol.* (1944) 7:359–90. doi: 10.1152/jn.1944.7.6.359
63. Tootell RB, Mendola JD, Hadjikhani NK, Ledden PJ, Liu AK, Reppas JB, et al. Functional analysis of V3A and related areas in human visual cortex. *J Neurosci.* (1997) 17:7060–78. doi: 10.1523/JNEUROSCI.17-18-07060.1997
64. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med.* (2002) 8:136–42. doi: 10.1038/nm0202-136
65. Vanagaite J, Pareja JA, Storen O, White LR, Sand T, Stovner LJ. Light-induced discomfort and pain in migraine. *Cephalalgia.* (1997) 17:733–41. doi: 10.1046/j.1468-2982.1997.1707733.x
66. Kowacs PA, Piovesan EJ, Werneck LC, Tatsui CE, Lange MC, Ribas LC, et al. Influence of intense light stimulation on trigeminal and cervical pain perception thresholds. *Cephalalgia.* (2001) 21:184–8. doi: 10.1046/j.1468-2982.2001.00178.x
67. Headache Classification Committee of the International Headache Society (HIS). The international classification of headache disorders, 3rd edition. *Cephalalgia.* (2018) 38:1–211. doi: 10.1177/0333102417738202
68. Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology.* (2003) 60:935–40. doi: 10.1212/01.WNL.0000052998.58526.A9
69. Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. *Headache.* (1997) 37:492–5. doi: 10.1046/j.1526-4610.1997.3708492.x
70. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, et al. A neural mechanism for exacerbation of headache by light. *Nat Neurosci.* (2010) 13:239–45. doi: 10.1038/nn.2475
71. Schwedt TJ, Schlaggar BL, Mar S, Nolan T, Coalson RS, Nardos B, et al. Atypical resting-state functional connectivity of affective pain regions in chronic migraine. *Headache.* (2013) 53:737–51. doi: 10.1111/head.12081
72. Robinson DL, Petersen SE. The pulvinar and visual salience. *Trends Neurosci.* (1992) 15:127–32.
73. Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D. Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: implications for photophobia. *Hum Brain Mapp.* (2012) 33:75–88. doi: 10.1002/hbm.21194
74. Schankin CJ, Maniyar FH, Digre KB, Goadsby PJ. 'Visual snow' - a disorder distinct from persistent migraine aura. *Brain.* (2014) 137(Pt 5):1419–28. doi: 10.1093/brain/awu050
75. Schankin CJ, Maniyar FH, Sprenger T, Chou DE, Eller M, Goadsby PJ. The relation between migraine, typical migraine aura and "visual snow". *Headache.* (2014) 54:957–66. doi: 10.1111/head.12378
76. Lauschke JL, Plant GT, Fraser CL. Visual snow: a thalamocortical dysrhythmia of the visual pathway? *J Clin Neurosci.* (2016) 28:123–7. doi: 10.1016/j.jocn.2015.12.001
77. Puledda F, Lau T, Schankin C, Goadsby PJ. Clinical characterization of visual snow. *Cephalalgia.* (2017) 37:177.
78. Ffytche DH. The hodology of hallucinations. *Cortex.* (2008) 44:1067–83. doi: 10.1016/j.cortex.2008.04.005
79. Brown GC, Brown MM, Fischer DH. Photopsias: a key to diagnosis. *Ophthalmology.* (2015) 122:2084–94. doi: 10.1016/j.ophtha.2015.06.025
80. von Helmholtz H. *Verschiedene Subjective Erscheinungen. Handbuch der Physiologischen Optik.* 2nd ed. Hamburg; Leipzig: Verlag von Leopold Voss (1896). 572 p.
81. Tyler CW. Some new entoptic phenomena. *Vision Res.* (1978) 18:1633–9.
82. Sinclair SH, Azar-Cavanagh M, Soper KA, Tuma RF, Mayrovitz HN. Investigation of the source of the blue field entoptic phenomenon. *Invest Ophthalmol Vis Sci.* (1989) 30:668–73.
83. Santhouse AM, Howard RJ, Ffytche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. *Brain.* (2000) 123 (Pt 10):2055–64. doi: 10.1093/brain/123.10.2055
84. Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci USA.* (1999) 96:15222–7. doi: 10.1073/pnas.96.26.15222
85. Coppola G, Ambrosini A, Di Clemente L, Magis D, Fumal A, Gerard P, et al. Interictal abnormalities of gamma band activity in visual evoked responses in migraine: an indication of thalamocortical dysrhythmia? *Cephalalgia.* (2007) 27:1360–7. doi: 10.1111/j.1468-2982.2007.01466.x
86. Coppola G, Parisi V, Di Lorenzo C, Serrao M, Magis D, Schoenen J, et al. Lateral inhibition in visual cortex of migraine patients between attacks. *J Headache Pain.* (2013) 14:20. doi: 10.1186/1129-2377-14-20
87. Lakatos P, O'Connell MN, Barczak A. Pondering the pulvinar. *Neuron.* (2016) 89:5–7. doi: 10.1016/j.neuron.2015.12.022
88. Jaramillo J, Mejias JF, Wang X-J. Engagement of pulvino-cortical feedforward and feedback pathways in cognitive computations. *Neuron.* (2019) 101:321–36.e329. doi: 10.1016/j.neuron.2018.11.023
89. Ffytche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S. The anatomy of conscious vision: an fMRI study of visual hallucinations. *Nat Neurosci.* (1998) 1:738–42. doi: 10.1038/3738
90. Ffytche DH, Blom JD, Catani M. Disorders of visual perception. *J Neurol Neurosurg Psychiatry.* (2010) 81:1280–7. doi: 10.1136/jnnp.2008.171348
91. Chen BS, Lance S, Lallu B, Anderson NE. Visual snow: not so benign. *J Clin Neurosci.* (2019) 64:37–9. doi: 10.1016/j.jocn.2019.03.023
92. Eren O, Rauschel V, Ruscheweyh R, Straube A, Schankin CJ. Evidence of dysfunction in the visual association cortex in visual snow syndrome. *Ann Neurol.* (2018) 84:946–9. doi: 10.1002/ana.25372
93. Luna S, Lai D, Harris A. Antagonistic relationship between VEP potentiation and gamma power in visual Snow syndrome. *Headache.* (2018) 58:138–44. doi: 10.1111/head.13231
94. Yildiz FG, Turkyilmaz U, Unal-Cevik I. The clinical characteristics and neurophysiological assessments of the occipital cortex in visual snow syndrome with or without migraine. *Headache.* (2019) 59:484–94. doi: 10.1111/head.13494
95. McKendrick AM, Chan YM, Tien M, Millist L, Clough M, Mack H, et al. Behavioral measures of cortical hyperexcitability assessed in people who experience visual snow. *Neurology.* (2017) 88:1243–9. doi: 10.1212/WNL.0000000000003784
96. Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci.* (1992) 15:20–5. doi: 10.1016/0166-2236(92)90344-8
97. Zeki S, Watson JD, Lueck CJ, Friston KJ, Kennard C, Frackowiak RS. A direct demonstration of functional specialization in human visual cortex. *J Neurosci.* (1991) 11:641–9. doi: 10.1523/JNEUROSCI.11-03-00641.1991
98. Gilbert CD, Li W. Top-down influences on visual processing. *Nat Rev Neurosci.* (2013) 14:350–63. doi: 10.1038/nrn3476
99. Shine JM, Halliday GM, Naismith SL, Lewis SJ. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? *Mov Disord.* (2011) 26:2154–9. doi: 10.1002/mds.23896
100. Shine JM, Halliday GM, Gilat M, Matar E, Bolitho SJ, Carlos M, et al. The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. *Hum Brain Mapp.* (2014) 35:2206–19. doi: 10.1002/hbm.22321
101. Sedley W, Friston KJ, Gander PE, Kumar S, Griffiths TD. An integrative tinnitus model based on sensory precision. *Trends Neurosci.* (2016) 39:799–812. doi: 10.1016/j.tins.2016.10.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 09 January 2020
doi: 10.3389/fneur.2019.01356

The Chronic Migraine Brain: What Have We Learned From Neuroimaging?

Massimo Filippi[1,2,3]* *and Roberta Messina*[1,2]

[1] Neuroimaging Research Unit, Division of Neuroscience, Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy, [2] Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [3] Vita-Salute San Raffaele University, Milan, Italy

Chronic migraine is a highly disabling disease with a great impact on socioeconomic functioning and quality of life of migraine patients. Chronic migraine usually evolves from episodic migraine that gradually increases in attack frequency, supporting the view of migraine as a spectrum disorder. Pathophysiological mechanisms responsible for migraine chronification are not fully understood. Likewise episodic migraine, chronic migraine patients show widespread functional and structural alterations of cortical and subcortical pain-related brain areas. However, chronic migraine patients experience a more pronounced dysfunction of the pain inhibitory network and an increased sensitization of the central pain pathways, which might explain the higher susceptibility to migraine attacks. Imaging studies have highlighted that brain regions with a key role in migraine attack generation, like the pons and hypothalamus, might also be involved in migraine chronification. Whether brain alterations are biomarkers that predispose migraine patients to chronification or reflect adaptive or maladaptive responses to the increasing headache frequency is still a matter of debate. The central mechanisms of action of chronic migraine preventive treatments and imaging biomarkers that could predict patients' treatment response have also been explored. In this new era of migraine treatments, a better understanding of chronic migraine pathophysiology will pave the way for the development of new improved treatments specifically designed for chronic migraine patients.

Keywords: chronic migraine, neuroimaging, chronification, pain network, biomarkers

OPEN ACCESS

Edited by:
Sabina Cevoli,
IRCCS Institute of Neurological Sciences of Bologna (ISNB), Italy

Reviewed by:
Gianluca Coppola,
Sapienza University of Rome, Italy
Filippo Brighina,
University of Palermo, Italy

***Correspondence:**
Massimo Filippi
filippi.massimo@hsr.it

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *25 September 2019*
Accepted: *09 December 2019*
Published: *09 January 2020*

Citation:
Filippi M and Messina R (2020) The Chronic Migraine Brain: What Have We Learned From Neuroimaging? Front. Neurol. 10:1356. doi: 10.3389/fneur.2019.01356

INTRODUCTION

Chronic migraine is a highly disabling disease. Relative to episodic migraine, patients with chronic migraine have greater headache-related impact on socioeconomic functioning and worse quality of life (1). According to the International Classification of Headache Disorders (2), chronic migraine is defined as at least 15 days of headache occurring each month, including at least 8 days a month of headache attacks with migrainous features, for more than 3 months. The prevalence of chronic migraine is around 1–2% in the general population. Chronic migraine usually evolves from episodic migraine that gradually increases in attack frequency, with an annual progression rate of about 3% (3, 4). The main risk factors for transition are female sex, low educational status, baseline high attack frequency, obesity, stressful life events, snoring, ineffective acute treatments, and overuse of acute migraine medications (5, 6). At least 50% of patients with chronic migraine regularly overuse one

or more drugs usually taken for acute migraine treatment, thus fulfilling the diagnosis of chronic migraine with medication overuse (2, 7, 8). Compared to episodic migraine patients, patients with chronic migraine are more likely to have psychiatric comorbidities, like depression and anxiety, respiratory and cardiovascular diseases (1). Chronic migraine is a dynamic state, with patients moving in and out of the chronic condition. About 26% of patients with chronic migraine remit to the episodic form within 2 years (9).

Pathophysiological mechanisms responsible for migraine chronification are not fully understood. Patients with chronic migraine might have a lower sensory threshold and an increased susceptibility to migraine attacks (3). Central and peripheral sensitization processes can contribute to the pathophysiology of chronic migraine. Of note, compared to episodic migraine patients, patients with chronic migraine have higher plasma levels of vasoactive neuropeptides, such as the calcitonin gene related peptide and vasoactive intestinal peptide, thus suggesting an altered activity of the trigeminal and cranial autonomic system (3, 10, 11). Dysfunction of cortical and subcortical brain areas involved in pain processing, such as the thalamus, hypothalamus, somatosensory and anterior cingulate cortex, might also have a pivotal role in migraine transformation. There is evidence that an altered balance between the facilitatory and inhibitory activity of pain-related brain regions might contribute to the development of symptoms commonly reported by chronic migraine patients, like cutaneous allodynia (12, 13). Our understanding of the pathophysiology of chronic migraine has improved considerably with a series of imaging studies, which have provided insights into the function and structure of human brain networks that could be involved in migraine chronification. This review will focus the attention on neuroimaging studies in patients with chronic migraine, highlighting the evidence behind the involvement of key brain areas, such as the pons and hypothalamus, and the pain network in migraine chronification. **Table 1** summarizes the main findings of neuroimaging studies in chronic migraine patients.

IMAGING THE PAIN NETWORK IN CHRONIC MIGRAINE

Pain experience is a complex process involving sensory, affective, and cognitive brain networks. Similar to previous findings in episodic migraine patients (37), an altered functional recruitment of brain areas involved in the sensory-discriminative and affective aspects of pain, including the insula, prefrontal, anterior cingulate and somatosensory cortex, has been demonstrated in chronic migraine patients (20). Maladaptive functional activation of brain networks involved in attentive and executive functions, such as the executive control, default mode and dorsal attention network, have also been revealed in patients with chronic migraine. Thus, suggesting that the reaction to painful stimuli, preparation of responses, and allocation of attentional resources to pain are impaired in chronic migraine patients (14, 15, 17). Whether cognitive symptoms, particularly deficits in attention and executive functions, might influence the functional activity of brain cognitive networks has never been investigated. A comprehensive neuropsychological assessment should be included in future studies. The salience network has a key role in defining the saliency of incoming painful stimuli. In chronic migraine patients, the presence of cutaneous allodynia was associated to an increased activity of the salience network. These findings support a possible involvement of the salience network in central sensitization (14).

Several studies (29, 30, 34) demonstrated that chronic migraine is also associated with morphometric alterations of brain areas known to be involved in pain modulation and in the different aspects of pain processing. Regions of increased and decreased gray matter volume, including the brainstem, cerebellum, basal ganglia, amygdala, frontal, temporal and occipital areas, have been found in chronic migraine patients compared to controls (29, 30, 34).

Whether these functional and structural alterations are the consequence of the recurrence of headache attacks or might predispose to chronic migraine is still a matter of debate. Some studies demonstrated functional (14, 20) and structural (30, 33, 34) plasticity of nociceptive brain areas that are linked to the headache attack frequency and disease duration. Repetitive headache attacks can remodel the pain network, thus increasing the susceptibility to the onset of further attacks and leading to chronic central sensitization. On the other hand, other investigations did not confirm such correlation (29).

Dynamic functional (21, 26) and structural (32, 35) changes in pain processing structures were also revealed in chronic migraine patients with medication overuse. Interestingly, imaging alterations of the thalamus, insula, anterior cingulate, and parietal cortex reverted after medication withdrawal, probably reflecting the consequences rather than the causes of medication overuse in these patients. While alterations of mesocorticolimbic dopaminergic areas, such as the ventral tegmental area (23) and orbitofrontal cortex (26), persisted following detoxification, suggesting that these findings might represent a brain trait that predisposes certain migraine patients to the development of medication overuse.

Quantitative MRI techniques have shown increased iron deposition in the periaqueductal gray, red nucleus, and basal ganglia in migraine patients and patients with chronic daily headache (38–40). A higher risk to have iron deposition was associated to higher attack frequency or longer disease duration, suggesting a causal relationship between migraine and these abnormalities (38). The observed association between repeated migraine attacks and increased iron accumulation in the brainstem and deep gray matter nuclei involved in central pain processing support the possibility that migraine has cumulative effects on brain structure and homeostasis. However, a follow-up study did not find any significant progression of iron accumulation over 9 years (41).

A further unanswered question is whether neuroimaging alterations are common to episodic and chronic migraine patients or are specifically involved in migraine chronification. There is evidence showing a more pronounced dysfunction of the pain inhibitory (18) and thalamocortical (28) pathway in chronic than episodic migraine. Using resting state

TABLE 1 | A summary of the main findings of neuroimaging studies in chronic migraine patients.

Study	Study cohorts	Main findings	Potential confounders
RESTING STATE fMRI STUDIES			
Androulakis et al. (14, 15)	13 CM patients without MOH (all females), 16 CM patients with MOH (all females) vs. 19 controls (all females)	• Compared to controls, CM patients, regardless of MOH status, showed: - ↓ overall network connectivity of the DMN, SN and ECN • Frequency of headache attacks was negatively correlated with the strength of the SN and ECN intrinsic connectivity • Severity of cutaneous allodynia was positively correlated with the strength of the SN intrinsic connectivity	• 15 patients were taking migraine prophylaxis
Chen et al. (16)	16 CM patients without MOH, 18 EM patients vs. 21 controls	• Compared to controls and EM patients, CM patients had: - ↑ RS FC between the anterior hypothalamus and the right orbital gyrus	• 14 CM patients had headache without migraine features during MRI scanning
Coppola et al. (17)	20 CM patients without MOH vs. 20 controls	• Compared to controls, CM patients showed: - ↓ RS FC between the DMN and ECN - ↑ RS FC between the DAS and DMN - ↓ RS FC between the DAS and ECN. • The severity of headache was positively correlated with the strength of the DAS intrinsic connectivity • The severity of headache was negatively correlated with the strength of the ECN intrinsic connectivity	
Lee et al. (18)	19 CM patients without MOH vs. 45 EM patients	• Compared to EM patients, CM patients showed: - ↑ RS FC of pain processing areas, including the anterior cingulate cortex - ↓ RS FC between pain processing brain areas and the hypothalamus - ↑ RS FC between pain processing brain areas and the dorsal raphe nucleus	
Lerebours et al. (19)	25 CM patients with MOH vs. 22 EM patients	• Compared to EM patients, CM patients had: - ↑ RS FC between the anterior hypothalamus and the spinal trigeminal nucleus	• 16 CM patients had mild headache during the MRI • 6 CM patients were taking migraine prophylaxis
Schwedt et al. (20)	20 CM patients without MOH vs. 20 controls	• Atypical RS FC between: - Left anterior insula and left pulvinar, parieto-temporal areas, right precuneus, cingulate cortex and bilateral thalamus - Right anterior insula and left pulvinar, right periaqueductal gray, middle temporal cortex, and bilateral thalamus - Left amygdala and right superior frontal gyrus - Right amygdala and occipital cortex • Disease duration was positively correlated with: - RS FC between bilateral anterior insula and right thalamus - RS FC between right anterior insula and right periaqueductal gray • Anxiety scores were negatively correlated with: - RS FC between right anterior insula and right periaqueductal gray	• 8 patients were taking migraine prophylaxis

(Continued)

TABLE 1 | Continued

Study	Study cohorts	Main findings	Potential confounders
fMRI STUDIES OF NOCICEPTIVE STIMULATION			
Ferraro et al. (21)	9 CM patients with MOH (all females) vs. 9 controls (all females)	• Compared to controls, CM patients with MOH showed: - ↓ pain-related activity of bilateral inferior parietal lobule, somatosensory cortex and right supramarginal gyrus • In CM patients, the activity of pain processing regions normalized at 6 months after withdrawal	• During the MRI exam, all patients had a moderate headache
Schulte et al. (22)	17 CM patients without MOH, 18 EM patients vs. 19 controls	• Compared to controls, CM patients showed: - ↑ activation of the anterior right hypothalamus • Compared to controls and migraineurs (EM and CM) without headache, migraineurs with headache showed: - ↑ activation of the posterior hypothalamus bilaterally	• 4 CM patients were taking migraine prophylaxis • 19 patients (7 EM and 12 CM patients) had headache during the MRI
fMRI STUDIES DURING A DECISION-MAKING TASK			
Ferraro et al. (23)	8 CM patients with MOH (all females), 8 detoxified CM patients with MOH (all females), 8 CM patients without MOH (all females) vs. 8 controls (all females)	• Compared to controls, CM patients with MOH showed: - ↓ task-related activity in the substantia nigra/ventral tegmental area complex - ↑ task-related activity in the ventromedial prefrontal cortex • Compared to CM without MOH, CM patients with MOH showed: - ↓ task-related activity in the substantia nigra/ventral tegmental area complex • Compared to detoxified MOH patients, CM patients with MOH showed: - ↑ task-related activity in the ventromedial prefrontal cortex	• During the MRI exam, all patients had a moderate headache
fMRI STUDIES OF VISUAL STIMULATION			
Schulte et al. (24)	17 CM patients without MOH, 18 EM patients vs. 19 controls	• Compared to controls, CM patients showed: - ↑ activation of the spinal trigeminal nucleus and superior colliculi	• 4 CM patients were taking migraine prophylaxis • 19 patients (7 EM and 12 CM patients) had headache during the MRI
POSITRON EMISSION TOMOGRAPHY STUDIES			
Aurora et al. (25)	10 CM patients with or without MOH	• CM patients had: - ↑ metabolism in the pons and right temporal cortex compared to the global cerebral metabolism - ↓ metabolism in the bilateral caudate nuclei, frontal and parietal cortex compared to the global cerebral metabolism	
Fumal et al. (26)	16 CM patients with MOH vs. 68 controls	• Before withdrawal, compared to controls, CM patients with MOH showed: - ↓ metabolism of the bilateral thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula, ventral striatum, and right inferior parietal lobule - ↑ cerebellar metabolism • In CM patients with MOH, all dysmetabolic areas recovered to almost normal glucose uptake 3 weeks after withdrawal, except the orbitofrontal cortex where a further metabolic decrease was found	

(Continued)

TABLE 1 | Continued

Study	Study cohorts	Main findings	Potential confounders
Matharu et al. (27)	8 CM patients	• No significant differences in the activity of the dorsal rostral pons in CM patients during pain and in pain-free patients during bilateral suboccipital stimulation • ↓ activation of the anterior cingulate cortex in pain-free CM patients during bilateral suboccipital stimulation • ↑ activation of the anterior cingulate cortex and cuneus in CM patients during pain	
PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDIES			
Niddam et al. (28)	25 CM patients without MOH, 24 EM patients vs. 25 controls	• Compared to controls, CM patients had: - ↓ N-acetyl-aspartate concentration of the right thalamus and anterior cingulate cortex - Altered interregional N-acetyl-aspartate correlations between the thalamus and anterior cingulate cortex and between the thalamus and occipital cortex in the right hemisphere • Compared to controls and EM patients, CM patients had: - ↓ N-acetyl-aspartate concentration of the left thalamus • In CM patients, the right thalamic N-acetyl-aspartate concentrations was negatively correlated with patients' disease duration • In CM patients, there was a positive correlation between the N-acetyl-aspartate concentration and gray matter volume of the right anterior cingulate cortex	• 21 patients (3 EM and 18 CM patients) had headache the day of the MRI
MORPHOMETRIC STUDIES			
Bilgic et al. (29)	17 CM patients without MOH (all females), 7 CM patients with MOH (all females) vs. 24 controls (all females)	• Compared to controls, CM had: • ↓ cerebellar and brainstem volume	• 7 patients were taking migraine prophylaxis
Chen et al. (16)	16 CM patients without MOH, 18 EM patients vs. 21 controls	• Compared to controls and EM patients, patients with CM showed: - ↓ volume of the anterior hypothalamus • In CM patients, the anterior hypothalamic volume was positively correlated with headache frequency • Cut-off volume of the hypothalamus as 1.429 ml had a good diagnostic accuracy for CM with sensitivity of 81% and specificity of 100%	• 14 CM patients had headache without migraine features during MRI scanning
Coppola et al. (30)	20 CM patients without MOH vs. 20 controls	• Compared to controls, CM patients had: - ↓ gray matter volume of the right cerebellum, left pallidum, amygdala, orbitofrontal, temporal, and occipital cortex • In CM patients, the cerebellar gray matter volume was: - Negatively correlated with patients' disease duration - Positively correlated with the number of acute medications taken per month	• 4 patients had mild headache without migrainous features during the MRI exam

(Continued)

TABLE 1 | Continued

Study	Study cohorts	Main findings	Potential confounders
Hubbard et al. (31)	23 CM patients (11 responders and 12 non-responders to prophylactic treatment with onabotulinumtoxinA)	• Compared to non-responders, patients who responded to onabotulinumtoxinA showed: - ↑ cortical thickness of the right primary somatosensory cortex, anterior insula, left superior temporal gyrus and pars opercularis • In responders patients, disease duration was: - Negatively correlated with cortical thickness of fronto-parietal and temporo-occipital regions - Positively associated to the cortical thickness of the left primary motor cortex • In non-responders patients, disease duration was: - Negatively associated to the cortical thickness of the left primary motor cortex - Positively associated to the cortical thickness of the left inferior temporal gyrus and lateral occipital cortex	• Some patients in the non-responder group may have had mild headache the day of the MRI
Lai et al. (32)	33 CM patients with MOH (19 responders to common preventive treatments), 33 CM patients without MOH vs. 33 controls	• Compared to CM patients without MOH, patients with MOH showed: - ↓ gray matter volume of the bilateral orbitofrontal cortex and left middle occipital gyrus - ↑ gray matter volume of the left temporal pole/parahippocampus • In CM patients with MOH, clinical improvement after 12 months of preventive treatment was significantly associated to the gray matter volume of the orbitofrontal cortex • In CM patients, gray matter volume changes could predict the frequency of analgesics use	• 33 patients had migraine the day of the MRI exam (13 CM patients without MOH and 20 CM patient with MOH)
Liu et al. (33)	39 CM patients, 83 EM patients (15 patients with MOH) vs. 31 controls	• In CM and EM patients, the volume of the bilateral hippocampus and left amygdala varied as a function of headache frequency • At 2-year follow-up, the volume of the right hippocampus was positively associated with a good migraine outcome	
Neeb et al. (34)	6 CM patients without MOH, 15 CM patients with MOH, 21 EM patients vs. 21 controls	• Compared to controls, CM patients had: - ↑ gray matter volume of the right amygdala, superior parietal lobule, hippocampus, parahippocampus, left insula, and bilateral basal ganglia • Compared to EM patients, CM patients showed: - ↑ gray matter volume of bilateral temporal areas - ↓ gray matter volume of the left cuneus • In CM and EM patients, gray matter volume alterations were influenced by headache frequency	• 13 patients (9 CM and 4 EM patients) were taking migraine prophylaxis
Niddam et al. (28)	25 CM patients without MOH, 24 EM patients vs. 25 controls	• Compared to controls, CM patients had: - ↓ gray matter volume of the right anterior cingulate cortex	

(Continued)

TABLE 1 | Continued

Study	Study cohorts	Main findings	Potential confounders
Riederer et al. (35)	31 CM patients with MOH (10 responders and 8 non-responders to medication withdrawal)	• At baseline, compared to responder patients, non-responders had: - ↓ gray matter volume of the right orbitofrontal cortex • Only responders patients showed ↓ gray matter volume of the midbrain after medication withdrawal • Treatment response correlated positively with: - Baseline gray matter volume of the orbitofrontal cortex - Gray matter volume change in the midbrain after medication withdrawal	• 20 patients were taking migraine prophylaxis
Schwedt et al. (36)	15 CM patients without MOH, 51 EM patients vs. 54 controls	• Average accuracy of classifiers consisting of cortical surface area, cortical thickness, and regional volumes of fronto-temporal areas was: - 86.3% for CM patients vs. controls - 84.2% for CM vs. EM patients - 67.2% for EM patients vs. controls	

CM, chronic migraine; DAS, dorsal attention system; DMN, default mode network; EM, episodic migraine; ECN, executive control network; fMRI, functional magnetic resonance imaging; MOH, medication overuse headache; RS FC, resting state functional connectivity; SN, salience network.

functional MRI, Lee and coworkers (18) have shown an increased functional connectivity of pain processing brain areas, especially the anterior cingulate cortex, in chronic migraine patients compared to patients with episodic migraine (18). Reduced N-acetyl-aspartate concentration in the thalamus and anterior cingulate cortex has been found in chronic migraine patients, but not in patients with episodic migraine (28). Interestingly, the interregional correlations of N-acetyl-aspartate levels between the thalamus and the anterior cingulate cortex shifted from positive in controls to negative in chronic migraine patients. Thus, suggesting that neuronal reorganization in the thalamocortical pathway might contribute to migraine chronification.

