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The role of functional magnetic resonance imaging in clinically diagnosed cases of migraine

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ABSTRACT

Background: Migraine manifests as recurrent headaches associated with nausea, vomiting, and sensory hypersensitivity. Functional magnetic resonance imaging (fMRI) images activation in different parts of brain either on stimulation or at rest. **Aims and Objectives:** The aim of the study was to study the fMRI changes in brain in response to visual stimulation in migraine patients with and without aura compared with healthy volunteers. **Materials and Methods:** A prospective fMRI study was performed in 50 clinically diagnosed cases of migraine and 50 healthy volunteers above 18 years of age on a 3-Tesla MRI scanner. For fMRI, the visual stimulus was presented as a moving black and white checker board pattern. **Results:** All subjects demonstrated activation in bilateral occipital cortex (predominantly in V1 followed by V2 area). Group analysis of the occipital activation pattern in migraine patients versus control revealed that 56% (28/50) showed significantly increased activation in occipital cortex, 20% (10/50) revealed no significant difference in activation patterns, and 24% of total migraine patients (12/50) had equivocal results. Out of the 28 patients with increased activation in occipital cortex, 14 (50%) revealed increased activation in the left V5 cortex, 8 (28.5%) increased activation in the left V3 cortex, 4 (14.2%) increased activation in both left V3 and V5 cortex, and 2 (7.1%) had increased activation in both right V3 and right V5 areas. **Conclusion:** The current study revealed increased occipital stimulation mainly in the left V3 and V5 areas in clinically diagnosed cases of migraine in comparison to normal healthy subjects. The study also revealed clinically significant association between increased occipital stimulation and duration of migraine and absence of pharmacological aid.

Key words: Migraine; Functional; Stimulation; Occipital; Visual; Activation

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INTRODUCTION

Migraine is a kind of primary headache. It manifests as recurrent headaches associated with moderate to severe pulsating pain, vertigo, dizziness, sensory hypersensitivity, nausea, and vomiting. Despite the recent advances, the neural and vascular mechanisms causing migraine still incompletely understood. However, in the past few years discoveries in non-conventional neuroimaging techniques have broadened our understanding of migraine pathophysiology.

Functional magnetic resonance imaging (fMRI) uses MRI to view activation in different areas of brain tissue that is caused by either asking the subject to perform a particular task (task based fMRI) or it can occur spontaneously while the subject is at rest, not thinking anything consciously ("resting state fMRI).[1]

This technique works on blood oxygenation level dependent (BOLD) changes in brain tissue. The magnitude of BOLD signal is determined by regional cerebral blood flow, regional cerebral blood volume, and amount of oxygenation of the regional blood. The BOLD signal is an indirect measure of neuronal activity in a particular region.[1]

On neural activation in a region, oxygen consumption in that region increases along with increase in the regional blood flow. This leads to an increase in the ratio of oxyhemoglobin to deoxyhemoglobin which causes an increase in magnetic resonance (MR) signal compared

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to that of the surrounding tissue. Deoxyhemoglobin is paramagnetic while oxyhemoglobin is diamagnetic, these differential magnetic properties of hemoglobin are utilized to generate MR signal which denotes neural activity changes through this hemodynamically driven process.[1]

Studies done previously revealed hyper responsiveness in the visual cortex in patients of migraine. Additional stimulation in the red nucleus and substantia nigra was also noted which suggested that these brainstem structures are a part of the neuronal network activated during an attack of migraine.

Since, diagnosis of migraine has classically been based on clinical evaluation and the discretion of the treating physician, use of fMRI to objectively diagnose a primary headache as migraine will help improve the lives of millions of patients suffering from migraine, by providing confirmatory diagnosis, guide accurate therapeutic interventions, and monitor progress.

The aim of our research was to study the fMRI changes in brain in response to visual stimulation in migraine patients with and without aura compared with healthy volunteers.

Aims and objectives

To study the functional MRI changes in brain in response to visual stimulation in migraine patients with and without aura compared with healthy volunteers.

