Academic Journal of Neurology & Neurosurgery

Review

DOI: 10.51271/AJNN-0007

Is functional MRI meaningful in migraine?

Ruhsen Öcal, Merve Gürsoy Hasoğlan

Department of Neurology, Antalya Training and Research Hospital, University of Health Sciences, Antalya, Turkiye

Received: 02/04/2024 ◆ Accepted: 28/04/2024 ◆ Published: 30/04/2024

Cite this article: Öcal R, Gürsoy Hasoğlan M.Is functional MRI meaningful in migraine? *Acad J Neurol Neurosurg.* 2024;1(2):26-29.

Corresponding Author: Ruhsen Öcal, ruhsenocal@yahoo.com

ABSTRACT

Functional magnetic resonance imaging (fMRI) is an imaging method that enables us to understand brain anatomy, mapping and its function. While fMRI was previously used in experimental studies, it has now been used in clinical studies. Imaging in fMRI is based on measuring the increase in regional blood flow caused by cortical activation. fMRI indirectly demonstrates neural activation by detecting increases in oxygenation. fMRI relies on the sensitivity of magnetic resonance signals to changes in deoxyhemoglobin levels or perfusion, reflecting the metabolic and hemodynamic responses associated with neural activation. Imaging is arranged in the clinic for primary headaches if needed for a differential diagnosis. However, imaging studies are utilized in scientific research to elucidate the pathophysiology. Migraine is a common episodic disorder characterized by recurring attacks. Investigating the functional structure of the brain during both attack and interictal periods is crucial in understanding migraine pathology. However, capturing patients' migraine attacks for monitoring purposes without treatment is considered unethical in many countries. Moreover, conducting such studies is hindered by the requirement for prolonged hospital stays and extended imaging times, which significantly increase costs. Despite the challenges of conducting research in migraine patients, fMRI stands out as an excellent imaging method for investigating the functional brain structures involved in this episodic disorder. Several fMRI studies have yielded valuable insights into the pathophysiology of migraine. fMRI is believed to offer valuable guidance in refining our understanding of migraine-specific mechanisms, facilitating biomarker studies for migraine activity, and elucidating abnormal functions in regions affected by migraine. Monitoring treatment response using biomarkers is anticipated to be an effective tool for identifying targets for migraine treatment, including assessing treatment efficacy in the development of new migraine-specific therapies.

Keywords: Migraine, functional magnetic resonance imaging, pathophysiology

INTRODUCTION

The function of the brain and the mapping of these functions are fundamental topics in neuroscience.Traditional electrophysiological methods such as electroencephalography (EEG), electrocorticography (ECoG), and invasive EEG can illuminate the temporal dimension of brain functions, but only a rough idea can be obtained about neural localization. The cortex has high spatial complexity; the spatial resolution of surface EEG is weak, and the resolution of invasive electrodes is high but risky. Magnetoencephalographic methods combine the superior temporal resolution of EEG with high spatial resolution. However, due to being outside the skull, the sub-centimeter 5 mm and millisecond-level 1 ms temporal resolution include projection errors. The ability to record deep sources is limited. Nuclear imaging methods indirectly reveal regional blood flow, regional metabolic activities, and brain activation. Although SPECT and PET can sometimes be combined with computerized tomography (CT) and magnetic resonance imaging (MRI), the disadvantage of these techniques is the use of radioactive substances as biomarkers. They are not suitable for studies with healthy control groups and repetitive scientific studies but are suitable for experimental designs.[1]

As for Functional MRI (fMRI), this technique is a method that reveals brain anatomy with excellent spatial resolution. The combination of high spatial resolution with high temporal resolution has made brain mapping possible. fMRI not only allows the localization of simple sensory-motor activations but also enables the localization of cognitive processes. Cortical activation mapping is achieved by obtaining physiological data through non-invasive methods.[2] Since the year 2000, fMRI has transitioned from an

experimental method to being used in clinical studies. Being the most powerful tool used in mapping neural activities of the human brain, functional MRI (fMRI), was first studied in healthy individuals in areas such as vision, motor function, language, memory, emotion, and pain. Subsequently, studies have been conducted on conditions including stroke, epilepsy, multiple sclerosis, psychiatric disorders, and migraine, and it is used before brain surgery operations.[3] Initially, exogenous biomarkers were administered, and the temporal changes in their concentrations in the brain were recorded. The rate and amount of concentration change were then used to calculate regional cerebral blood flow, an indirect indicator of neural activation.