Chronic migraine is also associated to more extensive brain structural alterations. Schwedt and colleagues (36) reported that alterations of cortical thickness, cortical surface area and regional volumes of fronto-temporal brain areas could discriminate chronic migraine patients from controls and from patients with episodic migraine with an accuracy of 86 and 84%, respectively. While, the accuracy for discriminating episodic migraine patients from controls was of only 67%. A greater iron accumulation was found in chronic migraine patients compared to patients with episodic migraine (39, 40). Larger volume of iron deposits could identify chronic migraine with a sensitivity ranging from 80 to 93% and a specificity ranging from 71 to 97% (40). The increased iron levels in the anti-nociceptive network in chronic migraine patients might constitute a physiologic response to repeated activation of nuclei involved in central pain processing, which may play a role in the chronification of migraine.

In migraine patients, the perception of the headache pain can be exacerbated by the exposure of lights. There is evidence showing that photic signals coming from the retina can converge on thalamic trigeminovascular neurons that project to cortical areas involved in the processing of pain and visual perception. Thus, supporting the link between the visual and trigeminal pain processing system (42). Interestingly, compared to controls and episodic migraine patients, chronic migraine patients showed and increased activity of the spinal trigeminal nucleus and superior colliculi during visual stimulation with a rotating checkerboard. The increased trigeminal activation during visual stimulation was significantly influenced by the experience of headache. These findings corroborate the crosslink between the visual and trigeminal systems and demonstrate a more pronounced sensitization of these two pathways in patients with chronic migraine (24).

IMAGING THE MIGRAINE "GENERATORS" IN CHRONIC MIGRAINE

Although our understanding of the pathophysiology of migraine has progressed over the last years, where exactly migraine attacks originate is still an unresolved question. Several studies demonstrated a selective activation of the dorsal pons during spontaneous (43, 44) and nitroglycerin-triggered (45) migraine attacks, which persisted after complete pain-resolution due to triptan administration (44), in patients with episodic migraine. Thus, leading the authors to hypothesize that this brainstem region might represent the so-called migraine "generator." An increased cerebral metabolism in the pons has also been described in patients with chronic migraine during and outside the headache phase (25, 27). Similar to episodic migraine, the dysfunctional activation of this brainstem region did not change after electrical suboccipital stimulation, supporting the key role of this

region in migraine attack generation as well as in migraine chronification (27).

Recent MRI studies have pointed the attention to the role of the hypothalamus in migraine attack generation. Positron emission tomography (46) and functional MRI (43) studies revealed increased hypothalamic activity before and during the headache phase of the migraine attack in episodic migraine patients. An altered functional coupling between the hypothalamus and the spinal trigeminal nucleus during the precital phase and between the hypothalamus and the pons during the ictal phase have also been demonstrated (43). These findings suggest that the hypothalamus-brainstem network might be the real driver of migraine attacks.

Different regions of the hypothalamus seem be involved in the onset of the migraine attack and in migraine chronification. Chronic migraine patients with and without medication overuse showed a selective increased activity of the anterior hypothalamus during trigeminal painful stimulation (22) and in a rest condition (16, 19), compared to controls and patients with episodic migraine. Thus, suggesting that the anterior hypothalamus plays a crucial role in the pathophysiology of chronic migraine. While, the most posterior hypothalamic part was specifically linked to the acute headache phase of the migraine attack (22).

Relative to episodic migraine, an increased activation of the hypothalamus seems to facilitate the recruitment of cortical areas involved in pain processing in chronic migraine patients (18).

In conjunction with functional alterations, structural plasticity of the anterior hypothalamus has been demonstrated in patients with chronic migraine. A hypothalamic volume lower than 1.43 ml had a good diagnostic accuracy for chronic migraine with sensitivity of 81% and specificity of 100% (16).

IMAGING BIOMARKERS OF TREATMENT RESPONSE IN CHRONIC MIGRAINE

Imaging techniques can provide new insights into the central mechanisms of action of treatments commonly used for chronic migraine. A positron emission tomography study (27) showed significant functional modulation of brain regions involved in the affective aspects of pain, including the anterior cingulate cortex and cuneus, during bilateral electrical suboccipital stimulation in a small cohort of chronic migraine patients.

Now that new mechanism-based treatments specific for migraine are available a better prediction of treatment response might facilitate the selection of the most appropriate treatment for each patient. Chronic migraine patients who responded to OnabotulinumtoxinA treatment, as evidenced by reversal from a chronic to an episodic state, had distinct patterns of morphometric and functional alterations in pain processing areas compared to those patients who did not respond (31). The identification of the brain pathways that are involved in disease reversal or progression can lead to a better understanding of the mechanisms underlying the migraine chronification. All of this is critical to discovering new treatments that prevent or slow the progression to chronic migraine. Imaging biomarkers that could predict patients' treatment response have also been identified in chronic migraine patients with medication overuse. Rieder and coworkers (35) showed significant volumetric changes in the midbrain after the withdrawal of acute headache medications only in those patients who responded to the treatment. Moreover, decreased gray matter volume of the orbitofrontal cortex predicted a negative response to detoxification.

CONCLUSIONS

Significant advances in our understanding of chronic migraine pathophysiology have been made over the last years. Neuroimaging findings support the view that migraine is a spectrum disorder, with clinical and pathophysiological features that can progress over time. Chronic and episodic migraine share similar functional and structural alterations in brain regions implicated in the generation of the migraine attack and in pain processing. However, chronic migraine patients experience a more pronounced dysfunction of the pain inhibitory network and an increased sensitization of the central pain pathways, which might explain the higher susceptibility to migraine attacks. Whether brain alterations are biomarkers that predispose migraine patients to chronification or reflect adaptive or maladaptive responses to the increasing headache frequency is still debated. Longitudinal studies including large sample size of patients with episodic and chronic migraine are warranted. Future studies combining multimodal data, such as functional MRI, structural MRI and electroencephalographic data, might help us to achieve a better understanding of chronic migraine pathophysiology. In the future, imaging patterns that predict whether an episodic migraine patient will evolve to a chronic form should be identified. This might lead to an early prevention of migraine transformation. In this new era of migraine treatments, a better understanding of chronic migraine pathophysiology will pave the way for the development of new improved treatments specifically designed for chronic migraine patients.

AUTHOR CONTRIBUTIONS

MF and RM contributed to the study concept and drafting/revising the manuscript.

REFERENCES

1. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatr*. (2010) 81:428–32. doi: 10.1136/jnnp.2009.192492
2. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd Edn. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202
3. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. *Nat Rev Neurol*. (2016) 12:455–64. doi: 10.1038/nrneurol.2016.93

4. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. (2003) 106:81–9. doi: 10.1016/S0304-3959(03)00293-8
5. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. *Neurology*. (2009) 72(5 Suppl):S3–7. doi: 10.1212/WNL.0b013e3181974b19
6. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology*. (2004) 62:788–90. doi: 10.1212/01.WNL.0000113747.18760.D2
7. Schwedt TJ, Chong CD. Medication overuse headache: pathophysiological insights from structural and functional brain MRI research. *Headache*. (2017) 57:1173–8. doi: 10.1111/head.13037
8. Westergaard ML, Glumer C, Hansen EH, Jensen RH. Prevalence of chronic headache with and without medication overuse: associations with socioeconomic position and physical and mental health status. *Pain*. (2014) 155:2005–13. doi: 10.1016/j.pain.2014.07.002
9. Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology*. (2011) 76:711–8. doi: 10.1212/WNL.0b013e31820d8af2
10. Cernuda-Morollon E, Martinez-Camblor P, Alvarez R, Larrosa D, Ramon C, Pascual J. Increased VIP levels in peripheral blood outside migraine attacks as a potential biomarker of cranial parasympathetic activation in chronic migraine. *Cephalalgia*. (2015) 35:310–6. doi: 10.1177/0333102414535111
11. Cernuda-Morollon E, Larrosa D, Ramon C, Vega J, Martinez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology*. (2013) 81:1191–6. doi: 10.1212/WNL.0b013e3182a6cb72
12. Aurora SK, Brin MF. Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. *Headache*. (2017) 57:109–25. doi: 10.1111/head.12999
13. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and characteristics of allodynia in headache sufferers: a population study. *Neurology*. (2008) 70:1525–33. doi: 10.1212/01.wnl.0000310645.31020.b1
14. Androulakis XM, Krebs K, Peterlin BL, Zhang T, Maleki N, Sen S, et al. Modulation of intrinsic resting-state fMRI networks in women with chronic migraine. *Neurology*. (2017) 89:163–9. doi: 10.1212/WNL.0000000000004089
15. Androulakis XM, Krebs KA, Jenkins C, Maleki N, Finkel AG, Rorden C, et al. Central executive and default mode network intranet work functional connectivity patterns in chronic migraine. *J Neurol Disord*. (2018) 6:393. doi: 10.4172/2329-6895.1000393
16. Chen Z, Chen X, Liu M, Ma L, Yu S. Volume of hypothalamus as a diagnostic biomarker of chronic migraine. *Front Neurol*. (2019) 10:606. doi: 10.3389/fneur.2019.00606
17. Coppola G, Di Renzo A, Petolicchio B, Tinelli E, Di Lorenzo C, Parisi V, et al. Aberrant interactions of cortical networks in chronic migraine: a resting-state fMRI study. *Neurology*. (2019) 92:e2550–e8. doi: 10.1212/WNL.0000000000007577
18. Lee MJ, Park BY, Cho S, Kim ST, Park H, Chung CS. Increased connectivity of pain matrix in chronic migraine: a resting-state functional MRI study. *J Headache Pain*. (2019) 20:29. doi: 10.1186/s10194-019-0986-z
19. Lerebours F, Boulanouar K, Barege M, Denuelle M, Bonneville F, Payoux P, et al. Functional connectivity of hypothalamus in chronic migraine with medication overuse. *Cephalalgia*. (2019) 39:892–9. doi: 10.1177/0333102419833087
20. Schwedt TJ, Schlaggar BL, Mar S, Nolan T, Coalson RS, Nardos B, et al. Atypical resting-state functional connectivity of affective pain regions in chronic migraine. *Headache*. (2013) 53:737–51. doi: 10.1111/head.12081
21. Ferraro S, Grazzi L, Mandelli ML, Aquino D, Di Fiore D, Usai S, et al. Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) study. *Pain Med*. (2012) 13:255–62. doi: 10.1111/j.1526-4637.2011.01183.x
22. Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: evidence from high-resolution fMRI. *Neurology*. (2017) 88:2011–6. doi: 10.1212/WNL.0000000000003963
23. Ferraro S, Grazzi L, Muffatti R, Nava S, Ghielmetti F, Bertolino N, et al. In medication-overuse headache, FMRI shows long-lasting dysfunction in midbrain areas. *Headache*. (2012) 52:1520–34. doi: 10.1111/j.1526-4610.2012.02276.x
24. Schulte LH, Allers A, May A. Visual stimulation leads to activation of the nociceptive trigeminal nucleus in chronic migraine. *Neurology*. (2018) 90:e1973–e8. doi: 10.1212/WNL.0000000000005622
25. Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A. Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies. *Headache*. (2007) 47:996–1003; discussion 4–7. doi: 10.1111/j.1526-4610.2007.00853.x
26. Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, et al. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain*. (2006) 129(Pt 2):543–50. doi: 10.1093/brain/awh691
27. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. *Brain*. (2004) 127(Pt 1):220–30. doi: 10.1093/brain/awh022
28. Niddam DM, Lai KL, Tsai SY, Lin YR, Chen WT, Fuh JL, et al. Neurochemical changes in the medial wall of the brain in chronic migraine. *Brain*. (2018) 141:377–90. doi: 10.1093/brain/awx331
29. Bilgic B, Kocaman G, Arslan AB, Noyan H, Sherifov R, Alkan A, et al. Volumetric differences suggest involvement of cerebellum and brainstem in chronic migraine. *Cephalalgia*. (2016) 36:301–8. doi: 10.1177/0333102415588328
30. Coppola G, Petolicchio B, Di Renzo A, Tinelli E, Di Lorenzo C, Parisi V, et al. Cerebral gray matter volume in patients with chronic migraine: correlations with clinical features. *J Headache Pain*. (2017) 18:115. doi: 10.1186/s10194-017-0825-z
31. Hubbard CS, Becerra L, Smith JH, DeLange JM, Smith RM, Black DF, et al. Brain changes in responders vs. non-responders in chronic migraine: markers of disease reversal. *Front Hum Neurosci*. (2016) 10:497. doi: 10.3389/fnhum.2016.00497
32. Lai TH, Chou KH, Fuh JL, Lee PL, Kung YC, Lin CP, et al. Gray matter changes related to medication overuse in patients with chronic migraine. *Cephalalgia*. (2016) 36:1324–33. doi: 10.1177/0333102416630593
33. Liu HY, Chou KH, Lee PL, Fuh JL, Niddam DM, Lai KL, et al. Hippocampus and amygdala volume in relation to migraine frequency and prognosis. *Cephalalgia*. (2017) 37:1329–1336. doi: 10.1177/0333102416678624
34. Neeb L, Bastian K, Villringer K, Israel H, Reuter U, Fiebach JB. Structural gray matter alterations in chronic migraine: implications for a progressive disease? *Headache*. (2017) 57:400–16. doi: 10.1111/head.13012
35. Riederer F, Gantenbein AR, Marti M, Luechinger R, Kollias S, Sandor PS. Decrease of gray matter volume in the midbrain is associated with treatment response in medication-overuse headache: possible influence of orbitofrontal cortex. *J Neurosci*. (2013) 33:15343–9. doi: 10.1523/JNEUROSCI.3804-12.2013
36. Schwedt TJ, Chong CD, Wu T, Gaw N, Fu Y, Li J. Accurate classification of chronic migraine via brain magnetic resonance imaging. *Headache*. (2015) 55:762–77. doi: 10.1111/head.12584
37. Messina R, Filippi M, Goadsby PJ. Recent advances in headache neuroimaging. *Curr Opin Neurol*. (2018) 31:379–85. doi: 10.1097/WCO.0000000000000573
38. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? *Headache*. (2001) 41:629–37. doi: 10.1046/j.1526-4610.2001.041007629.x
39. Tepper SJ, Lowe MJ, Beall E, Phillips MD, Liu K, Stillman MJ, et al. Iron deposition in pain-regulatory nuclei in episodic migraine and chronic daily headache by MRI. *Headache*. (2012) 52:236–43. doi: 10.1111/j.1526-4610.2011.02056.x
40. Dominguez C, Lopez A, Ramos-Cabrer P, Vieites-Prado A, Perez-Mato M, Villalba C, et al. Iron deposition in periaqueductal gray matter as a potential biomarker for chronic migraine. *Neurology*. (2019) 92:e1076–e85. doi: 10.1212/WNL.0000000000007047
41. Palm-Meinders IH, Koppen H, Terwindt GM, Launer LJ, van Buchem MA, Ferrari MD, et al. Iron in deep brain nuclei in migraine? CAMERA follow-up MRI findings. *Cephalalgia*. (2017) 37:795–800. doi: 10.1177/0333102416668654

42. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. *Pain*. (2013) 154(Suppl 1):S44–S53. doi: 10.1016/j.pain.2013.07.021
43. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain*. (2016) 139(Pt 7):1987–93. doi: 10.1093/brain/aww097
44. Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med.* (1995) 1:658–60. doi: 10.1038/nm0795-658
45. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. (2014) 137(Pt 1):232–41. doi: 10.1093/brain/awt320
46. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. *Headache*. (2007) 47:1418–26. doi: 10.1111/j.1526-4610.2007.00776.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 28 January 2020
doi: 10.3389/fneur.2019.01336

Brain Structural and Functional Imaging Findings in Medication-Overuse Headache

*Catherine D. Chong**

Mayo Clinic, Phoenix, AZ, United States

This chapter overviews research neuroimaging findings of patients with medication-overuse headache (MOH). Results indicate; (i) correlations between neuropathology and medication-overuse; (ii) changes in brain morphology and cortical function; and (iii) brain recovery subsequent to withdrawal of medication that was overused. Results of this narrative review indicate exacerbated brain structural and functional changes in regions of the pain-matrix and in regions of the mesocortical-limbic circuit in patients with MOH compared to patients with migraine or compared to healthy controls. Modification of brain morphology as well as an association between brain recovery and medication withdrawal suggest that the MOH disease process involves state (brain modification) and trait-like (brain adaptation and recovery) neuromechanisms.

Keywords: medication-overuse headache, migraine, structural and functional neuroimaging, pathophysiology, resting-state connectivity

OPEN ACCESS

Edited by:
Milena De Felice,
University of Sheffield,
United Kingdom

Reviewed by:
Lanfranco Pellesi,
University of Modena and Reggio Emilia, Italy
Teshamae S. Monteith,
Leonard M. Miller School of Medicine, University of Miami, United States

***Correspondence:**
Catherine D. Chong
chong.catherine@mayo.edu

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *05 August 2019*
Accepted: *02 December 2019*
Published: *28 January 2020*

Citation:
Chong CD (2020) Brain Structural and Functional Imaging Findings in Medication-Overuse Headache. Front. Neurol. 10:1336. doi: 10.3389/fneur.2019.01336

INTRODUCTION

Medication-overuse headache (MOH) is a significant health concern affecting over 60 million people worldwide (1, 2). According to the International Headache Society (ICHD-3) guidelines (3), MOH is classified as a secondary headache disorder in patients who are overusing headache medication for treating a primary headache disorder. MOHs are classified as headaches occurring at least 15 days per month and overuse of headache medication is defined by the regular intake (>3 months) of medication for more than 10 days per month or more than 15 days per month, depending on the medication that is being overused. It is estimated that over 50% of patients in headache clinics who suffer from chronic forms of headache are overusing headache medication and develop MOH (4–7). The overuse of medication can lead to worsening of headache and the transition from episodic to chronic migraine. For patients with MOH, discontinuation of the medication that is being overused can result in a significant improvement of headache symptoms including a reduction in headache frequency (8–10); however, it is of note that the success rate of medication withdrawal varies widely among studies and likely depends on the medication that was being overused (11).

Although the neuropathology of MOH is still incompletely understood, research imaging of brain structure and function has helped our understanding of the involved neuromechanisms underlying MOH. This review will focus on studies that have used the following research neuroimaging techniques for evaluating brain structure, including T1-weighted MRI for interrogating gray and white matter structure, diffusion tensor imaging, for estimating integrity of white matter tracts, functional magnetic resonance imaging (fMRI) using resting-state paradigms to estimate the functional connectivity of brain networks, task-based fMRI to assess brain

responses to specific stimuli, and positron emission tomography (PET) to evaluate the metabolic changes in glucose uptake in the brain. Studies are highlighted that have evaluated structural and functional imaging findings in patients with MOH compared to migraine patients without MOH, have assessed associations between brain changes and disease burden, and have examined brain mechanisms of recovery subsequent to medication withdrawal. Lastly, research neuroimaging differences between patients with MOH and patients with migraine are compared to neuroimaging differences between patients with post-traumatic headache relative to healthy controls in order to better understand neuropathological similarities and differences between MOH and post-traumatic headache, which are both discussed within this review series.

METHODS

For this review, PubMed was queried for English language articles using the following search terms: "Medication-overuse headache" and "magnetic resonance imaging" or "resting-state" or "diffusion tensor imaging" or "positron emission tomography." Database search results were then limited to articles with relevance to the topic that were published between January 2000 and July 2019. Single-subject studies and studies that included <6 patients with MOH were excluded. Included in this review were 17 structural and functional imaging studies of patients with MOH (see **Table 1**).

RESULTS

Brain Function and the Mesocortical-Limbic Circuit

In a pivotal PET study published in 2006, Fumal et al. (20) first reported hypometabolism in the orbitofrontal cortex, thalamus, anterior cingulate, insula, and the inferior parietal lobule as well as hypermetabolism in the cerebellar vermis in patients with MOH compared to healthy controls. Interestingly, 3 weeks after medication withdrawal, regional metabolic changes normalized, except for persistent hypometabolism in the orbitofrontal region. The orbitofrontal cortex is known to play a role in addictive disorders (29–31) and is part of the mesocortical-limbic circuit, involved in behaviors such as reward, motivation, pleasure, and sensation-seeking. Subsequent studies have further explored the connection between MOH and the functional connectivity and activation of relevant nodes of the mesocortical-limbic circuit including the extended limbic system (insula, amygdala, hippocampus, thalamus, and caudate) midbrain regions (ventral tegmental area and substantia nigra) and cortical frontal areas (prefrontal and orbitofrontal cortex).

These functional activation and resting-state functional connectivity studies have largely corroborated mesocortical-limbic dysregulation in patients with MOH. Ferraro et al. (18, 19) demonstrated less activity using a decision-making paradigm in the ventral tegmental region in MOH compared to chronic migraine and reduced pain-related activation in the middle cingulate and insula during heat pain stimulation in MOH compared to healthy controls. Torta et al. (28) showed evidence of nucleus accumbens to orbitofrontal functional dysregulation of the reward system that distinguished individual patients with MOH from migraineurs with a 75% accuracy. Two studies by Androulakis and colleagues suggest alterations in frontal-limbic networks and less functional connectivity within the left prefrontal cortex and between the right prefrontal cortex and the left anterior thalamus (12, 13).

Using functional connectivity density, a scale-free measurement of the brain's total number of connections, Chen et al. (17) found decreased functional connectivity density in the right caudate and the left insula in MOH compared to episodic migraine as well as weaker resting-state functional connectivity in fronto-temporal connectivity.

Functional Alterations Within Regions of the Pain Matrix

In addition to mesocortical-limbic system dysfunction, patients with MOH have abnormalities within regions of the so-called "pain-matrix." Results by Bogdanov et al. (15) indicate stronger activation of pain-processing regions (premotor, supplementary motor, dorsolateral prefrontal cortex, anterior cingulate, primary somatosensory) as well as stronger activation in the lingual region in patients with MOH relative to migraineurs using warm/cold noxious stimulation. Results by Grazzi et al. (21) show less activation using mechanical pain stimulation in the "lateral pain matrix" (inferior and superior parietal and supramarginal gyrus) in MOH relative to healthy controls and Chanraud and colleges (16) demonstrated decreased functional connectivity within regions of the default-mode system in MOH relative to episodic migraineurs.

Functional Imaging: Before and After Medication Withdrawal

Multiple time-point studies in individual patients before and after withdrawal are undoubtedly the most informative for investigating how the brain changes or recovers subsequent to medication withdrawal and/or effective treatment. Krebs et al. (22) found improved functional connectivity within the salience and central executive networks after successful treatment using sphenopalatine ganglion (SPG) blocks in patients with MOH. SPG treatment in these patients resulted in decreased number of moderate to severe headache days per month, thus indicating that imbalance within both networks can be restored following successful treatment. Several studies have used nociceptive stimulation to investigate how the brain responds to pain before and after withdrawal. Mehnert et al. (24) found less activation in the left spinal trigeminal nucleus and the left posterior insula before withdrawal compared to after withdrawal and Grazzi et al. (21) demonstrated functional normalization in regions of the pain matrix subsequent to withdrawal.

Brain Structure and the Orbitofrontal Cortex

Consistent with functional data, results of structural imaging reveal abnormalities within major regions of the mesocortical-limbic circuit in patients with MOH, including less orbitofrontal cortex volume and thickness (23, 24, 26).

TABLE 1 | Medication overuse headache.