MATERIALS AND METHODS

The study was conducted as a prospective observational study at our department from August 2019 to July 2021. 50 clinically diagnosed cases of migraine more than 18 years of age in ictal phase of headache, inter-ictal period were included in the study. Cases <18 years of age and known cases of brain surgery, cerebrovascular accidents, brain tumors, brain infections, and congenital abnormalities in the brain were not included in the study. 50 healthy volunteers were also included in the study to act as controls.

- Informed and written consent was obtained from all cases and controls
- Institutional Ethical Committee clearance was obtained before the start of study
- Data were collected from the subjects on a pretested pro forma.

MRI examination was performed using on a 3-Tesla MRI scanner (Magnetom Vida Siemens Healthineers, Erlangen, Germany) using an 64 channel head and neck coil.

A three-dimensional T1 Weighted whole brain dataset was acquired. For the BOLD fMRI scan, aT2*w echo planar imaging sequence was used.

For fMRI, the stimulus was presented as a moving black and white checker board pattern with the use of the "Telemed medical system" (Istanbul, Turkey) through a liquid crystal display screen attached to the MRI head coil.

The task was a type of block design wherein 60 phases were taken-30 active, 30 passive. There was alternation of active and passive phases each comprising 56 s.

The subjects were instructed to look at the display screen during the entire scan. They were asked not to close their eyes or fall asleep during the examination. They were also instructed to avoid any kind of motion of body parts. No other additional stimulus was given to avoid any unrelated effects on response.

Data pre-processing and processing were performed using Syngo-Via -XA.20/Neuro workflow software. Pre-processing included 3D motion correction, slice scan time correction, linear trend removal, and spatial smoothing was automatically done by the above mentioned software. Colored maps depicting stimulation were acquired and assessed qualitatively. Statistical analysis was done using Win Pepi software using tests of statistical significance such as Chi-square test and Fischer-P test

RESULTS

In our study, we obtained fMRI on visual stimulation in 50 clinically diagnosed cases (13 males [26%] and 37 females [74%]) of migraine and 50 asymptomatic volunteers (22 males [44%] and 28 females [56%]) of ages between 18 and 66 years (mean age 32.54 years) among cases, and 19–65 (mean age 35.3 years) among controls.

All patients presented with complaints of throbbing headache - 18% right, 16% was left sided, and 66% was holocranial. They had associated complaints of nausea, vomiting, vertigo, phonophobia and photophobia, maximum number of patients (36%) suffered from migraine from duration of 6 months–1 years with an average of 3 attacks per month (46% patients). Most of the patients (74%) were not on any medications for migraine.

All subjects demonstrated activation in bilateral occipital cortex (predominantly in V1 followed by V2 area). Group analysis of the occipital activation pattern in migraine patients versus control revealed that 56% (28/50) showed significantly increased activation in occipital cortex, 20% (10/50) revealed no significant difference in activation patterns, 24% of total migraine patients (12/50) had equivocal results. Out of the 28 patients with increased activation in occipital cortex, 14 (50%) revealed increased

activation in left V5 cortex, 8 (28.5%) increased activation in left V3 cortex, 4 (14.2%) increased activation in both left V3 and V5 cortex, 2 (7.1%) had increased activation in both right V3 and right V5 areas.

DISCUSSION

fMRI is a new emerging modality of imaging in the field of neuroradiology. It maps the brain activity either in response to stimulus (task-based -visual, auditory, and motor) or in resting state without any conscious mentation. It is based on the principle of BOLD technique and utilizes the paramagnetic properties deoxyhemoglobin to generate an MR signal. While a plain MRI views the anatomical structures and the integrity of grey and white matter in brain, a fMRI indirectly tells about the nerve activity in different parts of brain by measuring the respective metabolic function.

The brain under normal physiological conditions is never idle, but remains neuro-electrically and metabolically active. fMRI in resting state helps in the identification of the resting state networks like the Default Mode Network, which consist of different anatomical regions of brain that are connected functionally. These regions depict a high level of correlated BOLD signal activity during the rest and are relatively deactivated during working memory tasks and visuo spatial tasks.