When it was discovered that endogenous deoxy-Hb could be used as a biomarker, the use of exogenous biomarkers was abandoned. Other blood spins have endogenous techniques, but they are not used due to their simpler mechanism and lower temporal resolution. Cortical activation leads to an increase in regional cerebral blood flow. With fMRI, the increase in oxygenation is detected, indirectly revealing neural activation. Regions with oxygen increase are seen as bright areas in structural images, and this method is called blood oxygen level-dependent enhancement (BOLD). Oxyhemoglobin is diamagnetic for biological tissues, so it does not affect the signal from the tissue. Deoxyhemoglobin, on the other hand, is paramagnetic, shortening the magnetic relaxation time and changing the signal intensity. In areas of brain activation, oxygen consumption rate increases. Oxyhemoglobin increases in active areas, while deoxyhemoglobin decreases. Thus, by detecting both the brain regions and the differences in activity within these regions during a mental task, various activation patterns associated with different functions in the brain can be identified.[4] In summary, fMRI is structured on the fact that magnetic resonance signals are sensitive to deoxyhemoglobin or perfusion changes that accompany metabolic and hemodynamic responses resulting from neural activation. Various brain functions such as motor, speech, and vision can be evaluated by assigning tasks. Increased activity in neurons undergoing activation leads to higher energy demands due to activities such as neurotransmitter release, action potential transmission, and maintaining ion balance, enabling functional imaging of the brain regions involved in performing the given task through increased blood flow. Resting State fMRI method is used for brain mapping obtained at rest, without being assigned a task. With this technique, networks are displayed, and connectomes are analyzed.[5]

In clinical practice, imaging is used for differential diagnosis in primary headaches, while in scientific studies, it is used to elucidate the pathophysiology. For this purpose, transcranial magnetic stimulation, PET, and increasingly, fMRI are being utilized. MRI is the preferred imaging modality due to its high resolution, low cost, lack of radiation, and repeatability for studies.[6,7]

The use of fMRI in the field of migraine has provided data for illuminating the pathophysiology of this condition. It has contributed to better defining specific mechanisms of migraine, conducting biomarker studies for migraine activity, and shedding light on atypical functions in regions exhibiting abnormal function in migraine. It is believed that fMRI can be an effective tool in studies aimed at determining targets for migraine treatment, such as imaging treatment response with biomarkers and developing new migraine-specific treatments based on treatment response.[8]

International Classification of Headache Disorders (3rd edition) defines migraine as a disorder consisting of five phases: asymptomatic period, prodromal period, aura period, headache period, and postdromal period. In functional imaging studies, three of these phases—asymptomatic, prodromal, and postdromal—are defined as the "interictal period," while aura and headache are defined as the "ictal period." In brain imaging studies with functional MRI, two types of fMRI have been used in migraine: Task-based fMRI and Resting-state fMRI. Both receive BOLD signals. 3D images of the brain are structured with voxels called small cubes.[8,9]

Task-based fMRI evaluates the activity of specific brain regions stimulated by an external stimulus. Visual rotating checkerboard or intranasal trigeminal stimulation can be used as stimuli. Increased BOLD signal indicates increased neuronal activity, while decreased signal indicates decreased activity. The obtained results are sometimes compared with those obtained from healthy controls and sometimes with the patient's interictal period.[9]

Resting-state fMRI, typically conducted while the patient lies in the scanner with eyes closed and no external stimuli, aims to capture brain activity during rest. Specific anatomical information is predefined, and BOLD signals from two brain regions showing synchronization are functionally connected areas. Increased synchronization in the frequency of BOLD signal indicates increased functional connectivity in the given network, while a decrease indicates decreased functional connectivity.[9]