References	Subject cohorts	Analysis	Findings
MEDICATION OVERUSE HEADACHE			
Androulakis et al. (12)	• CM ($n = 13$) • HC ($n = 19$) • MOH ($n = 16$)	• rs-fMRI	MOH and CM vs. HC: central executive network alterations; less fc between right ventrolateral prefrontal cortex and left anterior thalamus, and less fc between left dorsal prefrontal cortex and dorsomedial prefrontal cortex. Alterations were more widespread in MOH vs. CM MOH vs. HC: DMN disruptions in MOH only
Androulakis et al. (13)	• CM ($n = 13$) • HC ($n = 19$) • MOH ($n = 16$)	• rs-fMRI	MOH and CM vs. HC: salience network disruptions in MOH and CM. MOH vs. CM: frontal-limbic network alterations in MOH between left DLPC and ventral striatum; left prefrontal cortex to right insula; left ventral striatum to left supplementary motor
Beckmann et al. (14)	• MOH* ($n = 27$) • HC ($n = 27$) **Before and 6 months after medication withdrawal*	• VBM • TBSS	MOH (*before vs. after withdrawal*): no difference in brain volume or diffusion measures (FA, RD) MOH vs. HC: no difference in brain volume or diffusion measures (FA, RD)
Bogdanov et al. (15)	• Mig during attack ($n = 5$) • Mig between attacks ($n = 14$) • HC ($n = 24$) • MOH ($n = 7$)	• Task-based fMRI *noxious warm and cold stimulation*	All subjects (main effect analysis): activation of pain-matrix when switching from warm to cold stimulation Mig during attack and MOH vs. HC: stronger motor cortex and superior temporal sulcus activation MOH vs. Mig during attack: stronger activation in premotor, supplementary motor, DMPC, ACC, primary somatosensory and lingual cortex
Chanraud et al. (16)	• MOH ($n = 26$) • EM ($n = 23$) • HC ($n = 17$)	• VBM • rs-fMRI	MOH vs. EM and HC: no difference in brain volume MOH vs. EM: less fc between left precuneus to frontal and parietal regions (right precuneus, right middle frontal, left inf. parietal and left cerebellum. Stronger left precuneus to temporal (right sup. temporal, right precentral, right fusiform and right hippocampus) region connectivity Clinical correlation—MOH only: negative correlation between migraine duration and frontal, precuneus and hippocampal volume; negative correlation between migraine duration and fc between precuneus and frontal regions; positive correlation between disease dependence and fc between precuneus and frontal regions; positive correlation between disease duration and left precuneus connectivity with bilateral temporal (inferior and superior), fusiform and right middle temporal gyrus positive relationship between numbers of pills taken and fc between left precuneus and hippocampus
Chen et al. (17)	• EM ($n = 18$) • HC ($n = 32$) • MOH ($n = 37$)	• rs-fMRI	MOH vs. EM: decreased fc density of right caudate and left insula and decreased fronto-temporal connectivity
Ferraro et al. (18)	• HC ($n = 8$) • CM ($n = 8$) • MOH* ($n = 8$) *Before and 6 months after withdrawal	• Task-based fMRI *Decision-making paradigm*	MOH vs. CM: less task-related activity in ventral tegmental area MOH vs. HC: less task-related activity in ventral tegmental area and stronger task-related activity in ventromedial prefrontal cortex MOH *(before vs. 6-months post-withdrawal)*: MOH prior to withdrawal vs. post-withdrawal: increased activity in ventromedial prefrontal cortex and posterior cingulate
Ferraro et al. (19)	• HC ($n = 9$) • MOH* ($n = 9$) **Before and 6 months after withdrawal*	• Task-based fMRI *Noxious heat stimulation*	MOH (*at beginning of withdrawal*) vs. HC: reduced pain-related activation in somato-sensory cortex, inf. parietal lobule, supramarginal gyrus, middle cingulate and insula MOH (*at 6-month-post-withdrawal*) vs. HC: no difference in pain-related activity between groups
Fumal et al. (20)	• HC ($n = 68$) • MOH* ($n = 16$) **Before and 3 weeks after withdrawal*	• FDG-PET *Glucose metabolism*	MOH *(before withdrawal)*: hypometabolism in OFC, thalamus, anterior cingulate insula, and inf. parietal lobule. Hypermetabolism in cerebellar vermis MOH (*after withdrawal*): normalization of all regions except continued hypometabolism in OFC
Grazzi et al. (21)	• HC ($n = 11$) • MOH* ($n = 13$) **Before and 6 months after withdrawal*	• Tasked-based fMRI *mechanical pain-induced stimulation*	MOH (*before withdrawal*) vs. HC: Less activation in regions of "lateral pain matrix" (inf. and superior parietal and supramarginal gyrus). Functional activation normalized after withdrawal
Krebs et al. (22)	• HC ($n = 10$) • MOH* ($n = 10$) **Before and 6–weeks after sphenopalatine ganglion (SPG) blocks*	rs-fMRI	MOH (*before vs. after SPG blocks)*: Salience network: stronger fc between prefrontal cortex and insula, basal ganglia, motor and frontal cortex; stronger fc between temporal cortex and supramarginal gyrus and basal ganglia Executive network: stronger fc between prefrontal cortex and anterior thalamus and frontal cortex

(Continued)

TABLE 1 | Continued

References	Subject cohorts	Analysis	Findings
Lai et al. (23)	• CM ($n = 33$) • HC ($n = 33$) • MOH ($n = 33$)	• VBM	MOH and CM vs. HC: less volume in precuneus, cerebellum and in temporal and occipital regions MOH vs. CM: less volume in OFC and middle occipital. More volume in in left parahippocampal and temporal pole region. Volume changes explained 31.1% variance of analgesic use frequency Clinical correlation in MOH: volume over OFC predicted treatment response
Mehnert et al. (24)	• HC ($n = 18$) • MOH* ($n = 18$) *Before and a minimum of 8 weeks after withdrawal	• VBM • rs-fMRI • Task-based fMRI nociceptive stimulation	MOH (*before withdrawal*) vs. HC: less volume in hippocampus, precuneus, inf. frontal gyrus, bilateral OFC, medial orbital gyrus MOH (*after withdrawal*) vs. HC: additional decreased volume in cuneus, superior temporal gyrus, putamen and cerebellum Clinical correlations: positive correlation between medial orbital gyrus volume in MOH before withdrawal and positive outcome (fewer headache days per month post-withdrawal Task-based activation during nociceptive stimulation MOH *before vs. after withdrawal*: stronger activation in left spinal trigeminal nucleus, right operculum and left posterior insula after withdrawal
Riederer et al. (25)	• MOH* ($n = 22$) *11 responders* *11-non-responders* *Before and 3 months after withdrawal	• VBM	All MOH vs. HC: increased volume in PAG, ventral striatum, nucleus cuneiformis MOH -treatment responders: normalization in PAG, nucleus cuneiformis after withdrawal MOH-without treatment response: less OFC volume at baseline Clinical correlation: correlation between treatment response and OFC volume at baseline
Riederer et al. (26)	• HC ($n = 29$) • MOH ($n = 29$)	• SBM • Cortical thickness • gyrification	MOH vs. HC: less thickness in left prefrontal cortex. Higher gyrification over temporal, fusiform and right occipital pole Clinical correlation: higher gyrification over right occipital pole predicted poor treatment response
Schmidt-Wilcke et al. (27)	• MOH ($n = 20$) • Chronic tension-type headache ($n = 20$) • HC ($n = 40$)	• VBM	Chronic tension-type headache and MOH vs. HC: less volume in pain-processing regions in patients with Chronic tension-type headache compared to HC. No volume change in MOH compared to HC
Torta et al. (28)	• Migraine ($n = 15$) • MOH ($n = 15$)	• rs-fMRI	MOH vs. Migraine: machine-learning classification algorithms distinguished individual patients with MOH from patients with migraine with 75% accuracy based on the functional connectivity patterns of the nucleus accumbens

ACC, anterior cingulate cortex; CM, chronic migraine; DMN, default-mode network; DMPC, dorso-medial prefrontal cortex; EM, episodic migraine; FA, fractional anisotropy; fc, functional connectivity; FDG-PET, F-fluoro-deoxyglucose positron emission tomography; HC, healthy controls; inf, inferior; Mig, migraine; MO, medication-overuse; MOH, medication-overuse headache; MwoA, migraine without aura; OFC, orbito-frontal cortex; PAG, periaqueductal gray; RD, radial diffusivity; SBM, surface-based morphometry; rs-fMRI, resting-state functional magnetic resonance imaging; TBSS, tract-based spatial statistics; VBM, voxel-based morphometry.

Results of several studies suggest that patients with better treatment response to medication withdrawal had more orbitofrontal volume at baseline, i.e., before withdrawal compared to patients who *did not* respond successfully to medication withdrawal (23, 25). Chanraud et al. found a negative correlation between frontal gray matter volume and migraine disease duration in patients with MOH (16) and between number of pills taken and frontal gray matter volume.

These results are intriguing and may indicate that the orbitofrontal cortex could be a marker for treatment response or indicative of poor outcome. In addition, male patients with MOH had less thickness over the left prefrontal region compared to females with MOH, raising the possibility of sex-related influences to developing MOH. These results are in line with other studies that have demonstrated sex-related differences in brain structure and function in patients with migraine (32–35) which is the topic of a comprehensive review in this series entitled "*Is there an MRI pattern that discriminates female from male migraine patients*" by Nasim Maleki and Xiao Androulakis.

Compared to healthy controls, Riederer et al. (26) found higher cortical gyrification over the temporal and occipital cortex in MOH (but not over the orbitofrontal cortex). In addition, patients with higher occipital pole gyrification had poorer response to medication withdrawal. As brain gyrification patterns remain relatively stable throughout the human lifespan, cortical gyrification is considered a proxy measurement of cortical development. These results are interesting and suggest a neurodevelopmental component to migraine disease chronification or genetic (trait-like) predisposition to a more severe disease type.

It is noteworthy that several studies did not find changes in brain structure in patients with MOH compared to healthy controls (16, 27), or in patients with MOH before compared to after withdrawal (14). Possibly, MOH induces more detectable changes in functional networks rather than brain macrostructure. Beckmann et al. (14) found no differences in brain volume

or diffusion patterns in MOH patients before and after a 6-month withdrawal period. Interestingly, the patients included in this study were overusing medication an average of 4 years (including some patients who were overusing medication as long as 15 years). It is plausible that years of medication overuse decrease the ability of the brain to recover structurally, which might have contributed to the negative findings of this study.

DISCUSSION

Frequent medication overuse associates with exacerbated changes in regions of the pain matrix as well as with changes in structure and function of regions within mesocortical-limbic circuit. There is evidence of potential brain "traits" (higher occipital gyrification and less orbitofrontal cortex volume and thickness), which may contribute to the development of MOH or which may be a vulnerability factor for unsuccessful withdrawal.

Although the topic of "post-traumatic headache" (PTH) is part of another comprehensive review, entitled "Structural and Functional Brain Alterations in Post-traumatic Headache Attributed to Mild Traumatic Brain Injury," the potential similarities and differences in neuropathology between primary headaches (migraine) and secondary (MOH and PTH) headaches are intriguing.

Migraine, MOH, and PTH show overlapping pathophysiology in regions associated with the cognitive-affective, sensory, and modulatory components of the "pain-matrix," yet compared to migraine, patients with MOH and PTH have exacerbated changes within regions involved in multisensory integration (19, 21, 36, 37). MOH and PTH show *additional* neuropathology in brain systems that are not part of the pain matrix such as the visual cortex and specifically the lingual gyrus where hyperexcitability or sensitization is evident in both MOH and PTH (15, 36). Specifically, MOH has distinct structural and functional changes within regions of the mesocortical-limbic circuit implicated in addiction but also in reward, memory, motivation, and emotional response. Although there are currently no studies that have directly compared MOH to PTH, alterations within the mesocortical-limbic circuit and specifically the orbitofrontal cortex appear to be unique to MOH. There are some data suggesting rapid reorganization of cortical structure and function for both MOH and PTH. For example, several brain circuits demonstrate signs of brain normalization (or adaptation) weeks following successful withdrawal of patients with MOH. Similarly, patients with PTH at 1 week post-concussion show early alterations in brain structure. However, it is yet insufficiently understood whether these changes reflect mechanisms of neuronal repair, adaptation, or degeneration (38).

Although statements about the generalizability of neuroimaging findings in patients with MOH are premature, the number of studies published over the past few years has continued to increase our understanding of the neuropathology underlying MOH. Some of the current study discrepancies are likely due to between-study differences in sample sizes, the types of medications that were being overused (opiates vs. simple analgesics), the time frame over which overuse persisted (months vs. years), and whether patients experienced successful vs. unsuccessful withdrawal (headache relief vs. no headache relief, or relapse to MOH), which are important and often overlooked variables of the complex MOH disease mechanism (11) that will need to be better investigated and controlled for in future studies.

The most conclusive evidence of brain changes associated with MOH is derived from studies that have compared (i) patients with chronic migraine and MOH to patients with chronic migraine without MOH relative to cohorts of healthy controls; or assessed (ii) patients before and subsequent to medication withdrawal. Such studies are uniquely designed to interrogate and extract the disease pathology distinctive to medication overuse. Data from other studies that have compared MOH to healthy controls although informative are by design unable to extrapolate the pathology distinctive to medication overuse, as the migraine pathology and medication-overuse pathology are entangled.

CONCLUSION

Compared to patients with migraine, patients with MOH have exacerbated changes in brain structure and function in regions of the pain-matrix and in areas of the mesocortical-limbic circuit. Some of the brain structural alterations (i.e., changes in brain gyrification patterns) could indicate "brain traits" that contribute to the development of MOH. Additionally, the relationship between brain changes and medication overuse (i.e., number of pills overused) or the association between brain recovery and discontinuation of medication overuse suggest "state-dependent" brain adaption patterns. In summary, these findings of state and trait-like changes suggest modification of brain structure and function in patients with MOH, some of which are likely reversible as patients recover from headache. Lastly, the neuropathological similarities of patients with MOH and post-traumatic headache may indicate common disease pathways that need to be further investigated.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol.* (2004) 3:475–83. doi: 10.1016/S1474-4422(04)00824-5
2. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* (2016) 388:1545–602. doi: 10.1016/S0140-6736(16)31678-6
3. Headache Classification Committee of the International Headache Society (IHS) The international classification of headache disorders, 3rd edition. *Cephalalgia.* (2018) 38:1–211. doi: 10.1177/0333102417738202
4. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. *Lancet*

Neurol. (2010) 9:391–401. doi: 10.1016/S1474-4422(10)70008-9
5. Meskunas CA, Tepper SJ, Rapoport AM, Sheftell FD, Bigal ME. Medications associated with probable medication overuse headache reported in a tertiary care headache center over a 15-year period. *Headache*. (2006) 46:766–72. doi: 10.1111/j.1526-4610.2006.00442.x
6. Dodick DW, Silberstein SD. How clinicians can detect, prevent and treat medication overuse headache. *Cephalalgia*. (2008) 28:1207–17. doi: 10.1111/j.1468-2982.2008.01737.x
7. Stark RJ, Ravishankar K, Siow HC, Lee KS, Pepperle R, Wang SJ. Chronic migraine and chronic daily headache in the Asia-Pacific region: a systematic review. *Cephalalgia*. (2013) 33:266–83. doi: 10.1177/0333102412468677
8. Rossi P, Faroni JV, Nappi G. Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication overuse headache. *Eur J Neurol*. (2011) 18:396–401. doi: 10.1111/j.1468-1331.2010.03157.x
9. Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. *Cephalalgia*. (2006) 26:1192–8. doi: 10.1111/j.1468-2982.2006.01190.x
10. Kristoffersen ES, Straand J, Vetvik KG, Benth JŠ, Russell MB, Lundqvist C. Brief intervention by general practitioners for medication-overuse headache, follow-up after 6 months: a pragmatic cluster-randomised controlled trial. *J Neurol*. (2016) 263:344–53. doi: 10.1007/s00415-015-7975-1
11. Scher AI, Rizzoli PB, Loder EW. Medication overuse headache: an entrenched idea in need of scrutiny. *Neurology*. (2017) 89:1296–304. doi: 10.1212/WNL.0000000000004371
12. Androulakis XM, Krebs KA, Jenkins C, Maleki N, Finkel AG, Rorden C, et al. Central executive and default mode network intranet work functional connectivity patterns in chronic migraine. *J Neurol Disord*. (2018) 6:393. doi: 10.4172/2329-6895.1000393
13. Androulakis XM, Krebs K, Peterlin BL, Zhang T, Maleki N, Sen S, et al. Modulation of intrinsic resting-state fMRI networks in women with chronic migraine. *Neurology*. (2017) 89:163–9. doi: 10.1212/WNL.0000000000004089
14. Beckmann Y, Gökçe S, Zorlu N, Türe HS, Gelal F. Longitudinal assessment of gray matter volumes and white matter integrity in patients with medication-overuse headache. *Neuroradiol J*. (2018) 31:150–6. doi: 10.1177/1971400918756374
15. Bogdanov VB, Bogdanova OV, Viganò A, Noirhomme Q, Laureys S, Dallel R, et al. Increased cerebral responses to salient transitions between alternating stimuli in chronic migraine with medication overuse headache and during migraine attacks. *Cephalalgia*. (2019) 39:988–99. doi: 10.1177/0333102418825359
16. Chanraud S, Di Scala G, Dilharreguy B, Schoenen J, Allard M, Radat F. Brain functional connectivity and morphology changes in medication-overuse headache: clue for dependence-related processes? *Cephalalgia*. (2014) 34:605–15. doi: 10.1177/0333102413519514
17. Chen Z, Chen X, Liu M, Dong Z, Ma L, Yu S. Altered functional connectivity architecture of the brain in medication overuse headache using resting state fMRI. *J Headache Pain*. (2017) 18:25. doi: 10.1186/s10194-017-0735-0
18. Ferraro S, Grazzi L, Mandelli ML, Aquino D, Di Fiore D, Usai S, et al. Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) study. *Pain Med*. (2012) 13:255–62. doi: 10.1111/j.1526-4637.2011.01183.x
19. Ferraro S, Grazzi L, Muffatti R, Nava S, Ghielmetti F, Bertolino N, et al. In medication-overuse headache, fMRI shows long-lasting dysfunction in midbrain areas. *Headache*. (2012) 52:1520–34. doi: 10.1111/j.1526-4610.2012.02276.x
20. Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, et al. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain*. (2006) 129:543–50. doi: 10.1093/brain/awh691
21. Grazzi L, Chiapparini L, Ferraro S, Usai S, Andrasik F, Mandelli ML, et al. Chronic migraine with medication overuse pre-post withdrawal of symptomatic medication: clinical results and FMRI correlations. *Headache*. (2010) 50:998–1004. doi: 10.1111/j.1526-4610.2010.01695.x
22. Krebs K, Rorden C, Androulakis XM. Resting state functional connectivity after sphenopalatine ganglion blocks in chronic migraine with medication overuse headache: a pilot longitudinal fMRI study. *Headache*. (2018) 58:732–43. doi: 10.1111/head.13318
23. Lai TH, Chou KH, Fuh JL, Lee PL, Kung YC, Lin CP, et al. Gray matter changes related to medication overuse in patients with chronic migraine. *Cephalalgia*. (2016) 36:1324–33. doi: 10.1177/0333102416630593
24. Mehnert J, Hebestreit J, May A. Cortical and subcortical alterations in medication overuse headache. *Front Neurol*. (2018) 9:499. doi: 10.3389/fneur.2018.00499
25. Riederer F, Gantenbein AR, Marti M, Luechinger R, Kollias S, Sándor PS. Decrease of gray matter volume in the midbrain is associated with treatment response in medication-overuse headache: possible influence of orbitofrontal cortex. *J Neurosci*. (2013) 33:15343–9. doi: 10.1523/JNEUROSCI.3804-12.2013
26. Riederer F, Schaer M, Gantenbein AR, Luechinger R, Michels L, Kaya M, et al. Cortical alterations in medication-overuse headache. *Headache*. (2017) 57:255–65. doi: 10.1111/head.12993
27. Schmidt-Wilcke T, Leinisch E, Straube A, Kämpfe N, Draganski B, Diener HC, et al. Gray matter decrease in patients with chronic tension type headache. *Neurology*. (2005) 65:1483–6. doi: 10.1212/01.wnl.0000183067.94400.80
28. Torta DM, Costa T, Luda E, Barisone MG, Palmisano P, Duca S, et al. Nucleus accumbens functional connectivity discriminates medication-overuse headache. *Neuroimage Clin*. (2016) 11:686–93. doi: 10.1016/j.nicl.2016.05.007
29. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology*. (2009) 56 (Suppl 1):3–8. doi: 10.1016/j.neuropharm.2008.05.022
30. London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex*. (2000) 10:334–42. doi: 10.1093/cercor/10.3.334
31. Cupini LM, Calabresi P. Medication-overuse headache: pathophysiological insights. *J Headache Pain*. (2005) 6:199–202. doi: 10.1007/s10194-005-0184-z
32. Maleki N, Linnman C, Brawn J, Burstein R, Becerra L, Borsook D. Her versus his migraine: multiple sex differences in brain function and structure. *Brain*. (2012) 135:2546–59. doi: 10.1093/brain/aws175
33. Maleki N, Barmettler G, Moulton EA, Scrivani S, Veggeberg R, Spierings EL, et al. Female migraineurs show lack of insular thinning with age. *Pain*. (2015) 156:1232–9. doi: 10.1097/j.pain.0000000000000159
34. Dai Z, Zhong J, Xiao P, Zhu Y, Chen F, Pan P, et al. Gray matter correlates of migraine and gender effect: a meta-analysis of voxel-based morphometry studies. *Neuroscience*. (2015) 299:88–96. doi: 10.1016/j.neuroscience.2015.04.066
35. Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. *Cephalalgia*. (2010) 30:129–36. doi: 10.1111/j.1468-2982.2009.01904.x
36. Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Static and dynamic functional connectivity differences between migraine and persistent post-traumatic headache: a resting-state magnetic resonance imaging study. *Cephalalgia*. (2019) 39:1366–81. doi: 10.1177/0333102419847728
37. Schwedt TJ, Chong CD, Peplinski J, Ross K, Berisha V. Persistent post-traumatic headache vs. migraine: an MRI study demonstrating differences in brain structure. *J Headache Pain*. (2017) 18:87. doi: 10.1186/s10194-017-0796-0
38. De Felice M, Ossipov MH, Porreca F. Persistent medication-induced neural adaptations, descending facilitation, and medication overuse headache. *Curr Opin Neurol*. (2011) 24:193–6. doi: 10.1097/WCO.0b013e328346af25

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 25 March 2020
doi: 10.3389/fneur.2020.00140

Imaging the Premonitory Phase of Migraine

Nazia Karsan[1]* *and Peter J. Goadsby*[2]

[1] Headache Group, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [2] NIHR-Wellcome Trust King's Clinical Research Facility and SLaM Biomedical Research Centre, King's College London, London, United Kingdom

Migraine is a common and disabling brain disorder with a broad and heterogeneous phenotype, involving both pain and painless symptoms. Over recent years, more clinical and research attention has been focused toward the premonitory phase of the migraine attack, which can start up to days before the onset of head pain. This early phase can involve symptomatology, such as cognitive and mood change, yawning, thirst and urinary frequency and sensory sensitivities, such as photophobia and phonophobia. In some patients, these symptoms can warn of an impending headache and therefore offer novel neurobiological insights and therapeutic potential. As well as characterization of the phenotype of this phase, recent studies have attempted to image this early phase using functional neuroimaging and tried to understand how the symptoms are mediated, how a migraine attack may be initiated, and how nociception may follow thereafter. This review will summarize the recent and evolving findings in this field and hypothesize a mechanism of subcortical and diencephalic brain activation during the start of the attack, including that of basal ganglia, hypothalamus, and thalamus prior to headache, which causes a top-down effect on brainstem structures involved in trigeminovascular nociception, leading ultimately to headache.

Keywords: migraine, premonitory, neuroimaging, headache, prodrome

OPEN ACCESS

Edited by:
Raquel Gil-Gouveia, Hospital da Luz Lisboa, Portugal

Reviewed by:
Aynur Özge, Mersin University, Turkey
Marco Carotenuto, University of Campania Luigi Vanvitelli, Italy

***Correspondence:**
Nazia Karsan
nazia.karsan@kcl.ac.uk

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *14 November 2019*
Accepted: *07 February 2020*
Published: *25 March 2020*

Citation:
Karsan N and Goadsby PJ (2020) Imaging the Premonitory Phase of Migraine. Front. Neurol. 11:140. doi: 10.3389/fneur.2020.00140

INTRODUCTION

Migraine is a disabling condition that, in addition to headache, also involves often disabling non-headache symptoms. Although the pain phase of the migraine attack is well-recognized and characterized by moderate to severe headache with associated sensory sensitivities such as photophobia and phonophobia, and nausea and vomiting (1), increasingly, associated symptomatology such as cognitive dysfunction (2) and fatigue (3) are recognized to contribute to attack-related disability. It has been recognized for over a century that non-painful symptomatology can precede the migraine attack (4), but only over recent decades has the phenotype and prevalence of early attack symptoms been captured in both adults and children in detail (5–18), and the ability to reliably and reproducibly predict headache onset has been explored (8, 9, 19). This early phase of the migraine attack, when symptomatology outside of pain manifests, provides novel neurobiological and therapeutic insights into possible mechanisms behind attack initiation in a genetically predisposed individual, and into treatments that may work at aborting or preventing pain before its onset. Given migraine therapeutics is an evolving field, fundamental understanding of the underlying neurobiological mechanisms behind migraine attack initiation is key to advancing abortive therapeutics further by developing migraine-specific agents that are likely to be more efficacious and tolerable than currently available options.

Neurophysiological studies have suggested that the brain is already electrically different in the lead-up to migraine pain (20–24). One of the other ways in which the premonitory phase of the migraine attack has been studied has been with the increasing use of functional neuroimaging. This evolving field has allowed understanding of human disease in patients and has been pivotal in furthering understanding of several disorders. The functional neuroimaging "signature" of the pain phase of the migraine attack has been reproduced across several studies since the 1990's (25–29). Over the last few years, various methodologies have also been used in imaging the premonitory phase of both spontaneous and exogenously triggered migraine attacks and have alluded to early involvement of subcortical diencephalic and brainstem structures and their role in attack initiation (30).

This review will summarize these studies and hypothesize a possible network of brain dysfunction, which starts prior to pain onset and continues throughout migraine headache, and most likely even following headache resolution until the brain reverts to its true interictal state and the patient symptomatically feels back to normal function.

PERFUSION IMAGING

Various methods of functional neuroimaging, that is, using neuroimaging methodologies to understand human brain function, exist. Perfusion is one measure used as a surrogate for neuronal activity, on the basis that the more a region of brain is active, the more blood supply that area will require and the higher will be the regional blood flow in that area, which can be mapped with perfusion imaging using various modalities. One such modality is positron emission topography (PET), which can be used to assess perfusion if used along with a radioisotope of labeled water ($H_2^{15}O$). The first PET study using blood flow measurement in the premonitory phase of migraine was conducted in 2014 by Maniyar et al. (31). The authors used this imaging methodology to study the premonitory phase of nitroglycerin-triggered migraine in eight subjects in a repeated measures design. Despite the lack of a healthy control arm, the study was able to identify statistically significant areas of increased blood flow during both the early and late premonitory symptoms in the study subjects, in brain areas including the hypothalamus, thalamus, cingulate cortex, and dorsolateral pons, all areas that are believed to be important in the pain phase of migraine from other studies (25–27, 32). For the first time, this study provided a central and neuronal surrogate correlate for what patients experience during the premonitory phase [see **Figure 1**, reused with journal copyright permission, taken from Maniyar et al. (31)].

The same authors completed additional studies looking at some symptoms in particular, namely, nausea and photophobia. Using similar methodologies, the authors compared subjects with and without each symptom during the premonitory phase to try and elucidate which part of the brain these individual symptoms could be arising from (33, 34). The authors were able to hypothesize that photophobia, or specifically photic hypersensitivity (that is, a sensitivity or aversion to light without light exacerbating pain), involved the occipital lobes, which displayed increased perfusion in subjects with the symptom relative to those without (33). Similarly, nausea involved activations in a region including the nucleus tractus solitarius in the medulla, an area known as the chemoreceptor trigger zone. This area showed increased blood flow in those with nausea during the premonitory phase relative to those without (34).