Task based fMRI are being widely used in effective presurgical planning of brain tumors to evaluate the distance between the tumor and functionally active eloquent areas of brain thus improving the patient's quality of life and life expectancy. Other clinical applications of fMRI include the identification of patients with neurodegenerative disorders such as Alzheimer disease, Parkinsonism, and psychiatric diseases such as obsessive compulsive disorder, Epilepsy, and evaluating the response to different treatment options.

fMRI in migraine is a useful investigation that identifies the mechanisms that lead to sensory hypersensitivity in migraine by measuring the brain responses to different types of stimulations. It evaluates the functional organization of specific brain regions and networks responsible for sensory processing.[2]

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The study was completed well by all subjects. None of the migraine cases reported aura or headache during examination. The T1WI of all the subjects were reviewed and no structural abnormality was found. On the analysis of activation pattern in control group, all subjects demonstrated activation in bilateral occipital cortex, predominantly in V1 (primary visual cortex) followed by V2 area (Figure 1).

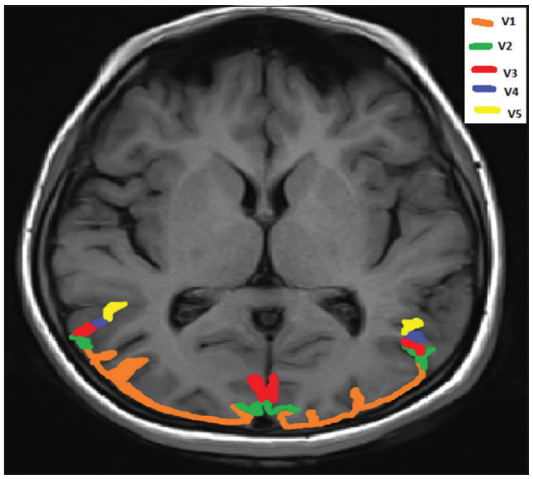

Figure 1: Axial T1WI depicting different visual areas in brain

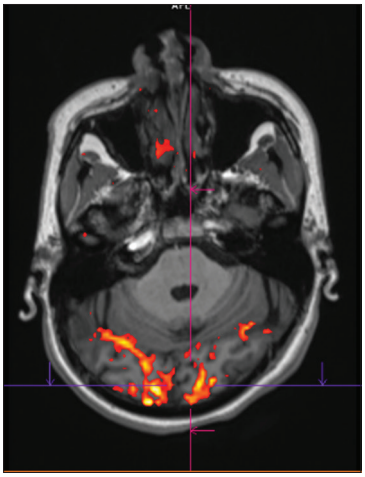

Figure 2: 25/M control subject showing increased stimulation in the right occipital lobe as compared to the left (predominantly in V1)

Of these, 80% of the controls revealed more activation in the right occipital cortex as compared to the left indicating lateralization to the right (Figure 2). Remaining 20% of the controls showed approximately symmetrical bilateral activation.

These findings of lateralization to right on visual stimulation in control subjects correlate well with a study done by Hougaard et al., published in 2015 on fMRI responses on visual stimulation. This study found the increased activation of the primary visual cortex on the right side in most of the subjects as compared to the left. It explained the greater grey matter volume of the early visual cortex on the right side as a possible explanation of this finding.[3]

On the analysis of activation pattern in migraine patients, all patients also revealed activation in bilateral occipital cortex

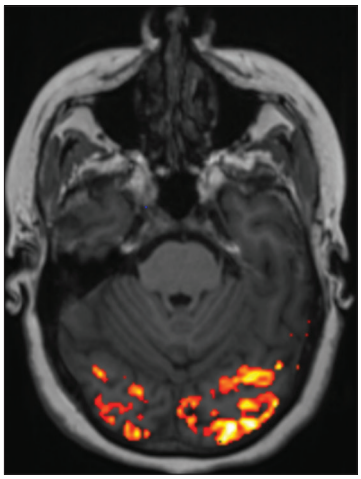

Figure 3: 43/F migraine case subject showing increased stimulation in the left V3 and left V5 visual areas