FUNCTIONAL MRI STUDY DESIGN AT MIGRAINE

Three main study models have been used to conduct fMRI in migraine. The first two are designed as case-control models, where asymptomatic (or rarely headache-prone) migraine patients are tested with fMRI on a headache-free day and during an attack, compared with healthy controls. The third model involves evaluating migraine by provoking it. In this model, typical prodromal, aura, and headache stages in the same patient are compared with the asymptomatic phase of the same patient. Many studies have been conducted using agents such as nitroglycerin, CGRP, and PACAP in this model. Additionally, this model can be used to investigate the side effects of drugs and their effects on brain functions.[10-13]

Most studies have been conducted during the asymptomatic phase. The absence of pain that would prevent patient participation has made imaging and studies most feasible. Numerous studies during the asymptomatic phase have shown functional reorganization at both cortical and subcortical levels contributing to abnormal sensory processes in migraine patients using fMRI.[14] Functional changes observed during the asymptomatic phase have been thought to represent the characteristics of the brain that predispose

individuals to migraine. These changes have been primarily observed in the thalamus, periaqueductal gray matter, insula, somatosensory, prefrontal, and anterior cingulate cortex, and it is accepted that they cause disorders in the processing of pain sensory, emotional and cognitive perspectives.[15,16]

Moreover,abnormalities in visual processing and hyperexcitability in the visual cortex have been detected in migraine patients in fMRI and PET studies conducted during the asymptomatic phase.[17,18]

In the literature, there are also studies in which no functional differences were found during the asymptomatic phase. This might be explained by factors such as the clinical characteristics of patients, groups with low frequency of pain, or short-duration disease. Additionally, it is suggested that functional interactions between brain regions involved in pain and visual function may develop over time.[19]

IMAGING DURING THE PRODROMAL PHASE AND EARLY ATTACK PHASE

Complaints such as yawning, difficulty concentrating, and pallor described by patients before the onset of headache are now accepted as indicative of a prodromal phase of migraine. Studies examining this period are limited. In a recent study where Pituitary Adenylate Cyclase-Activating Polypeptide-38 (PACAP38) and Vasoactive Intestinal Peptide (VIP) were used as triggers, the early stage of migraine attack was investigated. Disturbances, particularly between the somatosensory and visual cortices, were found during the prodromal period in patients triggered by PACAP38. Another study on the prodromal phase, where headache was triggered by glyceryl trinitrate, showed changes in hypothalamic activity.[20,21]

IMAGING DURING THE AURA PHASE

Aura, the shortest phase of migraine, is therefore a challenging area for neuroimaging studies. This phase, which rapidly begins and concludes within minutes, can manifest as typical positive visual disturbances (scintillation) or negative visual disturbances (scotoma), and in some patients, sensory symptoms may follow visual symptoms. Imaging was performed before, during, and after visual aura onset. One of the most important results obtained from this study was perhaps the pattern of spread of the BOLD response, which supported the cortical spreading depression theory. The first observed BOLD changes in the extrastriate cortex, an increase and subsequent decrease in cerebral blood flow, were consistent with the findings of the study conducted by Lauritzen et al.[22] using SPECT.

IMAGING DURING HEADACHE

Headache, typically lasting 4-72 hours with moderate to mild intensity and accompanied by nausea and photophobia, is a typical example of migraine. Imaging during headache is a challenging phase to study because it would require depriving the patient of treatment.[23] In a study evaluating nine patients with task-based functional MRI imaging methods for 30 days, changes in hypothalamic excitability were investigated, but no significant results were obtained. However, another resting-state fMRI study found changes in right thalamocortical connections.[24] In another study examining migraine headache triggered by GTN, a significant relationship between the somatosensory cortex and pons was found during the headache phase.[25]

IMAGING DURING THE POSTDROMAL PHASE

Symptoms vary widely, but some migraine patients describe postdromal complaints such as difficulty concentrating, neck pain, and fatigue after the headache. Conducting studies during this phase is ethically challenging as the duration is undefined and treatment may still be required, similar to the headache phase. It is known that this phase lasts less than 6 hours in 50% of patients. In a study focusing only on hypothalamic changes during the postdromal phase, it was found that the response to pain stimuli in the visual cortex was higher than during the headache phase.[26]