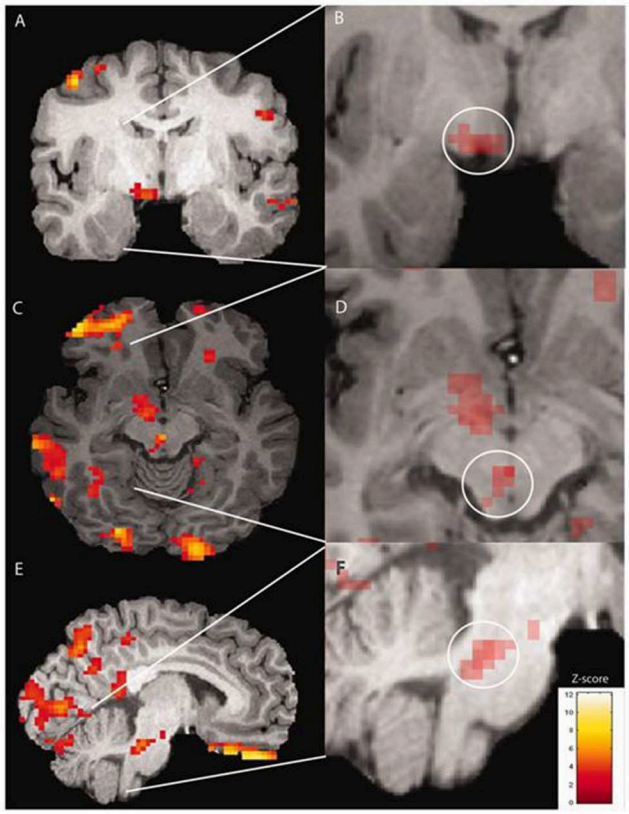


FIGURE 1 | Brain activations on PET imaging during the early premonitory phase of nitroglycerin-triggered migraine attacks, taken from Maniyar et al. (31) study.

A more recent study utilized perfusion MRI, using arterial spin labeling (ASL), to evaluate brain blood flow changes during the premonitory phase (35). This study again used nitroglycerin-triggered migraine attacks, because of the logistical issues with repeatedly and reliably capturing spontaneous premonitory symptoms. The authors studied premonitory symptoms in 25 subjects and compared the premonitory scans following nitroglycerin with scans obtained at the same time following placebo in 21 subjects to correct for any possible nitroglycerin-induced changes on cerebral blood flow. Similar areas of increased blood flow (and therefore the suggestion of increased neuronal activity) were identified as the Maniyar et al. study (31), including the hypothalamus, thalamus, basal ganglia, and limbic cortex, during the premonitory phase, supporting the theory of subcortical brain dysfunction in migraine attack initiation.

FUNCTIONAL MRI

The majority of the imaging work done in this field has used functional MRI approaches—either with external stimulation or without. The very first study was conducted by Stankewitz et al. and did not aim to study premonitory symptoms specifically (36). The study used trigemino-nociceptive stimulation with intranasal gaseous ammonia in migraineurs in the interictal state, and also in the preictal (12–48 h prior to the next migraine attack) and ictal states in *post-hoc* analyses, thereby capturing the lead-up to the headache phase of migraine. The study showed increased neuronal activity, measured using the blood oxygen level-dependent (BOLD) contrast signal intensity, in the region of the spinal trigeminal nucleus in the preictal phase in

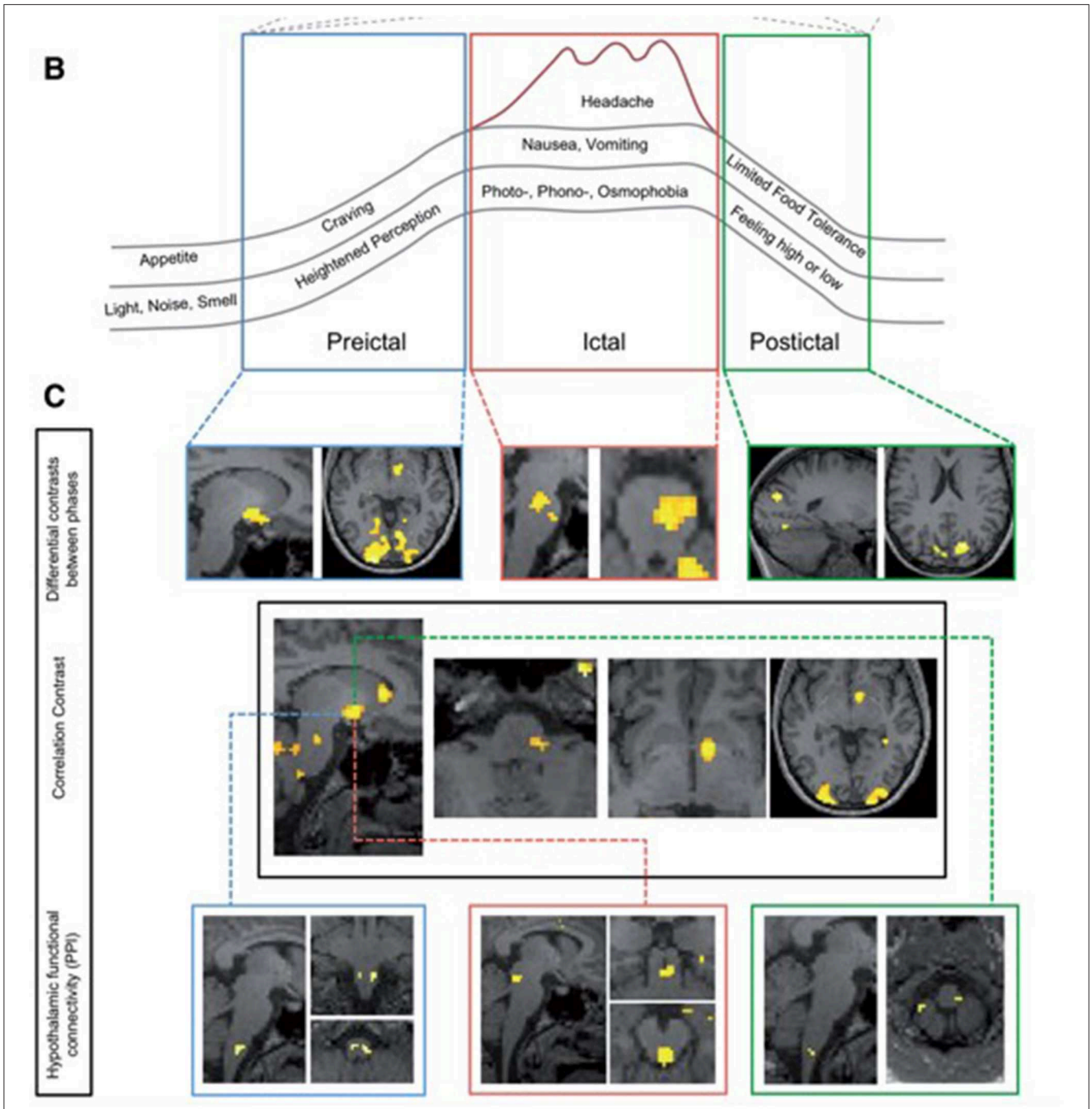


FIGURE 2 | Changes during the migraine cycle, taken from the Schulte et al. study (37). **(A)** Unpleasantness ratings for ammonia, rose odor, and checkerboard stimulation (red line and dots: ammonia-ratings; green line and crosses: rose odor ratings; blue line and asterisks: checkerboard ratings), with higher values representing a more unpleasant experience. Red areas: days of migraine pain with varying red color intensities indicating different intensities of migraine pain and blue areas representing the last scan before onset of migraine pain. **(B)** Overview of the migraine cycle. **(C)** Results from functional MRI.

migraineurs relative to the interictal phase and during the acute pain phase. Rostral pontine activation was only seen during acute pain, and not outside of pain. Interestingly, the intensity of the BOLD signal in response to nociceptive stimulation was able to predict the next headache, in that the stronger the BOLD response in the region of the spinal trigeminal nuclei, the closer the next headache would be.

Other studies have followed, studying the preictal or pre-headache phase of the migraine attack using fMRI approaches. An impressive study conducted by Schulte and colleagues in 2016 aimed to study further the theory of possible oscillatory brainstem responses during the migraine cycle and studied the same individual with daily scanning for 30 days, thereby capturing three spontaneous migraine attacks and the periods surrounding these (37). This study demonstrated an increase in hypothalamic activity in the period prior to headache in response to the same intranasal gaseous ammonia nociceptive stimulation. There was also altered functional connectivity between the hypothalamus and other migraine brain areas, including the spinal trigeminal nuclei region and the dorsal rostral pons during the day preceding headache. This study provided additional information to the prior study and suggested that as well as altered brainstem responses, altered hypothalamic and brainstem connectivity could be involved in the start of a migraine attack. Again, although this study did not phenotype the subject extensively before the pain-free scanning days, the lead-up phase to a migraine headache was captured and assessed using imaging. See **Figure 2**, reused with journal permission, taken from Schulte and May (37). The authors have recently presented an extension to this work by replicating the study in a further eight subjects who have also been imaged daily for 30 days, with 15 spontaneous migraine attacks captured, and have found additional results for increased functional connectivity between the right nucleus accumbens and left amygdala, hippocampus, and parahippocampal gyrus preictally compared with interictally, as well as increased connectivity between the right nucleus accumbens and dorsal rostral pons (38). These findings support theories of dopamine pathway involvement in the premonitory phase, as well as the involvement of the hypothalamus and limbic pathways.

Another study followed in 2018 and was conducted by Meylakh et al. (39). The authors used various fMRI approaches (infraslow oscillatory activity, connectivity, and regional homogeneity) to study spontaneous migraine preictally and postictally, as well as interictally and in healthy controls. The authors were able to demonstrate increased infraslow oscillatory activity in the brainstem and hypothalamic regions just before migraine headache, including the spinal trigeminal nucleus, dorsal pons, and hypothalamus. There was also increased functional coupling between these areas just before pain, as well as increased regional homogeneity. This finding was not present interictally, postictally, or in healthy controls. This study provided supportive evidence for oscillatory brainstem and hypothalamic activity in the lead-up to migraine headache and proposed a potential role for astrocytic involvement in attack initiation, rather than neuronal. Similarly, to previous studies, this study did not assess functional correlation, as subjects were not phenotyped in detail as to what, if anything, they were experiencing symptomatically on the preictal scan days. However, similar regions of interest emerge for the premonitory or pre-headache lead-up to the migraine as previous studies, and indeed as for previous migraine headache imaging studies.

A recent study performed fMRI using orofacial nociceptive stimulation in 31 migraine patients and 31 healthy controls during different parts of the migraine attack (40). There was an increase in pain ratings in response to nociceptive stimulation in the lead-up to the next migraine attack, and then these ratings decreased immediately prior to pain. Imaging responses in the spinal trigeminal nuclei dramatically increased in the 24 h prior to pain onset in response to noxious stimulation, with reduced functional connectivity between this region and the rostral ventral medulla. This study therefore suggests a pre-headache sensitivity to pain, or reduced threshold to pain, during the migraine attack (and therefore a susceptibility to exogenous triggers) and the subsequent implication of altered or dysfunctional endogenous pain modulation within the pain network in the brain during the migraine attack or cycle, which may be responsible for the sensation of pain felt following premonitory symptoms. The same authors have also recently demonstrated possible structural changes in similar brain areas (dorsolateral pons, periaqueductal gray, and spinal trigeminal nuclei) within 24 h of a migraine attack using mean diffusivity and fractional anisotropy (41).

We have recently presented our resting-state fMRI results looking at seed-based functional connectivity with the BOLD contrast, in nitroglycerin-triggered premonitory symptoms relative to placebo, and shown increased thalamocortical connectivity and functional uncoupling between the pons and the limbic lobe in the premonitory phase, with increased functional coupling between the pons and spinal trigeminal nuclei during migraine headache, thus suggesting changing alterations in subcortical and brainstem networks in the premonitory phase (42).

The imaging studies of the premonitory phase are summarized in **Table 1**.

FUNCTIONAL AND NEUROBIOLOGICAL CORRELATION WITH THE SYMPTOMATIC PREMONITORY PHASE

Although only few of these studies, namely, the perfusion studies, have phenotyped patients with regard to premonitory symptomatology prior to scanning, the similarities between implicated brain areas between all the studies and methodologies are striking and supports a network of altered brain activity involving pain processing, sensory integration, and limbic areas prior to migraine pain. These regions are likely functionally correlated to the symptomatology patients report during this phase. It can be reasonably assumed that mood and cognitive change may come from limbic pathway involvement, yawning and sleep disturbance may be mediated via the hypothalamus, and photophobia, allodynia, and other sensory sensitivities may arise from thalamocortical connections (30, 43–47).

TABLE 1 | Comparison of the imaging findings of the different studies examining the premonitory or lead-up to headache phase of the migraine attack.

Brain region	Stankewitz et al. (36) Task-evoked fMRI (trigemino-nociceptive stimulation)	Schulte et al. (37) Task-evoked fMRI (trigemino-nociceptive stimulation)	Schulte et al. (38) Task-evoked fMRI (trigemino-nociceptive stimulation)	Maniyar et al. (31) $H_2^{15}O$ perfusion PET (observed triggered attacks)	Karsan et al. (35) Perfusion arterial spin-labeled MRI (observed triggered attacks)	Meylakh et al. (39) Resting-state fMRI (infraslow oscillatory activity, regional homogeneity, and connectivity)	Marciszewski et al. (40) Task-evoked brainstem responses (noxious orofacial stimulation) and resting-state fMRI connectivity	Marciszewski et al. (41) Diffusion tensor imaging (DTI) and fractional anisotropy (FA)	Karsan et al. (42) Resting-state BOLD-fMRI (observed triggered attacks)
Hypothalamus		+	+	+	+	+			
Thalamus				+	+			+	+
Ventral tegmentum		+		+	+	+		+	
Caudate				+	+				
Putamen				+	+				
Pallidum				+	+				
Nucleus accumbens			+		+				
Spinal trigeminal nucleus	+	+				+	+	+	
Medulla								+	+
Dorsal pons		+	+	+		+		+	+
Frontal cortex				+	+				+
Precuneus/cuneus				+					+
Cerebellum				+					
Anterior cingulate				+	+				+
Occipital cortex				+	+				
Temporal cortex, including amygdala and hippocampus			+	+	+				

The brain regions that have been suggested to be implicated in five or more studies have been highlighted in bold text.

PREMONITORY SYMPTOMS, ATTACK INITIATION, AND NOCICEPTION

Although the ictus of the migraine attack is usually thought of as the pain phase, the onset of the attack could be regarded as when the brain is different to its interictal state, and this is likely to be days before the onset of pain, as suggested by neurophysiological studies. How the changes in brain function occur, therefore, are the answer to how an attack is mediated; and perhaps how these changes go from producing premonitory symptoms to producing pain is a second question. Many of the symptoms that patients report during the premonitory phase, including fatigue, cognitive dysfunction, and even photophobia, can also be present interictally in some individuals; and in our nitroglycerin-triggered experimental work, we have demonstrated the ability of the drug to provoke premonitory-like symptoms with no delayed migraine headache thereafter (48). This alludes to a possible intra-attack threshold, which could be explained by the oscillatory networks of brain activity demonstrated through the imaging studies discussed in this review, and suggests that as the networks of brain activity passing through the hypothalamus, brainstem, and cortex change throughout the migraine cycle, so do the pain thresholds. Although agents such as nitroglycerin and pituitary adenylate cyclase activating peptide (PACAP) can therefore trigger premonitory symptoms (49, 50), perhaps the likelihood of headache following thereafter is based on endogenous pain modulation systems and an individual's genetic and environmental susceptibility to developing a migraine headache that day.

PREMONITORY SYMPTOMS AND AURA

Although in some patients aura can be a warning of an impending headache, it is clear that aura can occur anytime during the migraine attack and indeed in the absence of headache too (51). Clinically, it is feasible that aura and premonitory symptoms may seem to overlap in patients who experience aura prior to headache. Aura is defined as the presence of gradually developing focal and transient neurological symptoms (1), and these can be positive or negative phenomena, whereas premonitory symptoms suggest a more global disturbance of brain function, without clear lateralizing neurological deficit, and with symptoms in general lasting longer than aura and likely occurring in a higher proportion of subjects than true migraine aura. In addition, the current understanding of migraine aura is that of a cortical phenomenon, characterized by cortical spreading depression of neuronal activity, which most commonly occurs in the visual cortex (52), whilst premonitory symptoms usually coexist with each other (53) and, as discussed in this manuscript, involve more global cortical and subcortical brain dysfunction.

CONCLUSIONS

This review has summarized the neuroimaging literature to date in the premonitory phase, or period leading up to pain, in migraine. The studies have consistently provided evidence for early brainstem involvement, as well as alluded to oscillatory brainstem, hypothalamic, and limbic networks prior to the onset of pain, with alterations in functional coupling between these regions and between pain modulatory regions such as the rostral ventral medulla and periaqueductal gray. Although the brain areas between pre-headache and during headache are similar, it is clear that thresholds may have a part to play in whether pain is perceived or not, despite similar neuroimaging findings in both the premonitory and headache phases of the attack. There is good functional correlation between the brain areas involved in the premonitory phase and the clinical phenotype of what sufferers experience during the premonitory phase of migraine.

AUTHOR CONTRIBUTIONS

NK collated and reviewed the existing literature and was responsible for writing the article. PG reviewed the article and provided expert opinion prior to submission. NK and PG were involved in some of the experimental work discussed in the article.

ACKNOWLEDGMENTS

The authors would like to thank the NIHR-Wellcome Trust King's Clinical Research Facility and SLaM Biomedical Research Centre for their support of the experimental work conducted by the authors' team, as well as all the altruistic volunteers who have taken part in the experimental research work of the team over the years, thus contributing to understanding migraine mechanisms through imaging.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS) The international classification of headache disorders, 3rd ed. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738673
2. Gil-Gouveia R, Martins IP. Clinical description of attack-related cognitive symptoms in migraine: a systematic review. *Cephalalgia*. (2018) 38:1335–50. doi: 10.1177/0333102417728250
3. Seo JG, Park SP. Significance of fatigue in patients with migraine. *J Clin Neurosci*. (2018) 50:69–73. doi: 10.1016/j.jocn.2018.01.032
4. Gowers W. *A Manual of Diseases of the Nervous System*. 3rd ed. Philadelphia: P. Blakiston, Son & Co (1899).
5. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia*. (1992) 12:221–8. doi: 10.1046/j.1468-2982.1992.1204221.x
6. Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia*. (1996) 16:239–45. doi: 10.1046/j.1468-2982.1996.1604239.x
7. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: a

questionnaire study in 461 patients. *Cephalalgia*. (2006) 26:1209–13. doi: 10.1111/j.1468-2982.2006.01195.x
8. Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology*. (2003) 60:935–40. doi: 10.1212/01.WNL.0000052998.58526.A9
9. Quintela E, Castillo J, Muñoz P, Pascual J. Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. *Cephalalgia*. (2006) 26:1051–60. doi: 10.1111/j.1468-2982.2006.01157.x
10. Blau JN. Migraine prodromes separated from the aura: complete migraine. *Br Med J*. (1980) 281:658–60. doi: 10.1136/bmj.281.6241.658
11. Drummond PD, Lance JW. Neurovascular disturbances in headache patients. *Clin Exp Neurol*. (1984) 20:93–9.
12. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache*. (2004) 44:865–72. doi: 10.1111/j.1526-4610.2004.04168.x
13. Laurell K, Artto V, Bendtsen L, Hagen K, Häggström J, Linde M, et al. Premonitory symptoms in migraine: a cross-sectional study in 2714 persons. *Cephalalgia*. (2016) 36:951–9. doi: 10.1177/0333102415620251
14. Cuvellier JC, Mars A, Vallée L. The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents. *Cephalalgia*. (2009) 29:1197–201. doi: 10.1111/j.1468-2982.2009.01854.x
15. Karsan N, Prabhakar P, Goadsby PJ. Characterising the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. *J Headache Pain*. (2016) 17:94. doi: 10.1186/s10194-016-0689-7
16. Jacobs H, Pakalnis A. Premonitory symptoms in episodic and chronic migraine from a pediatric headache clinic. *Pediatr Neurol*. (2019) 97:26–29. doi: 10.1016/j.pediatrneurol.2019.03.023
17. Waelkens J. Warning symptoms in migraine: characteristics and therapeutic implications. *Cephalalgia*. (1985) 5:223–8. doi: 10.1046/j.1468-2982.1985.0504223.x
18. Amery WK, Waelkens J, Vandenbergh V. Migraine warnings. *Headache*. (1986) 26:60–6. doi: 10.1111/j.1526-4610.1986.hed2602060.x
19. Gago-Veiga AB, Pagan J, Henares K, Heredia P, González-García N, De Orbe M-I, et al. To what extent are patients with migraine able to predict attacks? *J Pain Res*. (2018) 11:2083–94. doi: 10.2147/JPR.S175602
20. Kropp P, Gerber WD. Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. *Neurosci Lett*. (1998) 257:73–6. doi: 10.1016/S0304-3940(98)00811-8
21. Martins IP, Westerfield M, Lopes M, Maruta C, Gil-da-Costa R. Brain state monitoring for the future prediction of migraine attacks. *Cephalalgia*. (2020) 40:255–65. doi: 10.1177/0333102419877660
22. Evers S, Quibeldey F, Grotemeyer KH, Suhr B, Husstedt IW. Dynamic changes of cognitive habituation and serotonin metabolism during the migraine interval. *Cephalalgia*. (1999) 19:485–91. doi: 10.1046/j.1468-2982.1999.019005485.x
23. Judit A, Sándor PS, Schoenen J. Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. *Cephalalgia*. (2000) 20:714–9. doi: 10.1111/j.1468-2982.2000.00122.x
24. Sand T, Zhitniy N, White LR, Stovner LJ. Visual evoked potential latency, amplitude and habituation in migraine: a longitudinal study. *Clin Neurophysiol*. (2008) 119:1020–7. doi: 10.1016/j.clinph.2008.01.009
25. Weiller C, May A, Limmroth V, Jüptner M, Kaube H, Schayck RV, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med*. (1995) 1:658–60. doi: 10.1038/nm0795-658
26. Afridi SK, Giffin NJ, Kaube H, Friston KJ, Ward NS, Frackowiak RS, et al. A positron emission tomographic study in spontaneous migraine. *Arch Neurol*. (2005) 62:1270–5. doi: 10.1001/archneur.62.8.1270
27. Afridi SK, Matharu MS, Lee L, Kaube H, Friston KJ, Frackowiak RS, et al. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. *Brain*. (2005) 128:932–9. doi: 10.1093/brain/awh416
28. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. *Headache*. (2007) 47:1418–26. doi: 10.1111/j.1526-4610.2007.00776.x
29. Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM. Functional MRI-BOLD of brainstem structures during visually triggered migraine. *Neurology*. (2002) 59:72–8. doi: 10.1212/WNL.59.1.72
30. Karsan N, Goadsby PJ. Biological insights from the premonitory symptoms of migraine. *Nat Rev Neurol*. (2018) 14:699–710. doi: 10.1038/s41582-018-0098-4
31. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. (2014) 137:232–41. doi: 10.1093/brain/awt320
32. Bahra A, Matharu MS, Buchel C, Frackowiak RS, Goadsby PJ. Brainstem activation specific to migraine headache. *Lancet*. (2001) 357:1016–7. doi: 10.1016/S0140-6736(00)04250-1
33. Maniyar F, Sprenger T, Schankin C, Goadsby PJ. Photic hypersensitivity in the premonitory phase of migraine- a positron emission topography study. *Eur J Neurol*. (2014) 21:1178–83. doi: 10.1111/ene.12451
34. Maniyar FH, Sprenger T, Schankin C, Goadsby PJ. The origin of nausea in migraine-a PET study. *J Headache pain*. (2014) 15:84. doi: 10.1186/1129-2377-15-84
35. Karsan N, Bose P, Zelaya FO, Goadsby, PJ. Alterations in cerebral blood flow associated with the premonitory phase of migraine. *Cephalalgia*. (2018) 38:36.
36. Stankewitz A, Aderjan D, Eippert F, May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *J Neurosci*. (2011) 31:1937–43. doi: 10.1523/JNEUROSCI.4496-10.2011
37. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain*. (2016) 139:1987–93. doi: 10.1093/brain/aww097
38. Schulte LH, Menz M, Haaker J, May A. Brain networks in migraine: continuous resting state fMRI over 30 days. *Cephalalgia*. (2018) 38:32–33.
39. Meylakh N, Marciszewski KK, Di Pietro F, Macefield VG, Macey PM, Henderson LA. Deep in the brain: changes in subcortical function immediately preceding a migraine attack. *Hum Brain Mapp*. (2018) 39:2651–63. doi: 10.1002/hbm.24030
40. Marciszewski KK, Meylakh N, Di Pietro F, Mills EP, Macefield VG, Macey PM, et al. Changes in brainstem pain modulation circuitry function over the migraine cycle. *J Neurosci*. (2018) 38:10479–88. doi: 10.1523/JNEUROSCI.1088-18.2018
41. Marciszewski KK, Meylakh N, Di Pietro F, Macefield VG, Macey PM, Henderson LA. Fluctuating regional brainstem diffusion imaging measures of microstructure across the migraine cycle. *eNeuro*. (2019) 6:ENEURO.0005-19.2019. doi: 10.1523/ENEURO.0005-19.2019
42. Karsan N, Bose P, O'Daly O, Zelaya FO, Goadsby PJ. Alterations in functional connectivity during nitroglycerin (NTG)-triggered premonitory symptoms and migraine headache assessed using blood oxygen level dependant (BOLD) functional resonance magnetic imaging (fMRI). *Cephalalgia*. (2019) 39:14.
43. Akerman S, Karsan N, Bose P, Hoffmann JR, Holland PR, Romero-Reyes M, et al. Nitroglycerine triggers triptan-responsive cranial allodynia and trigeminal neuronal hypersensitivity. *Brain*. (2019) 142:103–19. doi: 10.1093/brain/awy313
44. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, et al. A neural mechanism for exacerbation of headache by light. *Nat Neurosci*. (2010) 13:239–45. doi: 10.1038/nn.2475
45. Noseda R, Kainz V, Borsook D, Burstein R. Neurochemical pathways that converge on thalamic trigeminovascular neurons: potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PLoS ONE*. (2014) 9:e103929. doi: 10.1371/journal.pone.0103929
46. Noseda R, Borsook D, Burstein R. Neuropeptides and neurotransmitters that modulate thalamo-cortical pathways relevant to migraine headache. *Headache*. (2017) 57(Suppl. 2):97–111. doi: 10.1111/head.13083
47. Kagan R, Kainz V, Burstein R, Noseda R. Hypothalamic and basal ganglia projections to the posterior thalamus: possible role in modulation of migraine headache and photophobia. *Neuroscience*. (2013) 248:359–68. doi: 10.1016/j.neuroscience.2013.06.014
48. Karsan N, Bose P, Goadsby PJ. The phenotype of premonitory symptoms and migraine headache triggered with nitroglycerin. *Cephalalgia*. (2016) 36:53. doi: 10.1136/jnnp-2016-315106.166

49. Afridi SK, Kaube H, Goadsby PJ. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. *Pain*. (2004) 110:675–80. doi: 10.1016/j.pain.2004.05.007
50. Guo S, Vollesen AL, Olesen J, Ashina M. Premonitory and nonheadache symptoms induced by CGRP and PACAP38 in patients with migraine. *Pain*. (2016) 157:2773–81. doi: 10.1097/j.pain.0000000000000702
51. Charles A. The evolution of a migraine attack - a review of recent evidence. *Headache*. (2013) 53:413–9. doi: 10.1111/head.12026
52. Eriksen MK, Thomsen LL, Andersen I, Nazim F, Olesen J. Clinical characteristics of 362 patients with familial migraine with aura. *Cephalalgia*. (2004) 24:564–75. doi: 10.1111/j.1468-2982.2003.00718.x
53. Güven B, Güven H, Çomoglu SS. Migraine and yawning. *Headache*. (2018) 58:210–16. doi: 10.1111/head.13195

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

OPINION
published: 09 April 2020
doi: 10.3389/fneur.2020.00221

What We Gain From Machine Learning Studies in Headache Patients

Roberta Messina[1,2*] *and Massimo Filippi*[1,2,3]

[1] Neuroimaging Research Unit, Division of Neuroscience, Institute of Experimental Neurology, Milan, Italy, [2] Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [3] Vita-Salute San Raffaele University, Milan, Italy

Keywords: headache, neuroimaging, machine learning, migraine, biomarkers, cluster headache

Primary headache disorders, such as migraine and cluster headache, are among the most prevalent and debilitating neurological diseases worldwide (1). An increasing recognition of the importance of these diseases has led to a growing interest in understanding their pathophysiology and developing new treatments. From the once popular *Vascular* theory that described primary headaches as vascular disorders, the field has now moved to the *Neuronal* theories involving either the peripheral or central nervous system, or both (2). It is now recognized that primary headaches are not simply a disease of recurrent pain attacks but a complex and multifaceted brain disorder. There is evidence that in predisposed headache patients various cortical, subcortical, and brainstem regions are activated, and key neuropeptides are released during the headache attack (3). Neuroimaging techniques have made a tremendous contribution to our understanding of headache pathophysiology, providing insights into human brain networks that might account for the pain and the broad symptomatology characterizing the headache attacks. The brainstem, including the trigeminovascular pathway, thalamus and hypothalamus seem to have a pivotal role in triggering the migraine and cluster headache attacks. Widespread structural and functional alterations in multisensory processing brain areas have also been shown in both conditions during the interictal and ictal phase (4).