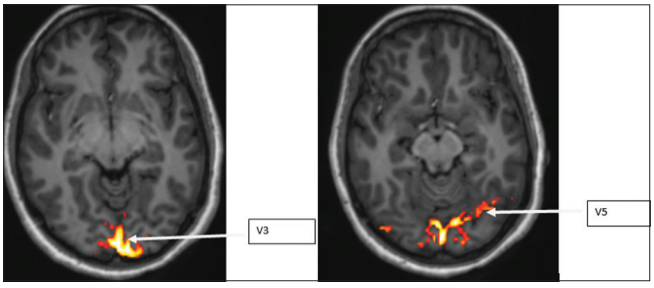

Figure 4: 36/F migraine case subject showing increased stimulation in the left V3 and left V5 visual areas

Table 1: Distribution of relative occipital stimulation in cases with respect to controls

Occipital stimulation	Frequency	Percentage
Increased	28	56
Similar	10	20
Equivocal	12	24
Total	50	100

predominantly in V1 area. However, group analysis of the occipital activation pattern in migraine patients versus control revealed that 56% (28/50) of migraine patients showed significantly increased activation in occipital cortex.

Out of these 28 patients, 14 (50%) patients revealed increased activation in the left V5 cortex, 8 (28.5%) patients revealed increased activation in the left V3 cortex, 4 (14.2%) patients revealed increased activation in both left V3 and V5 cortex (Figures 3 and 4), and 2 (7.1%) patients revealed increased activation in both right V3 and right V5 areas. About 20% of total migraine patients (10/50) revealed no significant difference in activation patterns as compared to controls. About 24% of total migraine patients (12/50) revealed equivocal results (Table 1).

Our study correlates well with a study done by Griebe et al., published in 2013 on assessment of moving visual stimulation on migraine patients with aura. It suggested significantly increased activation in seven areas in migraine patients as compared to controls predominantly in the left V5 and V3 areas.

Lateralization to the right occipital lobe on visual stimulation in controls as well as migraine subjects as seen in our study was mentioned in this study also.[4]

Significant association was noted between increased occipital stimulation and duration of migraine in patients (P=0.01).

Significant association was also found between increased occipital stimulation and absence of intake of any kind of medications for migraine in patients our study (P=0.001).

No significant association was noted between increased stimulation in the left occipital lobe and age, gender, side of headache, any of the associated symptoms, or number of attacks per month.

Limitations of the study

1. MR scanning was done on 3Tesla machine which has its own limitation. Better scanning possible with higher strength scanners like 7 Tesla
2. Mainly a qualitative study, better post-processing software is required for better evaluation and quantification of BOLD responses
3. None of the migraine patients presented with aura. Hence, the fMRI changes such as stimulation of other regions such as superior parietal lobule, inferior frontal gyrus, inferior parietal lobule in symptomatic hemisphere as illustrated by a study done by Hougaard et al.; in 2013, were not possible[5]
4. All the patients presented in interictal period. Hence, fMRI changes during ictal phase could not be evaluated
5. Qualitative data analysis was done by a single radiologist using visual color maps obtained after post-processing. Assessment of data acquired by two or more radiologist and calculation of inter observer variance could increase the credibility of the study
6. Noise artifacts caused by respiration and cardiac events interfere with the fMRI study.

CONCLUSION

The current study shows that fMRI is a helpful imaging tool in patients presenting with migraine in clinical practice.

Majority of patients with migraine showed increased occipital stimulation mainly in the left V3 and V5 areas in comparison to normal healthy subjects. The study revealed clinically significant association between increased occipital stimulation and duration of migraine and absence of pharmacological aid.

Further research will aid better understanding of functional connectivity and neuronal mechanisms in migraine patients that might be helpful in identifying new targets for preventive therapy of migraine.

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Authors' Contributions:
TMK- Concept and design of the study, prepared first draft of manuscript; **KA**- Prepared first draft of manuscript, interpreted the results: Reviewed the literature and manuscript preparation; **AG**- Concept, coordination,statistical analysis; **VC**- Statistical analysis and revision of manuscript.

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