Only one study examined a patient during the postdromal phase using resting-state fMRI, but no difference was found compared to the asymptomatic phase. Hyperexcitability was also observed in the visual cortex [24] hours after the pain subsided, and it was interpreted that these findings could explain the continued light sensitivity in some patients after the pain has resolved.[27]

MIGRAINE FMRI: CONTRIBUTIONS AND POTENTIAL

In studies involving sensory stimuli, atypical responses of the migraine brain, the lack of expected normal habituation response between attacks, and atypical functional connections in sensory processing are recognized as established migraine pathophysiological features.[28]

In individuals with visual aura migraines, disruptions in cognitive and limbic connections, abnormal function in the visual cortex, marked light sensitivity, and involvement of the brainstem and hypothalamus at the onset of attacks have been demonstrated.[29]

The anterior insula plays a significant role, particularly in migraines with aura, in autonomic and sensory functions. This region, which controls cardiovascular parasympathetic tone, may be related to the cardiovascular features of migraine.[30]

Transcutaneous vagus nerve stimulation has been shown to modulate the thalamocortical pathway in migraine patients, emphasizing the role of fMRI in developing and testing treatment options.[31]

CONCLUSION

Despite the lack of an optimal method for fMRI studies and the weak statistical power based on the small number of patients, these studies have facilitated our understanding of many pathophysiologies in migraine. As prospective models of these studies increase over time, which enables to identification of specific markers for migraine and