A better understanding of the mechanisms responsible for the generation of the headache attacks allows the identification of novel therapeutic targets. In conjunction with progress in theories of the pathophysiology of primary headaches, the understanding of the mechanisms of action of acute and preventive treatments for migraine and cluster headache has evolved. A few neuroimaging studies have explored the therapeutic effects of pharmacological and non-pharmacological therapeutic approaches commonly used against migraines and cluster headaches, suggesting a potential central mechanism of action of these therapies (5–7).

Although much progress has been made in the understanding of migraine and cluster headache, there are still many unsolved questions to address. Many studies suggested that brain alterations in headache patients might change dynamically over time, since they differ according to the headache phase, frequency of attacks, and disease duration (8, 9). However, some brain alterations are not influenced by the disease activity, suggesting that they might represent brain biomarkers that predispose to the disease (10, 11). Further unanswered questions are whether it is possible to identify a specific neuroimaging pattern for each different headache phenotype and if alterations in the function and structure of nociceptive brain areas are headache-specific or common to other chronic pain disorders. Moreover, imaging biomarkers that could predict treatment response of headache patients are scarce.

A valuable strategy to reduce the unmet needs in the understanding of primary headaches is to study headache patients using machine learning approaches. These methods have been employed to study patients with neurological or psychiatric conditions—like Alzheimer's disease, depression, and chronic pain disorders—in order to identify neuroimaging biomarkers, which could be used to

OPEN ACCESS

Edited by:
Raquel Gil-Gouveia, Hospital da Luz Lisboa, Portugal

Reviewed by:
Stefan Evers, University of Münster, Germany
Andreas Gantenbein, RehaClinic, Switzerland

***Correspondence:**
Roberta Messina
messina.roberta@hsr.it

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *27 September 2019*
Accepted: *09 March 2020*
Published: *09 April 2020*

Citation:
Messina R and Filippi M (2020) What We Gain From Machine Learning Studies in Headache Patients. Front. Neurol. 11:221. doi: 10.3389/fneur.2020.00221

predict clinical outcomes, including diagnostic categories, measures of symptoms, prediction of disease evolution, and treatment response (12, 13). There are two main machine learning approaches: supervised and unsupervised. Supervised machine learning algorithms are trained to automatically classify individuals into predefined groups, e.g., patients or healthy controls, and yield an associated accuracy indicative of how well the model could generalize to future individual cases (12, 14). At a more detailed level, a machine learning classifier is a function that takes the values of various features (e.g., different imaging patterns) in an example and predicts the class that example belongs to (e.g., patient or control). The goal is to develop a "classifier" that identifies the relation between each example and its respective category with high accuracy (15). Based on what the algorithm has learned, it will be then able to classify new, previously unseen data to one of the predefined categories (12). By contrast, unsupervised machine learning models are data-driven automated approaches that, without the availability of a priori information supplied by the operator, seek to classify uncategorized data, with the primary aim of discovering unknown, but potentially useful information in the data (15). These classification models include a "training" phase in which training data are used to develop an algorithm able to discriminate between groups, and a "testing" phase in which the algorithm is used to blind-predict the group to which a new observation belongs.

The main advantages of using machine learning approaches are that they allow inference on an individual patient basis and are sensitive to subtle and spatially distributed patterns of disease-induced changes in the brain that might be undetectable at group level comparisons (12, 16). The evaluation of the performance of the model in a new subset of individuals provides valid estimates of how well the discriminative model generalizes to new data, enhancing the clinical significance of these approaches (16).

Recent machine learning studies have focused on the diagnosis of migraine. Machine learning algorithms based on brain resting state functional magnetic resonance imaging (MRI), or morphometric MRI data have been used to identify brain signatures that discriminate migraine patients from controls (17–19). The functional connectivity of brain regions involved with processing the affective components of pain, like the insula, amygdala, temporal, and frontal lobes, discriminated migraine patients from controls with an accuracy rate of 86%. The discrimination between patients with longer (>14 years) and shorter (≤14 years) disease duration achieved the highest accuracy, suggesting that disease burden might influence functional reorganization in the brain. The altered patterns of functional connections that distinguish migraine patients from controls could represent migraine biomarkers that are further reinforced by recurrent pain (17). On the other hand, an unsupervised machine learning approach was not able to clearly separate migraineurs from healthy controls based upon brain morphometric measures (19). An improvement in classification performance in migraine identification can be achieved integrating functional and structural imaging metrics that disclose complementary information regarding the underlying biological processes (20).

A common objection to these studies is that the diagnosis of migraine is mainly based on taking a good clinical history. However, machine learning studies could be used to discriminate those headache patients who have challenging clinical presentations, such as patients with chronic migraine vs. patients with hemicrania continua, patients with probable migraine vs. tension type-headache or patients with episodic cluster headache vs. patients with paroxysmal hemicrania. Moreover, given the high prevalence of migraine, being sure that a control does not harbor migraine biology is very challenging. In the future, the identification of migraine-specific imaging patterns might improve the accuracy of the clinical criteria currently used for the diagnosis of migraine.

Supervised and unsupervised machine learning approaches have been applied for migraine patient stratification. Classifiers containing MRI measures of brain cortical thickness, cortical surface area, and regional volumes of areas involved in nociception accurately classified individuals as having chronic migraine, achieving an accuracy of 84% when compared to episodic migraine patients (18). A data-driven classification study identified two subgroups of migraine patients based upon their brain structures, with one subgroup having longer disease duration, higher migraine-related disability and more severe allodynia symptoms during migraine attacks. Thus, highlighting the role of machine learning models in identifying migraine patients with different disease courses (19). Future machine learning studies combining clinical, structural, and functional imaging measures will be valuable for identifying episodic migraine patients who are at risk of evolving into a chronic form. These models could provide a basis for early intervention, which can potentially prevent or even reverse the course of the disease. In the future, the study of patients with different types of headache and patients with other chronic pain disorders using machine learning techniques might provide brain "signatures" that are specific for the different conditions. Thus, providing important information about the relationships between disorders and symptoms at the biological level.

One of the most promising applications of machine learning techniques lies in their aid in customizing patients' treatment based on imaging brain fingerprints. Previous studies have shown the ability of machine learning approaches to predict treatment response in patients with major depression based on functional and structural brain imaging patterns (21, 22). It is desirable that future use of machine learning techniques, imaging, and clinical data, would allow us to identify objective biomarkers that might facilitate the selection of the most appropriate treatment for each headache patient. Objective biomarkers that predict treatment response can improve headache patients' management and reduce unmet treatment needs. Optimized treatments tailored to the individual patient are essential to improve headache patients' quality of life and increase patients' productivity.

Despite increasing interest in these emerging techniques, many challenges remain to be solved. None of the machine learning studies in headache patients have validated the accuracy

of their models in independent datasets, so far. Moreover, the generalizability of the classification models across different sites and scanners should be evaluated. Large-scale datasets of headache patients are also needed.

AUTHOR CONTRIBUTIONS

RM and MF have both contributed to the study concept and drafting and revising the manuscript.

REFERENCES

1. Collaborators GBDN. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:459–80. doi: 10.1016/S1474-4422(18)30499-X
2. Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. *J Neurol.* (2017) 264:2031–9. doi: 10.1007/s00415-017-8434-y
3. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev.* (2017) 97:553–622. doi: 10.1152/physrev.00034.2015
4. Messina R, Filippi M, Goadsby PJ. Recent advances in headache neuroimaging. *Curr Opin Neurol.* (2018) 31:379–85. doi: 10.1097/WCO.0000000000000573
5. Kroger IL, May A. Triptan-induced disruption of trigemino-cortical connectivity. *Neurology.* (2015) 84:2124–31. doi: 10.1212/WNL.0000000000001610
6. Hebestreit JM, May A. The enigma of site of action of migraine preventives: no effect of metoprolol on trigeminal pain processing in patients and healthy controls. *J Headache Pain*. (2017) 18:116. doi: 10.1186/s10194-017-0827-x
7. Akram H, Miller S, Lagrata S, Hariz M, Ashburner J, Behrens T, et al. Optimal deep brain stimulation site and target connectivity for chronic cluster headache. *Neurology*. (2017) 89:2083–91. doi: 10.1212/WNL.0000000000004646
8. Yang FC, Chou KH, Kuo CY, Lin YY, Lin CP, Wang SJ. The pathophysiology of episodic cluster headache: insights from recent neuroimaging research. *Cephalalgia*. (2017) 38:970–83. doi: 10.1177/0333102417716932
9. Messina R, Rocca MA, Colombo B, Pagani E, Falini A, Goadsby PJ, et al. Gray matter volume modifications in migraine: a cross-sectional and longitudinal study. *Neurology*. (2018) 91:e280–92. doi: 10.1212/WNL.0000000000005819
10. Rocca MA, Messina R, Colombo B, Falini A, Comi G, Filippi M. Structural brain MRI abnormalities in pediatric patients with migraine. *J Neurol.* (2014) 261:350–7. doi: 10.1007/s00415-013-7201-y
11. Messina R, Rocca MA, Colombo B, Valsasina P, Horsfield MA, Copetti M, et al. Cortical abnormalities in patients with migraine: a surface-based analysis. *Radiology*. (2013) 268:170–80. doi: 10.1148/radiol.13122004
12. Orru G, Pettersson-Yeo W, Marquand AF, Sartori G, Mechelli A. Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review. *Neurosci Biobehav Rev*. (2012) 36:1140–52. doi: 10.1016/j.neubiorev.2012.01.004
13. O'Muircheartaigh J, Marquand A, Hodkinson DJ, Krause K, Khawaja N, Renton TF, et al. Multivariate decoding of cerebral blood flow measures in a clinical model of on-going postsurgical pain. *Hum Brain Mapp.* (2015) 36:633–42. doi: 10.1002/hbm.22652
14. Pettersson-Yeo W, Benetti S, Marquand AF, Joules R, Catani M, Williams SC, et al. An empirical comparison of different approaches for combining multimodal neuroimaging data with support vector machine. *Front Neurosci.* (2014) 8:189. doi: 10.3389/fnins.2014.00189
15. Pereira F, Mitchell T, Botvinick M. Machine learning classifiers and fMRI: a tutorial overview. *Neuroimage.* (2009) 45(1 Suppl):S199–209. doi: 10.1016/j.neuroimage.2008.11.007
16. Woo CW, Chang LJ, Lindquist MA, Wager TD. Building better biomarkers: brain models in translational neuroimaging. *Nat Neurosci*. (2017) 20:365–77. doi: 10.1038/nn.4478
17. Chong CD, Gaw N, Fu Y, Li J, Wu T, Schwedt TJ. Migraine classification using magnetic resonance imaging resting-state functional connectivity data. *Cephalalgia*. (2017) 37:828–44. doi: 10.1177/0333102416652091
18. Schwedt TJ, Chong CD, Wu T, Gaw N, Fu Y, Li J. Accurate classification of chronic migraine via brain magnetic resonance imaging. *Headache*. (2015) 55:762–77. doi: 10.1111/head.12584
19. Schwedt TJ, Si B, Li J, Wu T, Chong CD. Migraine subclassification via a data-driven automated approach using multimodality factor mixture modeling of brain structure measurements. *Headache*. (2017) 57:1051–64. doi: 10.1111/head.13121
20. Zhang Q, Wu Q, Zhang J, He L, Huang J, Zhang J, et al. Discriminative analysis of migraine without aura: using functional and structural MRI with a multi-feature classification approach. *PLoS ONE*. (2016) 11:e0163875. doi: 10.1371/journal.pone.0163875
21. Gong Q, Wu Q, Scarpazza C, Lui S, Jia Z, Marquand A, et al. Prognostic prediction of therapeutic response in depression using high-field MR imaging. *Neuroimage*. (2011) 55:1497–503. doi: 10.1016/j.neuroimage.2010.11.079
22. Costafreda SG, Khanna A, Mourao-Miranda J, Fu CH. Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. *Neuroreport*. (2009) 20:637–41. doi: 10.1097/WNR.0b013e3283294159

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 10 June 2020
doi: 10.3389/fneur.2020.00453

An Update on Imaging in Idiopathic Intracranial Hypertension

David Moreno-Ajona[1,2], *James Alexander McHugh*[3] *and Jan Hoffmann*[1,2]*

[1] Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [2] NIHR-Wellcome Trust King's Clinical Research Facility/SLaM Biomedical Research Centre, King's College Hospital, London, United Kingdom, [3] Department of Ophthalmology, King's College Hospital NHS Trust, London, United Kingdom

Neuroimaging plays an essential role in the diagnostic workup of idiopathic intracranial hypertension with the aims to exclude secondary causes of elevated intracranial pressure and to identify imaging signs that are commonly observed in this disorder. As a valuable expansion of brain imaging, the imaging of the retina using optical coherence tomography has been of increasing value. In particular, this is the case with the latest devices that allow a more accurate distinction between a reduction in retinal nerve fiber layer thickness due to an improvement of papilledema or due to a worsening caused by optic nerve atrophy. Although optical coherence tomography does not yet replace the other elements of the diagnostic workup, it is likely to play an increasing role in diagnosis and follow-up of idiopathic intracranial hypertension. The review focuses on the main findings in neuroimaging, including structural and vascular alterations as well as on the relevance of optical coherence tomography.

Keywords: headache, idiopathic intracranial hypertension (iih), neuroimaging, optical coherence tomography, pain

OPEN ACCESS

Edited by:
Roberta Messina, Vita-Salute San Raffaele University, Italy

Reviewed by:
Giorgio Lambru, Guy's Hospital, United Kingdom
Aynur Özge, Mersin University, Turkey

***Correspondence:**
Jan Hoffmann
jan.hoffmann@kcl.ac.uk

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *24 December 2019*
Accepted: *28 April 2020*
Published: *10 June 2020*

Citation:
Moreno-Ajona D, McHugh JA and Hoffmann J (2020) An Update on Imaging in Idiopathic Intracranial Hypertension. Front. Neurol. 11:453. doi: 10.3389/fneur.2020.00453

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is defined as an elevation of intracranial pressure (ICP) in the absence of a brain lesion or any other secondary etiology (1). IIH generally affects obese young women of childbearing age. Given the relationship to obesity, the prevalence of IIH, which is currently estimated at 0.5–2.0 per 100,000 of the general population (2), is increasing along with the worldwide increasing incidence of obesity (3). The potential similarity of the clinical picture to primary headaches, in particular chronic migraine, probably results in IIH still being underdiagnosed (4).

In this article, we review our understanding of IIH with a special focus on the current imaging techniques and their utility in diagnosing and managing IIH.

Clinical Picture

The clinical picture of IIH is dominated by headache and ophthalmic features resulting from the pressure-induced papilledema (1, 5). Headache is the most common clinical symptom of IIH and a key factor in the reduction of quality of life (4, 6). The headache can vary substantially in its clinical presentation, hence, the relatively unspecific definition in the diagnostic criteria of the International Headache Society. Frequently, the headache has a migraine phenotype, raising the question to what extent is the headache primarily driven by the elevated ICP or by a pressure-induced exacerbation of a pre-existing migraine. This uncertainty is fuelled further by the fact that most IIH patients do not experience a sustained improvement of their headache once ICP is normalized with an adequate

treatment. Despite causing major morbidity in IIH and having an immense impact on patients' quality of life, no clinical trials exist that focus exclusively on the headache component of IIH (7).

The second cardinal feature of IIH is the papilledema caused by the elevation of ICP. In the majority of cases, papilledema is bilateral, but in up to 4% of cases, it can be asymmetrical. If IIH is untreated, the papilledema leads to numerous visual symptoms, including visual field defects, obscurations, and ultimately to the complete loss of eyesight resulting from an atrophy of the optic nerve. Due to the potential irreversibility of visual symptoms, a quick and accurate assessment is essential in the diagnostic workup of IIH.

Pathophysiology

The pathophysiology remains unknown although our understanding has evolved significantly over the last decades. The first studies led to the belief that IIH may be due to increased CSF (8–10). This idea was refuted by Dandy and coworkers in the late 1930s as they saw no ventricular size alteration on ventriculography. The authors hypothesized IIH was related to an increased intracranial blood volume as a result of vasomotor control (11). Indeed, they suggested changes in the vascular bed would explain better the rapid changes in the intracranial pressure they observed. In the early 1950s, venography studies showed obstruction of the superior sagittal sinus (SSS) and dominant transverse sinus (12). Studies, including brain biopsy, in the late 1950s demonstrated intracellular and extracellular cerebral edema (13, 14). In the 1970s, after performing isotope cisternography and ventriculography, Johnston and coworkers hypothesized that a pressure increase within the SSS may lead to reduced CSF absorption (15). Raichle and coworkers, utilizing tracer techniques, showed a reduction in cerebral blood flow despite an increase in cerebral blood volume and pointed to an abnormality in the cerebral microvasculature (16). More recently, in 1995, with the use of cerebral venography and manometry, venous hypertension was shown in the SSS and the transverse sinus (17). In line with some studies performed in the 1930s and 1950s, a 3D volumetric MR imaging study showed normal ventricular volume in IIH. Nevertheless, the authors also observed increased extraventricular CSF volume (18). A phase-contrast MRI performed to measure the interaction between CSF and blood flows demonstrated the presence of a small phase shift of venous outflow leading to increased arteriovenous pulsatility, which ultimately would lead to an increase in CSF and (ICP) (19). The venous sinus stenosis hypothesis has led to venous sinus stenting as a therapy, the efficacy of which appears to be related to the pressure gradient prior to surgery (18).

Recently, the role obesity may play has also been addressed. A pathophysiological link is supported by reports of patients whose CSF opening pressure was normalized following bariatric surgery (20). Indeed, two cases showed reduction in venous sinus pressure as measured by intracranial venography following surgery (21). As a causative factor, recent evidence points to androgen excess, specifically testosterone, concentrations of which were found to be higher in both blood and CSF as compared to obese females with and without polycystic ovary syndrome (22).

Structural MRI

Structural MRI is a key element in the diagnostic workup of IIH with the aim of ruling out a secondary cause of elevated ICP and to identify neuroimaging signs that are typically observed in IIH. One of the most suggestive neuroimaging abnormalities that is highly suggestive of IIH is the reduction of the midsagittal height of the pituitary gland ("empty sella") (23). This is reflected in a significant reduction in its volume when performing an MR-based volumetric measurement (24). It is not entirely clear how a long-term increase of ICP causes the size reduction of the pituitary gland, but it is thought to be the result of a herniation of arachnocele through the diaphragma sellae (25). Interestingly, most abnormal morphometric neuroimaging findings do not improve after CSF pressure has been normalized and papilledema has resolved (26). However, healthy participants in research studies or patients who are scanned for a different reason may show an "empty sella." Although, in the context of IIH, treatment should be based on the principle of treating clinical symptoms and not radiological signs, recent evidence suggests that a close follow-up of these patients may be recommendable (27).

Another typical neuroimaging finding in IIH is the distension of the optic nerve sheath (ONS) observed on T2-weighted MR-images (23, 24, 28). The distension of the ONS results from increased CSF pressure in the perioptic subarachnoid space. The adaptation of CSF pressure in the ONS to the ICP is not immediate due to the capillary CSF communication in the optic canal. For this reason, changes in the ONS are not seen in acute ICP changes (e.g., intracranial hemorrhage) (29) or within a few hours after normalization of ICP (30) although the exact time of the delay remains unknown. In contrast, although the ONS shows a macroscopic distention and the optic nerve may appear tortuous, the size and volume of the optic nerve remain unchanged (23, 24). However, when imaging is performed with diffusion tensor imaging (DTI) to analyze microstructural properties, changes in the optic nerve are identified (28, 30). These changes are in line with a microstructural tissue compression and are reversed after normalization of ICP (30). The fact that microstructural alterations within the optic nerve improve within 24 hours of lumbar puncture but the macroscopic size of the ONS does not highlights the delayed effect on the perioptic space after normalization of ICP and may suggest a higher sensitivity when imaging microscopic alterations using DTI compared to macroscopic changes in ONS using T2-weighted MRI. Nevertheless, the data from this study is based on a small number of patients and, therefore, requires a larger study to be confirmed (30). In line with microstructural imaging of the optic nerve, DTI of the optic disc shows abnormal values of fractional anisotropy in patients with IIH compared to healthy controls (31).

A posterior flattening of the optic globe is also commonly observed, but compared to the previously mentioned neuroimaging signs, it has an inferior sensitivity (23).

Finally, unilateral or bilateral transverse sinus stenoses (TSS) are commonly observed in IIH. Data on the prevalence of TSS in IIH vary substantially as MR-venography is frequently affected by imaging artifacts. It still remains controversial whether these are the cause or consequence of elevated ICP.

However, increasing evidence suggest that TSS are secondary to increased ICP as they can resolve after normalization of ICP (32). The fact that bilateral stenting can resolve elevated ICP could be explained by a vicious cycle in which elevated

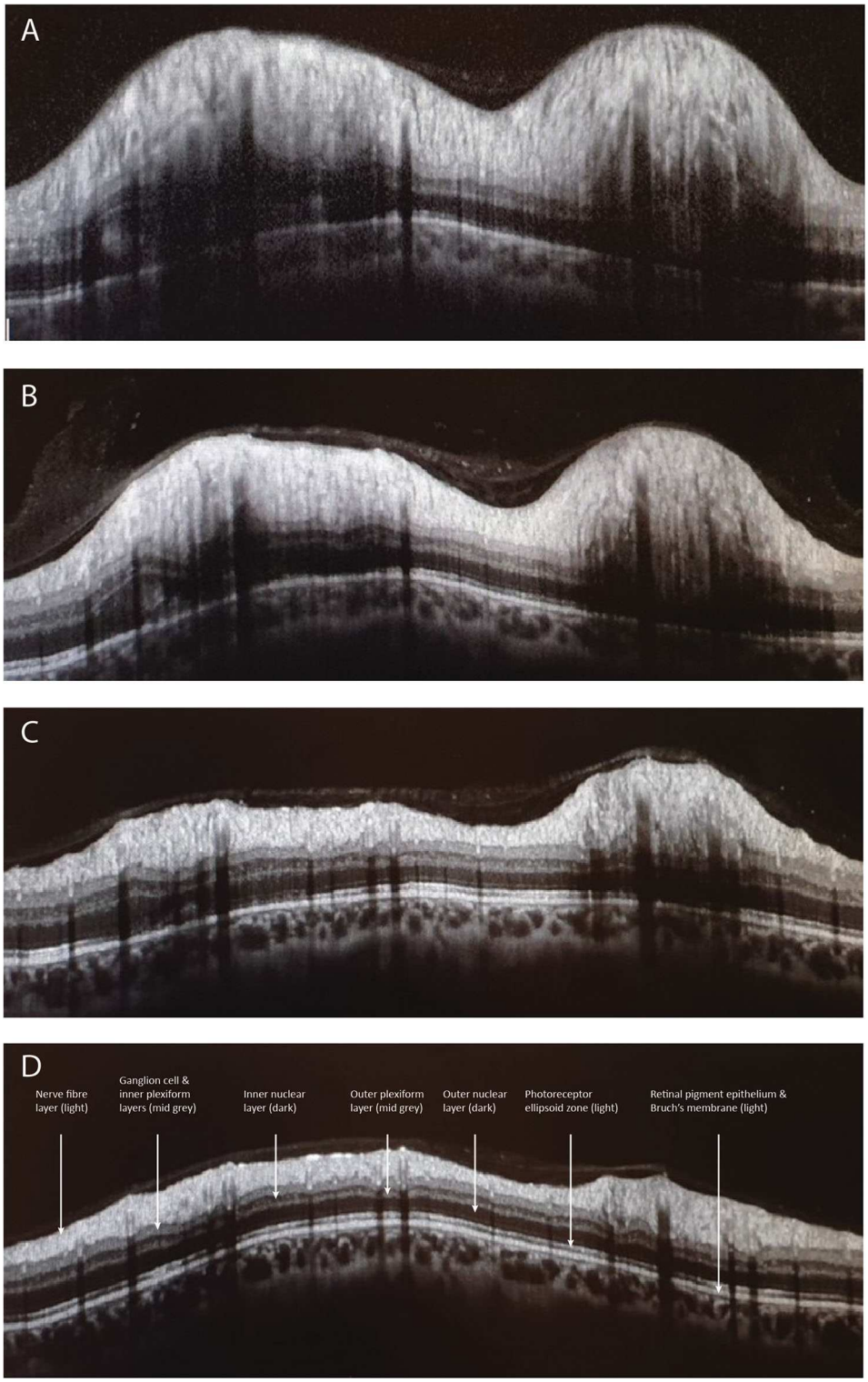


FIGURE 1 | Depicts the peripapillary retinal nerve fiber thickness (pRNFL) scan performed with optical coherence tomography. Image **(A)** illustrates a pRNFL scan with severe disc swelling in IIH compared to day 5 **(B)**, day 30 **(C)**, and day 70 **(D)** after placing a ventriculoperitoneal shunt.

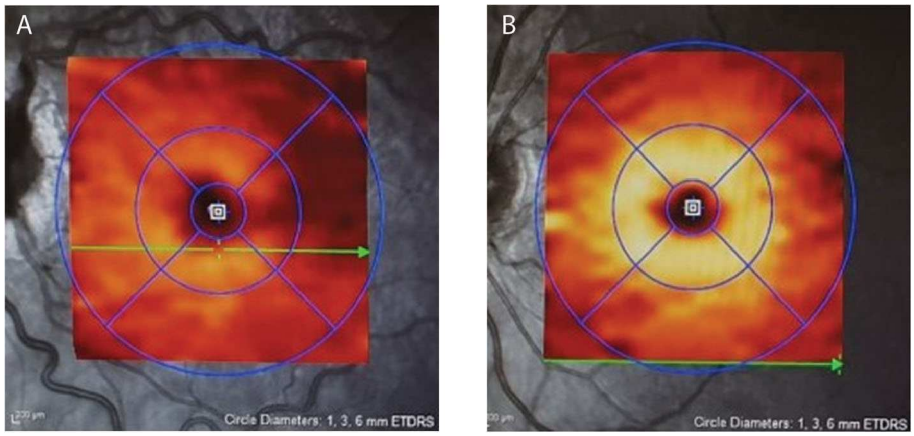


FIGURE 2 | Depicts the moderate macular ganglion cell layer (mGCL) thinning in IIH **(A)** vs. a healthy control **(B)**. Note on image A the dilated, tortuous veins resulting from papilledema.

ICP causes compression of the transverse sinuses, further aggravating the situation by obstructing venous outflow and thereby reducing the pressure gradient over the arachnoid villi (4, 33).

Optical Coherence Tomography

Optical coherence tomography (OCT) uses a low-energy near-infrared laser beam that is projected onto the retina, and the light reflected from the retina interacts with a reference laser beam to create an interference pattern, which is analyzed to determine the reflectance of retinal tissue at different depths (34). Up to 100,000 points are scanned per second, creating exquisitely detailed profiles (axial resolution currently up to 3 μm) from which thickness maps of different retinal layers can be derived. Modern spectral-domain and swept-source OCTs use en-face laser ophthalmoscopic images of fundus vessels to ensure that follow-up scans in a given patient are exactly aligned with baseline scans, allowing tiny changes in retinal elevation and the thickness of individual retinal layers to be reliably measured.

OCT Measurement of Papilledema in IIH

OCT has a well-established role in assessing and monitoring papilledema (35–37). A number of different OCT scanning protocols are used to assess the optic disc in ophthalmology. The most widely used is a 3.4 mm line scan measuring retinal nerve fiber layer thickness (pRNFL). Papilledema causes thickening of the pRNFL, and greater thickness is associated with higher lumbar puncture opening pressure (35, 38, 39). In very early papilledema, retinal nerve fiber layer thickening may not extend far enough from the disc to be picked up by a pRNFL scan (40) although, in severe RNFL thickening, automated segmentation analysis is often unreliable, requiring manual correction to ensure valid longitudinal data (35).

A variety of OCT scanning strategies have been described to quantify the elevation and volume of the disc itself in papilledema, which may offer some advantages over conventional pRNFL scans, especially in very early swelling (41–45). It has been shown that treatment of IIH with acetazolamide, successful weight loss, or ventriculo-peritoneal shunt causes corresponding improvement in OCT measures of disc height, volume, and pRNFL (43, 44, 46, 47) (**Figure 1**).

Deformation of the Peripapillary Retina

A number of methods have been described for measuring deformation of the layers deep into the neural retina (peri-papillary retinal pigment epithelium and Bowman's membrane) toward the vitreous, equivalent to inward deformation of the posterior sclera seen on MRI. The degree of deformation is related to lumbar puncture opening pressure and improves with ICP-lowering treatment (36, 41, 43, 48–50).

Diagnosis of Pseudopapilledema

OCT can readily distinguish tilted discs, the crowded hypermetropic discs, and buried disc drusen from true papilledema. The use of enhanced depth imaging allows OCT to image as deep as the lamina cribrosa of the sclera to detect even very small drusen (51–53).

OCT Macular Ganglion Cell Layer Imaging in IIH

A significant challenge in monitoring IIH-related papilledema is to determine whether a reduction in the degree of disc or pRNFL swelling is due to improvement of edema due to falling ICP from successful treatment or, conversely, to the loss of RNFL fibers as optic atrophy develops. Macular OCT imaging is extremely helpful in this situation. The macular ganglion cell layer (mGCL), which contains the cell bodies of axons of the optic nerve, does not swell in papilledema. Disc damage due to papilledema causes early thinning of the mGCL before frank thinning of the pRNFL develops (47, 54) (**Figure 2**). Conversely, finding that a patient with chronic papilledema despite medical therapy has no thinning (or no progression of thinning) of the mGCL offers reassurance that the optic nerve is not losing axons at an abnormal rate.

Other Applications of OCT Systems in IIH

Various other OCT features may have value in diagnosing or monitoring IIH. These include imaging retinal and choroidal folds due to papilledema, of which some subtypes may improve with treatment (55, 56); OCT imaging of venular diameter, which increases in papilledema and decreases when elevated ICP is reduced (57); and OCT angiographic imaging of peripapillary capillaries, which have increased diameter and tortuosity in papilledema (58).

In patients suspected of having IIH without papilledema or in whom established optic atrophy prevents disc swelling, OCT systems can be used to obtain motion-stabilized laser ophthalmoscopic videos, which are extremely sensitive in detecting spontaneous retinal venous pulsation (SVP) (59). The presence of SVP signifies a healthy pressure gradient between the eye and the retrobulbar perineural CSF, and videography using OCT systems has shown that SVP reliably disappears when ICP becomes moderately elevated (60).

CONCLUSIONS

Neuroimaging in IIH has substantially improved diagnostic accuracy in IIH. Although it is unlikely that it will replace diagnostic lumbar puncture, it is feasible that, in a few years, improved MR imaging, including microstructural imaging as well as the rapidly improving quality of OCT imaging of papilledema, may offer a possibility to reduce the number of lumbar punctures for diagnostic follow-up as they could provide reliable markers that could be used in indirectly assessing ICP (32, 61).

AUTHOR CONTRIBUTIONS

DM-A, JM, and JH performed the literature review and drafted the manuscript.

REFERENCES

1. Hoffmann J, Mollan SP, Paemeleire K, Lampl C, Jensen RH, Sinclair AJ. European headache federation guideline on idiopathic intracranial hypertension. *J Headache Pain.* (2018) 19:93. doi: 10.1186/s10194-018-0919-2
2. Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. *Lancet Neurol.* (2016) 15:78–91. doi: 10.1016/S1474-4422(15)00298-7
3. Almarzouqi SJ, Morgan ML, Lee AG. Idiopathic intracranial hypertension in the Middle East: A growing concern. *Saudi J Ophthalmol.* (2015) 29:26–31. doi: 10.1016/j.sjopt.2014.09.013
4. Hoffmann J, Goadsby PJ. Update on intracranial hypertension and hypotension. *Curr Opin Neurol.* (2013) 26:240–7. doi: 10.1097/WCO.0b013e328360eccc
5. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology.* (2013) 81:1159–65. doi: 10.1212/WNL.0b013e3182a55f17
6. Mulla Y, Markey KA, Woolley RL, Patel S, Mollan SP, Sinclair AJ. Headache determines quality of life in idiopathic intracranial hypertension. *J Headache Pain.* (2015) 16:45. doi: 10.1186/s10194-015-0521-9
7. Mollan SP, Hoffmann J, Sinclair AJ. Advances in the understanding of headache in idiopathic intracranial hypertension. *Curr Opin Neurol.* (2019) 32:92–8. doi: 10.1097/WCO.0000000000000651
8. Bandyopadhyay S. Pseudotumor cerebri. *Arch Neurol.* (2001) 58:1699–701. doi: 10.1001/archneur.58.10.1699
9. Degnan AJ, Levy LM. Pseudotumor cerebri: brief review of clinical syndrome and imaging findings. *AJNR Am J Neuroradiol.* (2011) 32:1986–93. doi: 10.3174/ajnr.A2404
10. Johnston I. The historical development of the pseudotumor concept. *Neurosurg Focus.* (2001) 11:E2. doi: 10.3171/foc.2001.11.2.3
11. Dandy WE. Intracranial pressure without brain tumor: diagnosis and treatment. *Ann Surg.* (1937) 106:492–513. doi: 10.1097/00000658-193710000-00002
12. Ray BS, Dunbar HS. Thrombosis of the dural venous sinuses as a cause of pseudotumor cerebri. *Ann Surg.* (1951) 134:376–86. doi: 10.1097/00000658-195113430-00009
13. Foley J. Benign forms of intracranial hypertension; toxic and otitic hydrocephalus. *Brain.* (1955) 78:1–41. doi: 10.1093/brain/78.1.1
14. Joynt RJ, Sahs AL. Brain swelling of unknown cause. *Neurology.* (1956) 6:801–3. doi: 10.1212/WNL.6.11.791
15. Johnston I, Paterson A. Benign intracranial hypertension. II. CSF pressure and circulation. *Brain.* (1974) 97:301–12. doi: 10.1093/brain/97.1.301
16. Raichle ME, Grubb RL Jr, Phelps ME, Gado MH, Caronna JJ. Cerebral hemodynamics and metabolism in pseudotumor cerebri. *Ann Neurol.* (1978) 4:104–11. doi: 10.1002/ana.410040203
17. King JO, Mitchell PJ, Thomson KR, Tress BM. Cerebral venography and manometry in idiopathic intracranial hypertension. *Neurology.* (1995) 45:2224–8. doi: 10.1212/WNL.45.12.2224
18. McDougall CM, Ban VS, Beecher J, Pride L, Welch BG. Fifty shades of gradients: does the pressure gradient in venous sinus stenting for idiopathic intracranial hypertension matter? A systematic review. *J Neurosurg.* (2018) 130:999. doi: 10.3171/2017.8.JNS17459
19. Capel C, Baroncini M, Gondry-Jouet C, Bouzerar R, Czosnyka M, Czosnyka Z, et al. Cerebrospinal fluid and cerebral blood flows in idiopathic intracranial hypertension. *Acta Neurochir Suppl.* (2018) 126:237–41. doi: 10.1007/978-3-319-65798-1_48
20. Sugerman HJ, Felton WL, 3rd, Salvant JB Jr, Sismanis A, Kellum JM. Effects of surgically induced weight loss on idiopathic intracranial hypertension in morbid obesity. *Neurology.* (1995) 45:1655–9. doi: 10.1212/WNL.45.9.1655
21. Nadkarni T, Rekate HL, Wallace D. Resolution of pseudotumor cerebri after bariatric surgery for related obesity. *J Neurosurg.* (2004) 101:878–80. doi: 10.3171/jns.2004.101.5.0878
22. O'Reilly MW, Westgate CS, Hornby C, Botfield H, Taylor AE, Markey K, et al. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. *JCI Insight.* (2019) 4:e125348. doi: 10.1172/jci.insight.125348
23. Hoffmann J, Huppertz HJ, Schmidt C, Kunte H, Harms L, Klingebiel R, et al. Morphometric and volumetric MRI changes in idiopathic intracranial hypertension. *Cephalalgia.* (2013) 33:1075–84. doi: 10.1177/0333102413484095
24. Hoffmann J, Schmidt C, Kunte H, Klingebiel R, Harms L, Huppertz H-J, et al. Volumetric assessment of optic nerve sheath and hypophysis in idiopathic intracranial hypertension. *AJNR Am J Neuroradiol.* (2014) 35:513–8. doi: 10.3174/ajnr.A3694
25. Brodsky MC, Vaphiades M. Magnetic resonance imaging in pseudotumor cerebri. *Ophthalmology.* (1998) 105:1686–93. doi: 10.1016/S0161-6420(98)99039-X
26. Chang RO, Marshall BK, Yahyavi N, Sharma A, Huecker J, Gordon MO, et al. Neuroimaging features of idiopathic intracranial hypertension persist after resolution of papilloedema. *Neuroophthalmology.* (2016) 40:165–70. doi: 10.1080/01658107.2016.1179767

27. Yilmaz A, Gok M, Altas H, Yildirim T, Kaygisiz S, Isik HS. Retinal nerve fibre and ganglion cell inner plexiform layer analysis by optical coherence tomography in asymptomatic empty sella patients. *Int J Neurosci.* (2020) 130:45–51. doi: 10.1080/00207454.2019.1660328
28. Schmidt C, Wiener E, Lüdemann L, Kunte H, Kreutz KM, Becker N, et al. Does IIH alter brain microstructures? - A DTI-based approach. *Headache*. (2017) 57:746–55. doi: 10.1111/head.13039
29. Patterson DF, Ho ML, Leavitt JA, Smischney NJ, Hocker SE, Wijdicks EF, et al. Comparison of Ocular Ultrasonography and Magnetic Resonance Imaging for Detection of Increased Intracranial Pressure. *Front Neurol.* (2018) 9:278. doi: 10.3389/fneur.2018.00278
30. Hoffmann J, Kreutz KM, Csapó-Schmidt C, Becker N, Kunte H, Fekonja LS, et al. The effect of CSF drain on the optic nerve in idiopathic intracranial hypertension. *J Headac Pain.* (2019) 20:59. doi: 10.1186/s10194-019-1004-1
31. Razek AAKA, Batouty N, Fathy W, Bassiouny R. Diffusion tensor imaging of the optic disc in idiopathic intracranial hypertension. *Neuroradiology*. (2018) 60:1159–66. doi: 10.1007/s00234-018-2078-1
32. Lublinsky S, Kesler A, Friedman A, Horev A, Shelef I. Quantifying response to intracranial pressure normalization in idiopathic intracranial hypertension via dynamic neuroimaging. *J Magn Reson Imaging.* (2018) 47:913–27. doi: 10.1002/jmri.25857
33. Ahmed RM, Wilkinson M, Parker GD, Thurtell MJ, Macdonald J, McCluskey PJ, et al. Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. *AJNR Am J Neuroradiol.* (2011) 32:1408–14. doi: 10.3174/ajnr.A2575
34. Fercher AF, Hitzenberger CK, Drexler W, Kamp G, Sattmann H. In vivo optical coherence tomography. *Am J Ophthalmol.* (1993) 116:113–4. doi: 10.1016/S0002-9394(14)71762-3
35. Scott CJ, Kardon RH, Lee AG, Frisen L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. *Arch Ophthalmol.* (2010) 128:705–11. doi: 10.1001/archophthalmol.2010.94
36. Kupersmith MJ, Sibony P, Mandel G, Durbin M, Kardon RH. Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema. *Invest Ophthalmol Vis Sci.* (2011) 52:6558–64. doi: 10.1167/iovs.10-6782
37. Sheils CR, Fischer WS, Hollar RA, Blanchard LM, Feldon SE. The relationship between optic disc volume, area, and frisen score in patients with idiopathic intracranial hypertension. *Am J Ophthalmol.* (2018) 195:101–9. doi: 10.1016/j.ajo.2018.07.032
38. Rebolleda G, Muñoz-Negrete FJ. Follow-up of mild papilledema in idiopathic intracranial hypertension with optical coherence tomography. *Invest Ophthalmol Vis Sci.* (2009) 50:5197–200. doi: 10.1167/iovs.08-2528
39. Skau M, Yri H, Sander B, Gerds TA, Milea D, Jensen R. Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension. *Graefes Arch Clin Exp Ophthalmol.* (2013) 251:567–74. doi: 10.1007/s00417-012-2039-z
40. Pardon LP, Cheng H, Tang RA, Saenz R, Frishman LJ, Patel NB. Custom optical coherence tomography parameters for distinguishing papilledema from pseudopapilledema. *Optom Vis Sci.* (2019) 96:599–608. doi: 10.1097/OPX.0000000000001408
41. Patel MD, Malhotra K, Shirazi Z, Moss HE. Methods for quantifying optic disc volume and peripapillary deflection volume using radial optical coherence tomography scans and association with intracranial pressure. *Front Neurol.* (2019) 10:798. doi: 10.3389/fneur.2019.00798
42. Kaufhold F, Kadas EM, Schmidt C, Kunte H, Hoffmann J, Zimmermann H, et al. Optic nerve head quantification in idiopathic intracranial hypertension by spectral domain OCT. *PLoS ONE.* (2012) 7:e36965. doi: 10.1371/journal.pone.0036965
43. Wang JK, Kardon RH, Ledolter J, Sibony PA, Kupersmith MJ, Garvin MK. Peripapillary retinal pigment epithelium layer shape changes from acetazolamide treatment in the idiopathic intracranial hypertension treatment trial. *Invest Ophthalmol Vis Sci.* (2017) 58:2554–65. doi: 10.1167/iovs.16-21089
44. Albrecht P, Blasberg C, Ringelstein M, Muller AK, Finis D, Guthoff R, et al. Optical coherence tomography for the diagnosis and monitoring of idiopathic intracranial hypertension. *J Neurol.* (2017) 264:1370–80. doi: 10.1007/s00415-017-8532-x
45. Patel MD, Khushzad F, Moss HE. Comparison of cross sectional optical coherence tomography images of elevated optic nerve heads across acquisition devices and scan protocols. *Eye Vis (Lond).* (2018) 5:17. doi: 10.1186/s40662-018-0112-3
46. Auinger P, Durbin M, Feldon S, Garvin M, Kardon R, Keltner J, et al. Papilledema outcomes from the optical coherence tomography substudy of the idiopathic intracranial hypertension treatment trial. *Ophthalmology.* (2015) 122:1939–45.e2. doi: 10.1016/j.ophtha.2015.06.003
47. Athappilly G, Garcia-Basterra I, Machado-Miller F, Hedges TR, Mendoza-Santiesteban C, Vuong L. Ganglion cell complex analysis as a potential indicator of early neuronal loss in idiopathic intracranial hypertension. *Neuroophthalmology.* (2019) 43:10–7. doi: 10.1080/01658107.2018.1476558
48. Sibony P, Kupersmith MJ, Honkanen R, Rohlf FJ, Torab-Parhiz A. Effects of lowering cerebrospinal fluid pressure on the shape of the peripapillary retina in intracranial hypertension. *Invest Ophthalmol Vis Sci.* (2014) 55:8223–31. doi: 10.1167/iovs.14-15298
49. Malhotra K, Patel MD, Shirazi Z, Moss HE. Association between peripapillary bruch's membrane shape and intracranial pressure: effect of image acquisition pattern and image analysis method, a preliminary study. *Front Neurol.* (2018) 9:1137. doi: 10.3389/fneur.2018.01137
50. Gampa A, Vangipuram G, Shirazi Z, Moss HE. Quantitative association between peripapillary bruch's membrane shape and intracranial pressure. *Invest Ophthalmol Vis Sci.* (2017) 58:2739–45. doi: 10.1167/iovs.17-21592
51. Fard MA, Fakhree S, Abdi P, Hassanpoor N, Subramanian PS. Quantification of peripapillary total retinal volume in pseudopapilledema and mild papilledema using spectral-domain optical coherence tomography. *Am J Ophthalmol.* (2014) 158:136–43. doi: 10.1016/j.ajo.2014.03.008
52. Traber GL, Weber KP, Sabah M, Keane PA, Plant GT. Enhanced depth imaging optical coherence tomography of optic nerve head drusen: a comparison of cases with and without visual field loss. *Ophthalmology.* (2017) 124:66–73. doi: 10.1016/j.ophtha.2016.09.022
53. Malmqvist L, Bursztyn L, Costello F, Digre K, Fraser JA, Fraser C, et al. The optic disc drusen studies consortium recommendations for diagnosis of optic disc drusen using optical coherence tomography. *J Neuro-Ophthalmol.* (2018) 38:299–307. doi: 10.1097/WNO.0000000000000585
54. Marzoli SB, Ciasca P, Curone M, Cammarata G, Melzi L, Criscuoli A, et al. Quantitative analysis of optic nerve damage in idiopathic intracranial hypertension (IIH) at diagnosis. *Neurol Sci.* (2013) 34 Suppl 1:S143–5. doi: 10.1007/s10072-013-1373-1
55. Sibony PA, Kupersmith MJ, Feldon SE, Wang J-K, Garvin M, Trial OSGftNIIHT. Retinal and choroidal folds in papilledema. *Invest Ophthalmol Vis Sci.* (2015) 56:5670–80. doi: 10.1167/iovs.15-17459
56. Kupersmith MJ, Sibony PA, Feldon SE, Wang JK, Garvin M, Kardon R. The effect of treatment of idiopathic intracranial hypertension on prevalence of retinal and choroidal folds. *Am J Ophthalmol.* (2017) 176:77–86. doi: 10.1016/j.ajo.2016.12.017
57. Moss HE, Vangipuram G, Shirazi Z, Shahidi M. Retinal vessel diameters change within 1 hour of intracranial pressure lowering. *Transl Vis Sci Technol.* (2018) 7:6. doi: 10.1167/tvst.7.2.6
58. Rougier M-B, Le Goff M, Korobelnik J-F. Optical coherence tomography angiography at the acute phase of optic disc edema. *Eye Vis.* (2018) 5:15. doi: 10.1186/s40662-018-0109-y
59. McHugh JA, D'Antona L, Toma AK, Bremner FD. Spontaneous venous pulsations detected with infrared videography. *J*

Neuroophthalmol. (2019) 40:174–77. doi: 10.1097/WNO.0000000000000815
60. D'Antona L, McHugh JA, Ricciardi F, Thorne LW, Matharu MS, Watkins LD, et al. Association of intracranial pressure and spontaneous retinal venous pulsation. *JAMA Neurology.* (2019) 76:1502–5. doi: 10.1001/jamaneurol.2019.2935
61. Hoffmann J. The utility of the lumbar puncture in idiopathic intracranial hypertension. *Cephalalgia.* (2018) 39:171–72. doi: 10.1177/0333102418787301

Conflict of Interest: JH is consulting for and/or serves on advisory boards of Allergan, Autonomic Technologies, Inc. (ATI), Chordate Medical AB, Eli Lilly, Hormosan Pharma, Novartis and Teva. He has received honoraria for speaking from Allergan, Chordate Medical AB, Novartis and Teva. He received personal fees for Medico-Legal Work as well as from Sage Publishing, Springer Healthcare and Quintessence Publishing.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 30 June 2020
doi: 10.3389/fneur.2020.00535

Understanding Cluster Headache Using Magnetic Resonance Imaging

Stefania Ferraro[1], *Anna Nigri*[1]*, *Greta Demichelis*[1], *Chiara Pinardi*[1], *Luisa Chiapparini*[1], *Luca Giani*[2], *Alberto Proietti Cecchini*[2] *and Massimo Leone*[2]

[1] Neuroradiology Department, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, [2] Neurology Department, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Cluster headache is an excruciating pain syndrome characterized by unilateral head pain attacks, lasting between 15 and 180 min, accompanied by marked ipsilateral cranial autonomic symptoms, such as lacrimation and conjunctival injection. Despite important insights provided by neuroimaging studies and deep brain stimulation findings, the pathophysiology of cluster headache and its pathways of chronicization are still elusive. In this mini-review, we will provide an overview of the functional and structural neuroimaging studies in episodic and chronic cluster headache conditions conducted to clarify the underlying pathophysiology.

OPEN ACCESS

Edited by:
Roberta Messina, Vita-Salute San Raffaele University, Italy

Reviewed by:
Lars Neeb, Charité—Universitätsmedizin Berlin, Germany
Aynur Özge, Mersin University, Turkey

***Correspondence:**
Anna Nigri
anna.nigri@istituto-besta.it

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: *21 November 2019*
Accepted: *14 May 2020*
Published: *30 June 2020*

Citation:
Ferraro S, Nigri A, Demichelis G, Pinardi C, Chiapparini L, Giani L, Proietti Cecchini A and Leone M (2020) Understanding Cluster Headache Using Magnetic Resonance Imaging. Front. Neurol. 11:535. doi: 10.3389/fneur.2020.00535

Keywords: cluster headache, resting-state fMRI, structural MRI, PET, DTI, hypothalamus

INTRODUCTION

The distinctive clinical characteristic of cluster headache (CH), in particular the recurrence of excruciating unilateral attacks accompanied by marked ipsilateral cranial autonomic symptoms in periods separated by the spontaneous remission (1), suggested specific brain networks involved in seasonal adaptation (2) to have a role in the pathophysiology of this disorder. Neuroimaging can track these functional and anatomical changes (3), irrespective if they are the cause of the disease or represent a brain adaptation/maladaptation to the painful condition.

Brain networks involved in different phases of CH, namely, the *in-bout* (out of attacks and during attacks) and *out-of-bout* phases, will be presented. We will describe and discuss resting-state functional magnetic resonance imaging (rs-fMRI), positron emission tomography (PET) and single-photon emission computed tomography (SPECT), structural MRI, and diffusion tensor imaging (DTI) studies. Due to the recognized importance of the hypothalamus in CH pathophysiology, first, we will present studies investigating the hypothalamic/midbrain tegmentum. Then, we will describe MRI/PE/SPECT studies focusing on other cerebral areas and DTI investigations.

SEARCH AND SELECTION OF STUDIES

We searched electronic databases PubMed and Google Scholar for articles published in English between January 1996 and December 2019 (see **Tables 1**, **2**). The search terms were: ("cluster headache") AND ("functional magnetic resonance imaging" OR "fMRI" OR "functional connectivity"); ("cluster headache") AND ("positron emission tomography" OR "PET" OR "single photon emission computed tomography" OR "SPECT" OR "cerebral blood flow"); ("cluster headache") AND ("gray matter" OR "voxel based morphometry" OR "VBM" OR "cortical thickness"); ("cluster headache") AND ("white matter" OR "diffusion tensor imaging" OR "DTI" OR "tractography"). We did not consider reviews and conference abstracts.

TABLE 1 | List of metabolic and functional studies on cluster headache.