determining target points for treatment, it is believed that they may shed light on the pathophysiology of migraine, which ranks high in terms of disability.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceed Nat Acad Sci.* 1992;89(13):5951-5955. doi: 10.1073/pnas.89.13.5951
2. Calautti C, Baron JC. Functional neuroimaging studies of motor recovery after stroke in adults: *a review. Stroke.* 2003;34(6):1553-1566. doi: 10.1161/01.STR.0000071761.36075.A6
3. Ashtari M, Perrine K, Elbaz R, et al. Mapping the functional anatomy of sentence comprehension and application to presurgical evaluation of patients with brain tumor. *Am J Neuroradiol.* 2005;26(6):1461-1468.
4. Bandettini PA. Twenty years of functional MRI: the science and the stories. *Neuroimage.* 2012;62(2):575-588. doi: 10.1016/j.neuroimage.2012.04.026
5. Murphy K, Birn RM, Bandettini PA. Resting-state fMRI confounds and cleanup. *Neuroimage.* 2013;80:349-359. doi:10.1016/j.neuroimage.2013.04.001
6. Dodick DW, Schembri CT, Helmuth M, Aurora SK. Transcranial magnetic stimulation for migraine: a safety review. *Headache: J Head Face Pain.* 2010;50(7):1153-1163. doi:10.1111/j.1526-4610.2010.01697.x
7. Chiapparini L, Ferraro S, Grazzi L, Bussone G. Neuroimaging in chronic migraine. *Neurologic Sci.* 2010;31(S1):19-22. doi: 10.1007/s10072-010-0266-9
8. Schwedt TJ, Chong CD. Functional imaging and migraine. *Curr Opin Neurol.* 2015;28(3):265-270. doi: 10.1097/WCO.0000000000000194
9. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia.* 2013;33(9):629-808. doi: 10.1177/0333102413485658
10. Ashina M, Hansen JM, á Dunga BO, Olesen J. Human models of migraine — short-term pain for long-term gain. *Nat Rev Neurol.* 2017;13(12):713-724. doi: 10.1038/nrneurol.2017.137
11. Schoonman GG, van der Grond J, Kortmann C, van der Geest RJ, Terwindt GM, Ferrari MD. Migraine headache is not associated with cerebral or meningeal vasodilatation—a 3T magnetic resonance angiography study. *Brain.* 2008;131(8):2192-2200. doi: 10.1093/brain/awn094
12. Ashina M, Hansen JM, Olesen J. Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience. *Cephalalgia.* 2013;33(8):540-553. doi: 10.1177/0333102412475234
13. Karsan N., Goadsby PJ. Imaging the premonitory phase of migraine. *Frontiers Neurol.* 2020,11:512238.
14. Skorobogatykh K, van Hoogstraten WS, Degan D, et al. Functional connectivity studies in migraine: what have we learned? *J Headache Pain.* 2019;20(1):108. doi: 10.1186/s10194-019-1047-3
15. Chen Z, Chen X, Liu M, Dong Z, Ma L, Yu S. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. *J Headache Pain.* 2017;18(1):7. doi: 10.1186/s10194-017-0722-5
16. Mainero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol.* 2011;70(5):838-845. doi: 10.1002/ana.22537
17. 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(9):978-984. doi: 10.1136/jnnp.2009.190223
18. Arngrim N, Hougaard A, Ahmadi K, et al. Heterogenous migraine aura symptoms correlate with visual cortex functional magnetic resonance imaging responses. *Ann Neurol.* 2017;82(6):925-939. doi: 10.1002/ana.25096
19. Hougaard A, Amin FM, Magon S, Sprenger T, Rostrup E, Ashina M. No abnormalities of intrinsic brain connectivity in the interictal phase of migraine with aura. *Eur J Neurol.* 2015;22(4):702. doi: 10.1111/ene.12636
20. Amin FM, Hougaard A, Magon S, et al. Change in brain network connectivity during PACAP38-induced migraine attacks. *Neurol.* 2016;86(2):180-187. doi: 10.1212/WNL.0000000000002261
21. Van Oosterhout WPJ, van Opstal AM, Schoonman GG, et al. Hypothalamic functional MRI activity in the initiation phase of spontaneous and glyceryl trinitrate-induced migraine attacks. *Eur J Neurosci.* 2021;54(3):5189-5202. doi: 10.1111/ejn.15369
22. Lauritzen M, Olesen J. Regional cerebral blood flow during migraine attacks by xenon-133 inhalation and emission tomography. *Brain.* 1984;107(2):447-461. doi: 10.1093/brain/107.2.447
23. Schulte LH, Menz MM, Haaker J, May A. The migraineur's brain networks: continuous resting state fMRI over 30 days. *Cephalalgia.* 2020;40(14):1614-1621. doi: 10.1177/0333102420951465
24. Qin ZX, Su JJ, He XW, et al. Altered resting-state functional connectivity between subregions in the thalamus and cortex in migraine without aura. *Eur J Neurol.* 2020;27(11):2233-2241. doi: 10.1111/ene.14411
25. Hougaard A, Amin FM, Larsson HBW, Rostrup E, Ashina M. Increased intrinsic brain connectivity between pons and somatosensory cortex during attacks of migraine with aura. *Hum Brain Mapp.* 2017;38(5):2635-2642. doi: 10.1002/hbm.23548
26. Schulte LH, Mehnert J, May A. Longitudinal neuroimaging over 30 days: temporal characteristics of migraine. *Ann Neurol.* 2020;87(4):646-651. doi: 10.1002/ana.25697
27. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain.* 2016;139(7):1987-1993. doi: 10.1093/brain/aww097
28. Messina R, Gollion C, Christensen RH, Amin FM. Functional MRI in migraine. *Curr Opin Neurol.* 2022;35(3):328-335. doi: 10.1097/WCO.0000000000001060
29. Russo A, Silvestro M, Tedeschi G, Tessitore A. Physiopathology of migraine: what have we learned from functional imaging? *Curr Neurol Neurosci Rep.* 2017;17(12):95. doi: 10.1007/s11910-017-0803-5
30. Gollion C, Lerebours F, Nemmi F, et al. Insular functional connectivity in migraine with aura. *J Headache Pain.* 2022;23(1):106. doi: 10.1186/s10194-022-01473-1
31. Zhang Y, Liu J, Li H, et al. Transcutaneous auricular vagus nerve stimulation at 1 Hz modulates locus coeruleus activity and resting state functional connectivity in patients with migraine: an fMRI study. *Neuroimage Clin.* 2019;24:101971. doi: 10.1016/j.nicl.2019.101971