Author(s)	Participants	Diagnosis: in/out of bout episodic, chronic	Whole brain/ROI analysis	Method	ROI coordinates	Aim/Hypothesis	Main results
Hseih et al. (4)	4 in-eCH, 3 out-eCH	in-eCH, out-eCH	Whole brain	[15(O)] Butanol-PET	-	To investigate the central processing of CH attacks provoked by sublingual NTG in in-eCH and out-eCH.	During CH attacks, decreased rCBF in prefrontal, posterior parietal and occipito-temporal cortex, while increased rCBF in right and rostro-caudal anterior cingulate cortex, temporo-polar cortex, supplementary motor area, bilaterally motor and premotor areas, opercular region, insula, putamen, and lateral inferior frontal cortex.
Di Piero et al. (5)	7 out-eCH, 12 HC	out-eCH	Whole brain	Xe-133-SPECT	-	To investigate the different patterns of activation of the structures involved in tonic pain perception in out-eCH patients.	Decreased CBF in controlateral primary sensory motor cortex and thalamus controlateral to pain side.
May et al. (3)	9 cCH, 8 out-eCH	out-eCH, cCH	Whole brain	$H_2^{15}O$-PET	-	To investigate changes in rCBF in cCH and out-eCH patients.	During CH attacks in cCH, significant activation was found in the ipsilateral inferior hypothalamic gray area (SPM MNI [−2, −18, −8]) with an additional increased rCBF in the thalamus, anterior cingulate cortex, and bilaterally in the insulae.
May et al. (6)	9 cCH, 8 out-eCH	out-eCH, cCH	Whole brain	$H_2^{15}O$-PET	-	To investigate the NTG-induced CH attacks in cCH and out-eCH patients.	Significant activations in acute pain state in the left insula and right inferior frontal cortex, around major basal vessels, and in the left (ipsilateral to the pain) hypothalamic gray area.
Sprenger et al. (7)	1 cCH	cCH	Whole brain	$H_2^{15}O$-PET	-	To investigate hypothalamic activation during a spontaneous CH attack in a cCH patient.	Increased activation in the ipsilateral inferior hypothalamus. Increased rCBF in the contralateral anterior cingulate cortex and the medial thalamus.
Sprenger et al. (8)	6 in-eCH, 1 cCH, 8 HC	in-eCH, cCH	Whole brain	[^{11}C] DPN-PET	-	To investigate if the pathophysiology of CH may relate to opioidergic dysfunction in biologic clock circuitries.	Reduced opioid receptor binding in the pineal gland in CH patient.
Sprenger et al. (9)	11 in-eCH (retested during out of bout), 11 HC	in-eCH, out-eCH	Whole brain	FDG-PET	-	To investigate alteration of brain metabolism in eCH patients in bout and out of bout.	eCH vs. HC showed a decreased metabolism in the prefrontal and orbitofrontal cortex and an increased FDG metabolism in the parietal lobe and postcentral gyrus. in-eCH vs. out-eCH presented increased metabolism in the anterior cingulate cortex, posterior cingulate cortex, orbitofrontal cortex including nucleus accumbens, ventrolateral and dorsolateral prefrontal cortex, and temporal cortex, while decreased metabolism in the bilateral cerebellopontine area was reported.
Morelli et al. (10)	4 in-eCH	in-eCH	Whole brain	rs-fMRI: GLM	-	To investigate the difference in cerebral activation in in-eCH patients between the pain state of a spontaneous headache attack and the pain-free state.	Each in-eCH patient showed significant activation in the ipsilateral hypothalamic area (Tal [−5, −8, −1]) in the comparison of the pain with the pain-free state. A trend of activation was also detected in the prefrontal cortex, cingulate cortex, insula, cerebellum, thalamus, and basal ganglia.
Rocca et al. (11)	13 out-eCH, 15 HC	out-eCH	Hypothalamus	rs-fMRI: SBA, ICA	5-mm sphere MNI [±2, −18, −8]*	To investigate thebrain resting-state networks abnormalities in eCH.	Out-eCH, compared to HC, presented increased FC in the thalamus and the hypothalamus and decreased fluctuations within primary visual and sensorimotor networks.

(Continued)

TABLE 1 | Continued

Author(s)	Participants	Diagnosis: in/out of bout episodic, chronic	Whole brain/ROI analysis	Method	ROI coordinates	Aim/Hypothesis	Main results
Morelli et al. (12)	1 cCH (pain state, pain-free state after 6 mg sumatriptan administration)	cCH	Whole brain	rs-fMRI: GLM	-	To investigate fMRI findings in a cCH patient during pain and pain-free state.	Significant activation in the ipsilateral hypothalamic area (Tal [−3, −3,−8]) and brainstem regions (ipsilateral trigeminal root entry zone, bilateral red nucleus, ventral pons) were reported in the pain compared with the pain-free state. Trends of activations also in the prefrontal cortex, cingulate cortex, insula, cerebellum, thalamus, and basal ganglia.
Qiu et al. (13)	12 in-eCH, 12 HC	in-eCH	Hypothalamus	rs-fMRI: SBA	6-mm sphere Tal [2, −18, −8]	To investigate the FC alteration of the hypothalamus "during attack" and "out of attack."	In-eCH, compared to HC, presented abnormal hypothalamic FC in the pain system during the spontaneous CH attacks. During CH attack, it extended beyond the pain system.
Yang et al. (14)	18 in-eCH, (retested during out of bout), 19 HC	in-eCH, out-eCH	Hypothalamus	rs-fMRI: SBA	4-mm sphere MNI [±4, −18, −8]	To investigate the resting-state FC of the hypothalamus in a group of eCH (scanned both in and out of bout) and compare them with HC.	eCH patients, in comparison to HC, presented hypothalamic FC changes with the medial frontal gyrus and occipital cuneus. in-eCH, compared to out-eCH, showed a decreased hypothalamic FC with the medial frontal gyrus, precuneus, and cerebellar areas. In all eCH, the number of annual bout correlated with hypothalamic FC in cerebellar regions.
Qiu et al. (15)	21 in-eCH, 21 HC	in-eCH	Hypothalamus	rs-fMRI: ICA	10-mm sphere MNI [±5, −18, −8]	To investigate if the FC of the hypothalamus and the salience network was altered during the remission state.	in-eCH, compared to HC, presented a decreased hypothalamus-salience network coactivation suggesting a possible role in the pathophysiology of the disorder.
Chou et al. (16)	17 in-eCH (retested during out of bout), 18 HC	in-eCH, out-eCH	Whole brain	rs-fMRI: ICA	-	To investigate the relationship between FC networks and the bout status.	All eCH (regardless of bout period), compared to HC, presented changes in FC in temporal, frontal, salience, default mode, somatosensory, dorsal attention, and visual networks. in-eCH, compared to out-eCH, presented FC changes in the frontal and dorsal attention networks. In all eCH, a lower FC in frontal network correlated with disease duration.
Faragò et al. (17)	17 out-eCH, 26 HC	out-eCH	Whole brain	rs-fMRI: ICA	-	To investigate the alteration of FC in out-eCH in order to find signatures of the increased excitability.	Out-eCH presented increased frequency-specific activity in the attention network ipsilateral to the headache side and in the contralateral cerebellar network.
Ferraro et al. (18)	17 cCH, 16 HC	cCH	Hypothalamus	rs-fMRI: SBA	Manual ROI: on coronal slices, 3 mm in the *y* direction, 7–10 mm posterior to the anterior commissure	To test the hypothesis of a defective FC between the posterior hypothalamus and diencephalic–mesencephalic regions in cCH.	cCH, compared to HC, showed increased FC between the ipsilateral posterior hypothalamus and a number of diencephalic–mesencephalic structures, comprising ventral tegmental area, dorsal nuclei of raphe, and bilateral substantia nigra, subthalamic nucleus, and red nucleus. No difference was found comparing the contralateral hypothalami.

In this table, we reported the regions as defined in the original manuscripts. ROI coordinates were reported as [x, y, z], unless otherwise noted. CH, cluster headache; in-eCH, in-bout episodic CH; out-eCH, out-of-bout episodic CH; cCH, chronic CH; HC, healthy controls; ROI, region of interest; SPECT, single-photon emission computed tomography; PET, positron emission tomography; FDG, ^{18}Fluoro-2-deoxy-D-glucose; NTG, nitroglycerin; [^{11}C]DPN, [^{11}C]diprenorphine; $H_2^{15}O$, 15O-labeled water; Xe-133, Xenon-133; CBF, cerebral blood flow; rCBF, regional cerebral blood flow; rs-fMRI, resting state functional magnetic resonance imaging; SBA, seed-based analysis; ICA, independent component analysis; FC, functional connectivity; Tal, Talairach coordinates; MNI, Montreal Neurological Institute. (*), May et al. (19) coordinates.

TABLE 2 | List of structural studies on cluster headache.

Author(s)	Participants	Diagnosis: in/out of bout episodic, chronic	Whole brain/ROI analysis	Method	ROI coordinates	Aim/Hypothesis	Main results
May et al. (19)	25 CH (14 active headache, 11 headache-free state), 29 HC	eCH, cCH	Whole brain	sMRI: VBM; PET	-	To investigate structural and functional metabolic brain alterations between CH patients and HC.	Colocalization of an increase in GM (SPM MNI [−4, −16, −10]) and functional activation (SPM MNI [−2, −18, −8]) ipsilateral to the pain side in the inferior posterior hypothalamus was identified in CH patients compared to HC. This structural alteration was also present when comparing patients during active headache and headache-free state with HC.
Matharu (20)	66 eCH, 96 HC	ND	Whole brain and hypothalamus	sMRI: VBM	-	To investigate structural brain alterations between eCH and HC.	No significant changes in GM and WM.
Owen et al. (21)	1 cCH, 13 HC	cCH	DBS-targeted region (hypothalamus)	DTI: probabilistic tractography	6 mm posterior, 2 mm lateral and 8 mm below the mid-commissural point*	To investigate the structural connectivity of the posterior inferior hypothalamus in HC, using coordinates derived from a patient implanted with a DBS electrode.	In the HC, the seed of the DBS target coordinates was connected with the medial lemniscus, ipsilateral fronto-orbital cortex, reticular nucleus, superior cerebellar peduncle, cerebellar cortex.
Teepker et al. (22)	1 in-eCH, 6 out-eCH, 7 HC	in-eCH, out-eCH	Whole brain	DTI: diffusivity maps	-	To investigate microstructural alterations in patients with eCH vs. HC.	Bilateral brainstem, internal capsule, superior/inferior temporal region, frontal lobe, occipital lobe, and right thalamus and cerebellum showed an altered WM microstructure in eCH patients compared to HC.
Absinta et al. (23)	15 out-eCH, 19 HC	out-eCH	Whole brain	sMRI: VBM; DTI: diffusivity maps	-	To investigate if the patterns of regional GM and WM alterations in out-eCH are confined to the hypothalamus or tend to be more widespread to the central nervous system.	A decrease in GM volume in several cortical and subcortical regions, part of the so-called "pain-matrix network," was reported in out-eCH patients vs. HC. A decrease in GM volume of left middle frontal gyrus significantly correlated with disease duration. No difference was found in WM between out-eCH and HC.
Seifert et al. (24)	12 out-eCH, 12 HC	out-eCH	Whole brain	sMRI: cortical thickness	-	To investigate cortical thickness abnormalities in out-eCH patients compared to HC. They expected changes in cortical thickness in pain-processing areas.	A reduction of cortical thickness in the angular gyrus and the precentral gyrus was shown in CH patients contralaterally to the headache side compared to HC. Cortical thickness in the primary sensory cortex correlated with disease duration.
Szabò et al. (25)	13 eCH, 16 HC	ND	Whole brain	DTI: diffusivity maps		To investigate WM microstructure in eCH patients with multiple diffusivity measures.	WM alterations in eCH compared to HC were found in frontal, parietal, temporal and occipital lobe, principally contralateral to the attack side.
Yang et al. (26)	49 in-eCH (12 retested during out bout period), 49 HC	in-eCH, out-eCH	Whole brain and hyphothalamus	sMRI: VBM, hyphotalamus (SVC)	MNI [−4, −16, −10]**	To investigate (1) if structural changes in in-CH patients are restricted to the hypothalamus or tend to be widespread to pain modulation regions; (2) longitudinal structural alterations of CH between in- and out-bout periods.	(1) A significant GM volume reduction in frontal pain modulation areas was reported in in-eCH and out-eCH patients compared with HC, while (2) a significant GM increase in the left anterior cingulate, insula, and fusiform gyrus was revealed in-eCH compared to out-eCH patients.

(Continued)

TABLE 2 | Continued

Author(s)	Participants	Diagnosis: in/out of bout episodic, chronic	Whole brain/ROI analysis	Method	ROI coordinates	Aim/Hypothesis	Main results
Chou et al. (27)	17 in-eCH (retested during out of bout), 17 HC	in-eCH, out-eCH	Whole brain for diffusivity maps, hypothalamus for tractography	DTI: diffusivity maps, probabilistic tractography	Hypothalamus (manual segmentation)	To investigate (1) WM alterations between in-eCH and out eCH and (2) the anatomical connections between the hypothalamus and brain areas with WM changes.	(1) Compared to HC, in-eCH showed significant differences in the right side in inferior and superior longitudinal fasciculus, anterior thalamic radiation. In out-eCH vs. HC, WM alterations were found in right inferior and superior longitudinal fasciculus, bilateral corpus callosum, and left cortico-spinal tract. Differences between in-eCH and out-eCH were present in the left cerebellum WM. (2) The ipsilateral hypothalamus showed projections with frontal and limbic areas and cerebellum.
Clelland et al. (28)	7 HC	-	DBS-targeted regions (midbrain tegmentum)	DTI: probabilistic tractography	From the midpoint of the AC-PC line [± 2, −3, −5]; [±2, −6, −8]; [±2.98, −3.53, −3.31]; [±4 mm from the 3rd ventricle wall, −2, −5]	To investigate the structural connectivity of efficacious DBS-targeted regions in HC in order to highlight anatomic connections that are involved in modulating CH attacks.	DBS target coordinates were located in the midbrain tegmentum gray matter. Common structural connections were found from DBS-targeted seeds to ipsilateral hypothalamus, ipsilateral reticular formation, and ipsilateral cerebellar cortex.
Naegel et al. (29)	46 out-eCH, 22 in-eCH, 23 cCH, 78 HC	in-eCH, out-eCH, cCH	Whole brain	sMRI: VBM	-	To investigate different GM change patterns corresponding to different stages of disease (in-eCH, out-eCH, cCH) in order to differentiate structural abnormalities associated with CH pathophysiology from changes related to the pain.	GM alterations (including also the temporal lobe, the hippocampus, the insular cortex, and the cerebellum) in the different stages of the disease were different for extension, location, and direction. Dynamic relation between pain vs. no-pain state was reported. No structural alterations in the hypothalamus were detected in CH patients compared to HC.
Akram et al. (30)	7 cCH	cCH	DBS-targeted regions (VTA)	-	DTI: probabilistic tractography	To investigate (1) the optimal DBS target in a sample of cCH and (2) structural connections pathway of this DBS target in responder patients.	(1) The target volume of responder DBS was located in the VTA (MNI [−4, −12, −8]), posterior to the hypothalamus in the ventral tegmentum; (2) in the responder group, this target showed a common pathway toward inferior-laterally to the amygdala and the temporal pole, anterosuperiorly to the prefrontal area and posteriorly to a dorsolateral position toward the trigeminal tract and nuclei.
Arkink et al. (31)	25 eCH, 27 cCH, 14 probable CH, 9 chronic paroxysmal hemicrania, 35 migraine, 48 HC	eCH, cCH	Whole brain and hypothalamus	sMRI: VBM, hypothalamus (SVC, manual segmentation)	MNI [(−12, 12), (6, −18), (0, −20)]	To investigate if (1) there are structural changes in the hypothalamus or other structural brain regions in eCH and cCH; (2) these changes are characteristic of CH or can also be found in other episodic headache disorders.	In comparison to HC, the anterior hypothalamus was enlarged in eCH, cCH, probable CH, and chronic paroxysmal hemicrania, but not in migraine. Widespread changes in pain modulation regions were reported in all patients with headache.

(Continued)

TABLE 2 | Continued

Author(s)	Participants	Diagnosis: in/out of bout episodic, chronic	Whole brain/ROI analysis	Method	ROI coordinates	Aim/Hypothesis	Main results
Kiraly et al. (32)	22 out-eCH, 94 HC	out-eCH	Subcortical nuclei	DTI: diffusivity maps (ROI analysis)	ROI from FSL MNI atlas	To investigate the GM alterations of the subcortical structures in out-eCH using diffusivity measures.	The subcortical gray nuclei microstructure was altered in eCH compared to HC in the bilateral amygdala, right caudate, and right pallidum.
Seijo-Fernandez et al. (33)	15 cCH, 11 HC	cCH	DBS-targeted region	DTI: deterministic and probabilistic tractography	4 mm lateral from the wall of the third ventricle, 2 mm behind and 5 mm below the intercommissural point	To investigate in HC subjects the structural connectivity of the mean target for DBS found in cCH patients.	In the HC, the structural connections between the stimulation target and posteriorly the cerebellar peduncle and the posterior mesencephalic tegmentum and anteriorly the frontal cortex and the forebrain were identified.
Giorgio et al. (34)	12 out-eCH, 13 migraine, 13 HC	out-eCH	Whole brain	sMRI: VBM; DTI: diffusivity maps; rs-fMRI: ICA, Network Analysis	-	To investigate structural and functional brain changes in out-CH compared to migraine patients and HC.	Out-eCH, compared to HC and migraine, showed decreased regional GM volume in the frontal cortex, higher short-range FC in networks involved in working memory and executive functions, while, when comparing them only to migraine, higher long-range FC in networks related to language processing were found. No differences in WM microstructure were reported.
Dantas et al. (35)	1 cCH	cCH	DBS-targeted region	DTI: deterministic tractography	1.5 mm lateral, 5 mm posterior, and 5 mm inferior relative to the midcommissural point	To investigate fiber tracts emerging from DBS target to explain the clinical effects of deep brain stimulation.	The fiber tracts projecting from the target region of DBS were the medial forebrain bundle, the dorsal longitudinal fasciculus, and the tracts connecting the hypothalamus to the brainstem.

In this table, we reported the regions as defined in the original manuscripts. ROI coordinates were reported as [x, y, z], unless otherwise noted. CH, cluster headache; in-eCH, in-bout episodic CH; out-eCH, out-of-bout episodic CH; cCH, chronic CH; HC, healthy controls; ND, not defined; ROI, region of interest; sMRI, structural magnetic resonance imaging; PET, positron emission tomography; DTI, diffusion tensor imaging; rs-fMRI, resting state functional magnetic resonance imaging; DBS, deep brain stimulation; GM, gray matter; WM, white matter; FC, functional connectivity; VBM, voxel-based morphometry; SVC, small volume correction; ICA, independent component analysis; AC-PC, anterior commissure–posterior commissure line; MNI, Montreal Neurological Institute; (*), Leone et al. (36) coordinates; (**), May et al. (19) coordinates.

NEUROIMAGING STUDIES INVESTIGATING THE HYPOTHALAMUS/MIDBRAIN TEGMENTUM

PET and rs-fMRI Studies

The circadian and circannual rhythmicity of attacks and neuroendocrinological findings pointed to hypothalamic involvement in the pathophysiology of the CH (2). In 1998, May et al., using PET, confirmed this hypothesis showing increased blood flow in the ipsilateral-to-the-pain posterior–inferior hypothalamus during nitroglycerin-induced attacks (3). This abnormal activity in the hypothalamus was considered to trigger the CH attacks because it was not observed in patients in *out-of-bout* phase who did not experience the attack under nitroglycerin (3). This seminal observation was confirmed by a subsequent PET study (6) and by a voxel-based morphometry study (19) showing hypothalamic volume abnormalities in CH patients (see the *Structural MRI studies* section). These results have opened the doors to hypothalamic deep brain stimulation (DBS) to successfully treat intractable chronic CH patients (36). Subsequently, the hypothesis of the hypothalamic involvement was supported by a single-case PET study (7) showing a metabolic activity during spontaneous attacks and by a ligand PET study showing opioidergic changes in the region identified by May et al. (3) in episodic CH patients during the *in-bout* phase (9).

More recently, the area reported as posterior–inferior hypothalamus by (3, 7, 19) has been suggested to localize in the midbrain tegmentum, possibly the ventral tegmental area (37, 38).

Despite this dispute, an fMRI study reported an evident activity in the ipsilateral-to-the pain hypothalamus during spontaneous attacks in a series of episodic CH patients (10). Importantly, this activity was not constrained by a region of interest approach centered on the results of the work of May et al. (3) but emerged using a whole-brain approach, reinforcing the hypothesis that the hypothalamus might play a role in CH. A paroxysmal activity during CH attacks in the red nuclei was also reported (12).

The observation that hypothalamic DBS in intractable chronic CH patients presents clinical effects after weeks of stimulation (39) and that it is not effective in terminating ongoing CH attacks (40) led us to hypothesize that the hypothalamus is a crucial region of a complex functional network that might disinhibit the hypothalamic–trigeminal pathway. In this new framework, the area reported by May et al. (3), hereafter "midbrain tegmentum" (37, 38), and the hypothalamus as such were investigated in a series of studies in CH patients using rs-fMRI to detect possible abnormalities in the functional connectivity (FC) of these regions.

The first study using rs-fMRI (11) showed that episodic CH patients have increased FC between the ipsilateral-to-the pain midbrain tegmentum and several regions known to be involved in pain processing, such as the anterior cingulate cortex, the bilateral secondary somatosensory cortex, the thalamus, and insula. Interestingly, abnormal FC was also observed between the midbrain tegmentum and striate and extra-striate visual regions, indicating the involvement of extra-pain-processing areas.

More recently, Qiu et al. (15) showed that episodic CH patients presented decreased bilateral midbrain tegmentum-salience network co-activation during the cluster period (*in-bout* phase). Previous works have shown that the dorsal anterior cingulate cortex and the fronto-insular cortex represent salient stimuli, such as hunger (41) and pain (42), and respond to emotional pain, such as during social rejection; in the seminal work of (43) these regions were appreciated with rs-fMRI as a robust functional network, namely, the salience network, also comprising subcortical structures such as thalamus, hypothalamus, and ventral tegmental area/substantia nigra. Seeley et al. (43) proposed that the relevant homeostatic stimuli, as sensory information, are integrated with visceral and autonomic functions, supporting a capital role of this network in pain processing. Based on this hypothesis (15), suggested that the bilateral midbrain tegmentum might play a role in the dysregulation of the salience network, in particular suggesting a defective pain control capable of generating CH attacks (15). The authors did not study CH patients *out-of-bout* phase: this does not allow one to make any inferences about the stability of this dysfunctional connectivity that might be dynamic (only during the *in-bout* phase) or a trait of CH patients. Notably, the same group showed that, in episodic CH patients investigated during attacks, the ipsilateral-to-the pain midbrain tegmentum presented abnormal dysfunctional connectivity with several cortical and subcortical areas (13). These areas comprised not only pain-processing regions but also extra-pain-processing areas. Notably, some of the identified areas (posterior cingulate cortex, inferior parietal lobule, ventral medial prefrontal cortex, and parahippocampal gyrus) belong to the default mode network.

Yang et al. (14) investigated for the first time the FC of the hypothalamus. They showed that, in accordance with its modulatory role, the hypothalamus is dynamically tuned, as it appears during the *in-bout* and the *out-of-bout* phases. During the *in-bout* phase, the ipsilateral-to-the pain hypothalamus presented, when compared to the *out-of-bout* phase, a decreased FC with the precuneus, a key region of the default mode network. This observation, with the results from the work of (13) during CH attacks, seems to confirm that dynamic alterations of the FC exist between the midbrain tegmentum/hypothalamus and regions belonging to the default mode network. Remarkably, the parasympathetic system is hypothesized to map onto the regions of the default mode network (44). Therefore, this dynamic dysregulation, present during the *in-bout* phase (13, 14), might indicate a parasympathetic dysfunction, possibly linked to the autonomic phenomena of CH. Further, Yang et al. (14) suggested that hypothalamic FC abnormalities in CH brain go beyond the pain matrix: when comparing patients *in-bout* vs. *out-of-bout* phase, the ipsilateral-to-the pain hypothalamus presented a decreased FC with the medial frontal gyrus and the cerebellar areas. These results seem to support dynamic alterations of hypothalamic FC in the disease. Moreover, the work of Yang et al. (14) showed that the annual bout frequency correlated

significantly with the degree of FC between the hypothalamus and the cerebellar areas, suggesting that this might be an effect of the CH pathophysiology (14).

It is important to note that dysfunctional connectivity between the posterior hypothalamic regions and the midbrain areas was observed in chronic CH patients out of attacks (18). The authors showed an increased FC between the ipsilateral posterior hypothalamus and several diencephalic–mesencephalic structures as the ventral tegmental area, the dorsal nuclei of raphe, and the bilateral substantia nigra, the subthalamic nucleus, and the red nucleus. These results suggest a deranged FC of the hypothalamic–midbrain pathway in CH mainly involving structures that are part of (i.e., ventral tegmental area, substantia nigra) or modulate (dorsal nuclei of raphe, subthalamic nucleus) the midbrain dopaminergic systems. The latter may have a role in the chronicization of CH. Future studies should address the question if this abnormality is specific to chronic CH or it is already presented, with a lesser extent, in episodic CH.

As a whole, the above results show that the paroxysmal functional hyperactivity in the hypothalamus/midbrain tegmentum during induced and spontaneous CH attacks (3, 7, 12) is a dynamic process that appears to involve, in particular, FC changes between the midbrain tegmentum and regions belonging to the default mode network (13). This might suggest a paroxysmal activity of the parasympathethic system.

During *in-bout* and *out-of-bout* phases, the hypothalamus/midbrain tegmentum presents FC changes with different regions of the salience network (15) and the default mode network (14), suggesting, respectively, defective pain control and parasympathethic dysfunction. Moreover, it is essential to note that abnormal FC between the midbrain tegmentum and pain and extra-pain-processing regions is also observed in *out-of-bout* phase (11). This might indicate the presence of stable deranged connectivity between the hypothalamus/midbrain tegmentum and those areas. However, the observation of Yang et al. seems to indicate that further FC abnormalities between the hypothalamus and extra-pain-processing areas might superimpose on the already present FC alterations during the *out-of-bout* phase (14).

Structural MRI Studies

The possible involvement of the region defined as inferior–posterior hypothalamus in the work of May et al. (3) during CH attacks was supported by a VBM study of the same group showing morphological alterations of this region in a relatively large cohort of episodic (*in-bout* and *out-of-bout phase*) or chronic CH patients (19).

Matharu in his PhD thesis (20) investigated a large sample of patients and analyzed the morphological data with updated software using also small volume correction in the region identified in the work of (3). Importantly, Matharu did not find volumetric abnormalities in this region and concluded that the previous VBM results (19) were false positive due to methodological limitations, possibly due to the susceptibility of the employed technique (VBM) to several confounders (45, 46).

In agreement, the VBM results from (3) were not replicated in subsequent morphological studies (23, 26, 47).

Despite these inconsistencies, a recent investigation showed an increased volume of the bilateral anterior hypothalamus of individuals with episodic (*out-of-bout*) and chronic CH but not in individuals with migraine (31). This study directly pointed to alterations of the suprachiasmatic nucleus, the site of the endogenous biological clock, and the paraventricular nucleus, both part of the anterior hypothalamus. Their abnormalities could explain the typical circadian rhythms of the recurrent attacks of CH, as well as some autonomic phenomena of the disease. These results confirm hypothalamic morphological alteration in episodic (in both *in-bout* and *out-of-bout*) and in chronic CH patients. It is important to note that possible dynamic morphological changes of the hypothalamus might have been underestimated due to the difficulties in investigating this relatively small structure with MRI.

NEUROIMAGING STUDIES INVESTIGATING PAIN-PROCESSING AREAS

PET/SPECT and rs-fMRI Studies

The excruciating nature of pain in CH led us to hypothesize a possible deficient top-down modulation of antinociceptive circuits (9). In line with this hypothesis, several works have shown functional alterations of the pain-processing areas. The first PET study on CH dated back to 1996: Hsieh et al. (4) found increased regional blood flow in the main cortical regions involved in pain processing (anterior cingulate cortex, insula cortex, and operculum) during induced CH attacks.

Decreased cerebral blood flow activity in controlateral primary sensory-motor cortex and thalamus was also described during the cold pressor test (5).

Metabolic alterations of several brain areas, comprising regions involved in pain processing, were also shown in episodic CH: during the *in-bout* phase, compared to the *out-of-bout* phase, increased metabolism was observed in the anterior and posterior cingulate cortex, prefrontal cortex, insula, thalamus, and temporal cortex, while a decreased metabolism in the cerebellopontine areas (9).

Alterations of the pain-processing pathways were also reported in rs-fMRI studies. Rocca et al. (11) reported reduced FC in the sensorimotor network in a group of episodic CH patients *out-of-bout.* Affected brain areas comprised the primary and secondary somatosensory area, the supplementary motor area, and the anterior cingulate cortex (11). These regions play a role in sensory discrimination and affective-cognitive processes evoked by painful conditions. Notably, the anterior cingulate cortex is part of the salience network (43, 48): alteration of the FC in this region reinforces the hypothesis of a strong involvement of this circuit in CH pathophysiology (15). These abnormalities were observed in *out-of-bout* phase, indicating stable brain alterations. Importantly, disease duration was negatively correlated with the strength of FC in the primary sensory-motor cortex, indicating that prolonged and severe painful condition may have induced those alterations.

FC alterations in the sensorimotor network were confirmed in another study in episodic CH, which reported abnormalities also in regions of the salience network (16). This study found no differences between the *in-bout* and *out-of-bout* phase, suggesting that the functional alterations in the sensorimotor and salience network could be a trait marker of CH.

As a whole, a dynamic dysregulation or adaptation in networks involved in pain processing and modulation of the parasympathetic activity, as suggested by functional abnormalities in regions of the default mode network (i.e., anterior cingulate cortex), seems to characterize CH patients. These functional alterations may represent a derangement of descending pain processing and autonomic pathways.

Structural MRI Studies

In patients with episodic CH during *out-of-bout* phase, volumetric alterations of the regions involved in pain processing such as thalamus, caudate nucleus, posterior cingulate cortex, prefrontal cortex, sensorimotor cortex, parietal cortex, insula, and middle temporal cortex have been reported (23, 34).

Notably, the chronic CH condition, compared to episodic CH, seems to be characterized by decreased gray matter in different regions of the pain matrix, i.e., anterior insula, cingulate cortex, secondary somatosensory cortex, hippocampus, left temporal lobe, and an increased gray matter in primary somatosensory cortex and supplementary motor cortex (47).

NEUROIMAGING STUDIES INVESTIGATING OTHER CORTICAL AND SUBCORTICAL AREAS

PET and rs-fMRI Studies

In a large group of episodic CH patients, functional alterations in the default mode network have been observed in both *in-bout* and *out-of-bout* phases of CH (16). This suggests that the default mode network is dysfunctional in episodic CH patients, possibly as a trait marker of CH.

Rocca et al. (11) and Chou et al. (16) consistently reported alterations in the FC of the visual network in CH patients: these abnormalities might be linked to photophobia and retro-orbital pain, frequently observed in CH (49). These abnormalities were observed in *in-bout* (16) and *out-of-bout* phase (11, 16) and were negatively correlated to disease duration, suggesting that they might be the consequence of a prolonged and severe pain condition.

In agreement with widespread alterations, dysfunctional connectivity within the attention network (in the ipsilateral superior frontal gyrus and medial frontal cortex) and the cerebellar network was observed (17) in episodic CH patients in the *out-of-bout* phase. Abnormal FC in temporal and visual networks irrespective of the illness phase was also present.

Structural MRI Studies

In VBM studies, volumetric gray matter alterations of the visual cortex (cuneus and occipital fusiform gyrus) have been observed (23, 34).

Volumetric alterations were observed by Naegel et al. in the temporal lobe, the hippocampus, the insular cortex, and the cerebellum in CH; (47) the location and direction of gray matter alterations varied according to the state of disease as well as to pain state (pain vs. no-pain). These dynamic changes may provide an explanation of the non-homogeneous results in previous VBM studies in pain.

DTI

DTI is an advanced MRI technique measuring water molecule diffusion: it allows one to study the integrity and architecture of the tissues through several parameters, such as fractional anisotropy or mean, axial, and radial diffusivity (50). These quantitative indices are sensible to microstructural brain tissue properties such as axon diameter, density and orientations, axon myelination, and membrane permeability (51). Studying the principal diffusion direction, it is also possible to reconstruct through tractography continuous white matter pathways of significant clusters of parallel axons (51).

In the last decade, DTI has been applied in a CH population using both quantitative indices, employing the abovementioned parameters, or tractography.

The studies using the quantitative approach showed different results in episodic CH patients. While some groups did not find any significant differences in diffusion parameters (23, 34) in the *out-of-bout* phase, others reported patterns of stable alterations (i.e., in both *in-bout* and *out-of-bout* phase) in the white matter, mainly localized in frontal and limbic lobes (27). Importantly, these regions were shown to present anatomical connections with the hypothalamus when using probabilistic tractography (27).

Gray matter microstructure abnormalities were also reported in several subcortical structures, in particular in the right amygdala, caudate, and globus pallidum (32).

Interestingly, an increased axial diffusivity in the left cerebellar white matter when comparing patients in the *in-bout* and *out-of-bout* phase was also reported (27).

Other quantitative studies, focused on relatively small cohorts of episodic CH patients, highlighted very widespread diffusion microstructural abnormalities in different white matter regions, encompassing mainly temporal, frontal, occipital, and cerebellar regions (22, 25).

Tractography studies were mainly focused on the anatomical connections of successful DBS targets in chronic CH patients in the effort to reveal the anatomical network responsible for the amelioration of the disorder. These studies confirmed the relevance, in CH pathophysiology, of the target-brainstem projections. Notably, different DBS targets were considered: inferior–posterior hypothalamus (21), midbrain tegmentum (28, 33), and ventral tegmental area (35, 52). In chronic CH patients, the structural connectivity of these regions also showed extended and relevant connections to pain-related areas, supporting the hypothesis of large pain matrix modulating CH attacks.

In particular, important anatomical connections were highlighted between the hypothalamus and the midbrain tegmentum, including the medial lemniscus, the dorsal

longitudinal and mamillo-tegmental fasciculi, the fronto-orbital cortex, the reticular shape, and the cerebellar cortex (21, 28, 33, 35).

In the case of DBS target stimulation in the VTA, further connections with the temporal cortex and brainstem areas in the proximity of the parabrachial nuclei, nucleus of the solitary tract, periaqueductal gray, and ending in the region of the trigeminal nucleus and tract and the superior salivatory nucleus were described (52). Despite these very interesting results, the small sample combined with heterogeneous inclusion criteria, the very different MRI sequences settings, and the different diffusion indices selection complicate the direct comparison between these works and may cause the observed discrepancy in particular in the results of quantitative diffusion analysis.

CONCLUSION

Notwithstanding the notable number of neuroimaging studies in CH, we are still far from fully understanding the brain mechanisms of this disorder. However, some, although tentative and not conclusive considerations, can be done. First of all, CH patients seem to present widespread FC and anatomical abnormalities across multiple networks and multiple cortical and subcortical areas, not only confined in regions involved in pain processing. This suggests that the CH brain is functionally and morphologically reorganized in a maladaptive or adaptive way. In particular, functional and anatomical abnormalities of cortical and subcortical areas involved in pain processing are consistently reported. In this perspective, the salience network seems to play a prominent role in CH pathophysiology: the here reviewed studies suggest that regions of this network presents a relatively stable functional alteration during the *in-bout* and the *out-of-bout* conditions (16). One can speculate that dysfunctional connectivity in the salience network might be the neural "tract" of the disease. Notably, alteration of the salience network suggests that CH patients present a dysfunctional ability to elaborate salient stimuli. In this regard, abnormalities of this network were observed in other chronic pain conditions, such as diabetic neuropathy (53), headache, (54, 55), and irritable bowel syndrome (56). This might indicate that the abnormalities in the salience network might predispose the chronification of CH. Importantly, disruption of the salience network has been reported in several neuropsychiatric conditions such as autism (57), schizophrenia (58), and addiction (59). Therefore, the observed alterations seem not to be specific to CH. Future studies should assess the role of this network in CH pathophysiology. Moreover, regions belonging to the default mode network seem to be abnormal in CH, irrespective of the phase (16). The parasympathetic system maps onto the default mode network (44), and this raises the possibility that default mode network alterations are consequences of the CH attacks. The default mode network plays a role in integrating sensory-visceromotor processing, self-referential activity, and recalling of previous experience (60). This might indicate that CH patients suffer a disturbance in the social–emotional spheres.

Second, supporting the above results, studies investigating the hypothalamic/midbrain tegmentum FC suggest a modulatory role of these structures within the salience network and the regions of the default mode network (15, 16).

Third, the abnormal FC between the hypothalamus and the midbrain dopaminergic system (in particular the ventral tegmental area) in chronic CH patients (18) suggests that the possible pathways of chronicization pass through the mesocorticolimbic system also in CH. It is now accepted that the midbrain dopaminergic system is also stimulated by aversive stimuli such as pain (61), and the nucleus accumbens, a key component of the mesocorticolimbic system receiving direct projections from the ventral tegmental area, seems to be involved in the chronicization of pain in humans (62–64). This possibility in CH is also fostered by the recent proposal of the ventral tegmental area as the main target of DBS (65) and by the observation that long-term DBS can revert chronic to episodic CH (66). It is important to note, however, that inhibition and facilitation of pain mechanisms were also suggested to be at the basis of the chronicization of the disease, as indicated by gray matter reorganization accordingly with the different pain states, possibly supported by highly dynamic changes in nociceptive and anti-nociceptive networks (29). Also, DBS in CH patients induces blood flow changes in the anterior cingulate, insula, and frontal lobe involved in pain chronicization (67).

Future studies should assess the validity of the above hypotheses clarifying the role of the hypothalamus/midbrain tegmentum in CH and chronic CH pathophysiology (68). Moreover, it would be of great interest to determine if the observed abnormalities in functional and anatomical networks are specific to CH or represent an unspecific response to pain.

AUTHOR CONTRIBUTIONS

SF, AN, GD, CP, LC, LG, and AP went through on literature and collected the articles. SF, AN, and ML wrote the manuscript. ML supervised all the steps of this minireview. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Italian Ministry of Health (research grant RF-2016-02364909).

REFERENCES

1. Headache Classification Comittee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia Int J headache*. (2018). 38:1–211. doi: 10.1177/0333102417738202
2. Leone M, Bussone G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. *Cephalalgia.* (1993) 13:309–17.
3. May A, Bahra A, Büchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. *Lancet.* (1998) 352:275–8. doi: 10.1016/S0140-6736(98)02470-2
4. Hsieh JC, Hannerz J, Ingvar M. Right-lateralised central processing for pain of nictoglycerin-inudced clustre headache. *Pain.* (1996) 67:59–68.
5. Di Piero V, Fiacco F, Tombari D, Pantano P. Tonic pain: a SPET study in normal subjects and cluster headache

patients. *Pain.* (1997) 70:185–91. doi: 10.1016/S0304-3959(96)03318-0
6. May A, Bahra A, Büchel C, Frackowiak RS, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. *Neurology.* (2000) 55:1328–35. doi: 10.1212/wnl.55.9.1328
7. Sprenger T, Boecker H, Tolle TR, Bussone G, May A, Leone M. Specific hypothalamic activation during a spontaneous cluster headache attack. *Neurology.* (2004) 62:516–7. doi: 10.1212/wnl.62.3.516
8. Sprenger T, Willoch F, Miederer M, Schindler F, Valet M, Berthele A, et al. Opioidergic changes in the pineal gland and hypothalamus in cluster headache: a ligand PET study. *Neurology.* (2006) 66:1108–10. doi: 10.1212/01.wnl.0000204225.15947.f8
9. Sprenger T, Ruether K V., Boecker H, et al. Altered metabolism in frontal brain circuits in cluster headache. *Cephalalgia Int J Headache.* (2007) 27:1033–42. doi: 10.1111/j.1468-2982.2007.01386.x
10. Morelli N, Rota E, Colombi D, Spallazzi M, Bodini FC, Marchesi G, et al. Functional magnetic resonance imaging in episodic cluster headache. *J Headache Pain.* (2009) 10:11–4. doi: 10.1007/s10194-008-0085-z
11. Rocca MA, Valsasina P, Absinta M, Colombo B, Barcella V, Falini A, et al. Central nervous system dysregulation extends beyond the pain-matrix network in cluster headache. *Cephalalgia.* (2010) 30:1383–91. doi: 10.1177/0333102410365164
12. Morelli N, Rota E, Gori S, Guidetti D, Michieletti E, De Simone R, et al. Brainstem activation in cluster headache: an adaptive behavioural response? *Cephalalgia.* (2013) 33:416–20. doi: 10.1177/0333102412474505
13. Qiu E, Wang Y, Ma L, Tian L, Liu R, Dong Z, et al. Abnormal brain functional connectivity of the hypothalamus in cluster headaches. Hou B, ed. *PLoS ONE.* (2013) 8:e57896. doi: 10.1371/journal.pone.0057896
14. Yang FC, Chou KH, Fuh JL, Lee PL, Lirng JF, Lin YY, et al. Altered hypothalamic functional connectivity in cluster headache: a longitudinal resting-state functional MRI study. *J Neurol Neurosurg Psychiatry.* (2015) 86:437–45. doi: 10.1136/jnnp-2014-308122
15. Qiu E, Tian L, Wang Y, Ma L, Yu S. Abnormal coactivation of the hypothalamus and salience network in patients with cluster headache. *Neurology.* (2015) 84:1402–8. doi: 10.1212/WNL.0000000000001442
16. Chou KH, Yang FC, Fuh JL, Kuo CY, Wang YH, Lirng JF, et al. Bout-associated intrinsic functional network changes in cluster headache: a longitudinal resting-state functional MRI study. *Cephalalgia.* (2017) 37:1152–63. doi: 10.1177/0333102416668657
17. Faragó P, Szabó N, Tóth E, Tuka B, Király A, Csete G, et al. Ipsilateral alteration of resting state activity suggests that cortical dysfunction contributes to the pathogenesis of cluster headache. *Brain Topogr.* (2017) 30:281–9. doi: 10.1007/s10548-016-0535-x
18. Ferraro S, Nigri A, Bruzzone MG, Brivio L, Proietti Cecchini A, Verri M, et al. Defective functional connectivity between posterior hypothalamus and regions of the diencephalic-mesencephalic junction in chronic cluster headache. *Cephalalgia.* (2018) 38:1910–8. doi: 10.1177/0333102418761048
19. May A, Ashburner J, Büchel C, McGonigle DJ, Friston KJ, Frackowiak RS, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med.* (1999) 5:836–8. doi: 10.1038/10561
20. Matharu MS. *Functional and structural neuroimaging in primary headache syndromes.* (PhD Thesis). London: Institute of Neurology, University of London (2006).
21. Owen SL, Green AL, Davies P, Stein JF, Aziz TZ, Behrens T, et al. Connectivity of an effective hypothalamic surgical target for cluster headache. *J Clin Neurosci.* (2007) 14:955–60. doi: 10.1016/j.jocn.2006.07.012
22. Teepker M, Menzler K, Belke M, Heverhagen JT, Voelker M, Mylius V, et al. Diffusion tensor imaging in episodic cluster headache. *Headache.* (2011) 52:274–82. doi: 10.1111/j.1526-4610.2011.02000.x
23. Absinta M, Rocca MA, Colombo B, Falini A, Comi G, Filippi M. Selective decreased grey matter volume of the pain-matrix network in cluster headache. *Cephalalgia.* (2012) 32:109–15. doi: 10.1177/0333102411431334
24. Seifert CL, Magon S, Staehle K, Zimmer C, Foerschler A, Radue EW, et al. A case-control study on cortical thickness in episodic cluster headache. *Headache.* (2012) 52:1362–8. doi: 10.1111/j.1526-4610.2012.02217.x
25. Szabó N, Kincses ZT, Párdutz Á, Tóth E, Szok D, Csete G, et al. White matter disintegration in cluster headache. *J Headache Pain.* (2013) 14:1–6. doi: 10.1186/1129-2377-14-64
26. Yang FC, Chou KH, Fuh JL, Huang CC, Lirng JF, Lin YY, et al. Altered gray matter volume in the frontal pain modulation network in patients with cluster headache. *Pain.* (2013) 154:801–7. doi: 10.1016/j.pain.2013.02.005
27. Chou KH, Yang FC, Fuh JL, Huang CC, Lirng JF, Lin YY, et al. Altered white matter microstructural connectivity in cluster headaches: a longitudinal diffusion tensor imaging study. *Cephalalgia.* (2014) 34:1040–52. doi: 10.1177/0333102414527649
28. Clelland CD, Zheng Z, Kim W, Bari A, Pouratian N. Common cerebral networks associated with distinct deep brain stimulation targets for cluster headache. *Cephalalgia.* (2014) 34:224–30. doi: 10.3851/IMP2701
29. Naegel S, Holle D, Desmarattes N, Theysohn N, Diener HC, Katsarava Z, et al. Cortical plasticity in episodic and chronic cluster headache. *NeuroImage Clin.* (2014) 6:415–23. doi: 10.1016/j.nicl.2014.10.003
30. Akram H, Miller S, Lagrata S, Hariz M, Ashburner J, Behrens T, et al. Optimal deep brain stimulation site and target connectivity for chronic cluster headache. *Neurology.* (2017) 89:2083–91. doi: 10.1212/WNL.0000000000005851
31. Arkink EB, Schmitz N, Schoonman GG, van Vliet JA, Haan J, van Buchem MA, et al. The anterior hypothalamus in cluster headache. *Cephalalgia.* (2016) 0:1–12. doi: 10.1177/0333102416660550
32. Király A, Szabó N, Párdutz Á, Tóth E, Tajti J, Csete G, et al. Macro- and microstructural alterations of the subcortical structures in episodic cluster headache. *Cephalalgia.* (2018) 38:662–73. doi: 10.1177/0333102417703762
33. Seijo-Fernandez F, Saiz A, Santamarta E, Nader L, Alvarez-Vega MA, Lozano B, et al. Long-term results of deep brain stimulation of the mamillotegmental fasciculus in chronic cluster headache. *Stereotact Funct Neurosurg.* (2018) 96:215–22. doi: 10.1159/000489937
34. Giorgio A, Lupi C, Zhang J, De Cesaris F, Alessandri M, Mortilla M, et al. Changes in grey matter volume and functional connectivity in cluster headache versus migraine. *Brain Imaging Behav.* (2019) 14:496–504. doi: 10.1007/s11682-019-00046-2
35. Dantas SAF, Alho EJL, da Silva JJ, Mendes Neto NN, Fonoff ET, Hamani C. Deep brain stimulation modulates hypothalamic-brainstem fibers in cluster headache: case report. *J Neurosurgey.* (2019) 11:1–4. doi: 10.3171/2018.11.JNS181412
36. Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. *N Engl J Med.* (2001) 345:1428–9. doi: 10.1056/NEJM200111083451915
37. Sánchez del Rio M, Alvarez Linera J. Functional neuroimaging of headaches. *Lancet Neurol.* (2004) 3:645–51. doi: 10.1016/S1474-4422(04)00904-4
38. Matharu MS, Zrinzo L. Deep brain stimulation in cluster headache: hypothalamus or midbrain tegmentum? *Curr Pain Headache Rep.* (2010) 14:151–9. doi: 10.1007/s11916-010-0099-5
39. Leone M, Franzini A, Broggi G, Bussone G. Hypothalamic stimulation for intractable cluster headache : Long-term experience. *Neurology.* (2006) 67:4–7. doi: 10.1212/01.wnl.0000223319.56699.8a
40. Leone M, Franzini A, Broggi G, Mea E, Cecchini AP, Bussone G. Acute hypothalamic stimulation and ongoing cluster. *Neurology.* (2006) 67:1844–5. doi: 10.1212/01.wnl.0000247273.93084.49
41. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci.* (2002) 3:655–66. doi: 10.1038/nrn894
42. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. *a* review and meta-analysis 2000. *Neurophysiol Clin Neurophysiol.* (2000) 30:263–88. doi: 10.1016/S0987-7053(00)00227-6
43. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci.* (2007) 27:2349–56. doi: 10.1523/JNEUROSCI.5587-06.2007
44. Beissner F, Meissner K, Bär KJ, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci.* (2013) 33:10503–11. doi: 10.1523/JNEUROSCI.1103-13.2013
45. Henley SM, Ridgway GR, Scahill RI, Klöppel S, Tabrizi SJ, Fox NC, et al. Pitfalls in the use of voxel-based morphometry as a

biomarker:examples from huntington. *AJNR Am J Neuroradiol.* (2010) 31:711–9. doi: 10.3174/ajnr.A1939
46. Ashburner J. Computational anatomy with the SPM software. *Magn Reson Imaging.* (2009) 27:1163–74. doi: 10.1016/j.mri.2009.01.006
47. Naegel S, Holle D, Obermann M. Structural imaging in cluster headache. *Curr Pain Headache Rep.* (2014) 18:415. doi: 10.1007/s11916-014-0415-6
48. Borsook D, Edwards R, Elman I, Becerra L, Levine J. Pain and Analgesia the value of the salience circuit. *Prog Neurobiol.* (2013) 104:93–105. doi: 10.1016/j.pneurobio.2013.02.003.Pain
49. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology.* (2002) 58:354–61. doi: 10.1212/wnl.58.3.354
50. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology.* (1996) 201:637–48. doi: 10.1148/radiology.201.3.8939209
51. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage.* (2013) 73:239–54. doi: 10.1016/j.neuroimage.2012.06.081
52. Akram H, Miller S, Lagrata S, Hyam J, Jahanshahi M, Hariz M, et al. Ventral tegmental area deep brain stimulation for refractory chronic cluster headache. *Neurology.* (2016) 86:1676–82. doi: 10.1212/WNL.0000000000002632
53. Cauda F, D' Agata F, Sacco K, Duca S, Cocito D, et al. Altered resting state attentional networks in diabetic neuropathic pain. *J Neurol Neurosurg Psychiatry.* (2010) 81:806–11. doi: 10.1136/jnnp.2009.188631
54. Eck J, Richter M, Straube T, Miltner WH, Weiss T. Affective brain regions are activated during the processing of pain-related words in migraine patients. *Pain.* (2011) 152:1104–13. doi: 10.1016/j.pain.2011.01.026
55. Maleki N, Becerra L, Borsook D. Migraine: maladaptive brain responses to stress. *Headache J Head Face Pain.* (2012) 52:102–6. doi: 10.1111/j.1526-4610.2012.02241.x
56. Elsenbruch S, Rosenberger C, Bingel U, Forsting M, Schedlowski M, Gizewski ER. Patients with irritable bowel syndrome have altered emotional modulation of neural responses to visceral stimuli. *Gastroenterology.* (2010) 139:1310–9. doi: 10.1053/j.gastro.2010.06.054
57. Uddin LQ. The self in autism: an emerging view from neuroimaging. *Neurocase.* (2011) 17:201–8. doi: 10.1080/13554794.2010.509320
58. Palaniyappan L, Simmonite M, White TP, Liddle EB, Liddle PF. Article neural primacy of the salience processing system in schizophrenia. *Neuron.* (2013) 79:814–28. doi: 10.1016/j.neuron.2013.06.027
59. Geng X, Hu Y, Gu H, Salmeron BJ, Adinoff B, Stein EA, et al. Salience and default mode network dysregulation in chronic cocaine users predict treatment outcome. *Brain.* (2017) 140:1513–24. doi: 10.1093/brain/awx036
60. Raichle ME. The brain's default mode network. *Annu Rev Neurosci.* (2015) 38:433–47. doi: 10.1146/annurev-neuro-071013-014030
61. Taylor AM, Becker S, Schweinhardt P, Cahill C. Mesolimbic dopamine signaling in acute and chronic pain. *Pain.* (2016) 157:1. doi: 10.1097/j.pain.0000000000000494
62. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci.* (2013) 15:1117–9. doi: 10.1038/nn.3153
63. Chang PC, Pollema-Mays SL, Centeno MV, Procissi D, Contini M, Baria AT, et al. Role of nucleus accumbens in neuropathic pain: linked multi-scale evidence in the rat transitioning to neuropathic pain. *Pain.* (2014) 155:1128–39. doi: 10.1016/j.pain.2014.02.019
64. Makary MM, Polosecki P, Cecchi GA, DeAraujo IE, Barron DS, Constable TR, et al. Loss of nucleus accumbens low-frequency fluctuations is a signature of chronic pain. *Proc Natl Acad Sci USA.* (2020) 117:10015–23. doi: 10.1073/pnas.1918682117
65. Miller S, Akram H, Lagrata S, Hariz M, Zrinzo L, Matharu M. Ventral tegmental area deep brain stimulation in refractory short-lasting unilateral neuralgiform headache attacks. *Brain.* (2016) 139:2631–40. doi: 10.1093/aww233
66. Leone M, Franzini A, Proietti Cecchini A, Bussone G. Success, failure, and putative mechanisms in hypothalamic stimulation for drug-resistant chronic cluster headache. *Pain.* (2013) 154:89–94. doi: 10.1016/j.pain.2012.09.011
67. May A, Leone M, Boecker H, Sprenger T, Juergens T, Bussone G, et al. Hypothalamic deep brain stimulation in positron emission tomography. *J Neurosci.* (2006) 26:3589–93. doi: 10.1523/jneurosci.4609-05.2006
68. May A, Schwedt TJ, Magis D, Pozo-rosich P, Evers S. Cluster headache. *Nat Publ Gr.* (2018) 4:1–7. doi: 10.1038/nrdp.2018.6

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership