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Altered functional brain imaging in migraine patients: BOLD preliminary study in migraine with and without aura

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ABSTRACT

Design. Migraine is regarded as a complex brain dysfunction of sensory and modulatory networks with the secondary sensitisation of the trigeminal system as well as the affected brain area's activities. The particular role of the hippocampus and the brainstem in the first phase of the attack, the disrupted cognitive network, and the activation of the limbic and visual systems, are the main discoveries in the field of migraine imaging that have been achieved using functional techniques. Thus advanced neuroimaging has been widely employed to study the pathogenesis of migraine.

Objective. The evaluation of fMRI BOLD images of migraine patients with or without aura, with particular attention to the interictal phase.

Material and methods. The aim of this study was to compare brain activity during visual stimuli by fMRI BOLD in the interictal phase (black and white checkerboard tests, static or flickering) of 16 migraine patients, eight with aura and eight without.

Results. We demonstrated differences in the right part of the brainstem, the left part of the cerebellum, and in the right middle temporal gyrus. However, the bilateral brain activation in the occipital and frontal lobe remained similar.

Conclusions. Results of our preliminary study suggest that migraine with aura and migraine without aura might be separate disorders, and this requires further investigation.

Key words: migraine, fMRI, BOLD MRI, trigeminovascular system

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Study of the interictal phase of migraine using BOLD fMRI neuroimaging technique

The pathogenesis of migraine still remains elusive. The mechanism of a migraine attack includes pathological vasomotor regulation associated with neuronal processes and abnormal cortical neuronal activity [1]. Reduction of the regional cerebral blood flow (rCBF) occurs during the migraine aura in the occipital cortex, as reported by a historical study by Olesen at al. [2]. Advancing wavefront propagates rostrally and centrifugally [1, 3–6] and this is associated with the distribution of cortical inhibition of neuronal activity known as cortical spreading depression (CSD) [7], a term coined by Leao et al. [8]. Studies of vascular changes sampling the parenchymal compartment (PET, fMRI, SPECT and scintigraphy), distinct from larger vessels (TSD), have demonstrated a different vascular response [9]. Single photon emission computerised tomography (SPECT) studies have described a cerebral blood flow reduction during visual aura, initially in the occipital cortex, and an increase of the blood flow during the pain phase in 50% of migraine patients [10, 11]. PET

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Table 1. Demographic characteristics of the study population

Patients	Sex M/F	Mean age+SD [years]	Mean attacks of migraine frequency
M n = 16	3/13	38 +/– 9	1 per 1 month
MwA n = 8	3/5	44 +/– 7.5	1 per 3 weeks
MWA n = 8	0/8	33 +/– 7	1 per 3 months

M — all patients with migraine; MwA — patients with migraine without aura; MWA — patients with migraine with aura

studies have reported minute, but significant, blood flow reduction in the occipital region contralateral to visual aura with normalisation of during pain phase. FMRI studies have demonstrated the presence of certain processes that still require elucidation in the field of basic research [12]. Nevertheless, studies based on blood oxygenation level-dependent MRI (BOLD-MRI) indicate the same course of events in both phases [13–16]. Thus, the BOLD-MRI technique has become one of the most widely used methods for measuring a migraineur's brain abnormalities more accurately, due to a larger resolution, the temporal (minor remark) and the spatial image of the brain's activity and its connectivity. BOLD neuroimaging may be the most promising methodological advance in functional migraine studies. However, our preliminary data requires further investigation.

Materials and methods

Participants were recruited from 16 migraine patients who had received treatment in the outpatient Headache Clinic: eight with aura (MWA), all females with a mean age of 33 + 7 years) and eight without aura (MwA), five females and three males with a mean age of 44 + 7.5 years. The mean age of the entire group was 38 + 9 years and the duration of the disease was between two and 35 years. All patients eligible for inclusion in the study were diagnosed with MWA or MwA using the International Headache Society (IHS) criteria (Tab. 1), based on the most recent 3rd edition from 2018 [19] and were examined by an experienced clinician. The frequency of migraine attacks ranged from one per week to one per annum (mean frequency: one per month).

The study group consisted of patients who visited the clinic during a spontaneous migraine attack. MWA patients with aura arrived at the clinic usually earlier than MwA patients without aura. Patients had to be chronologically chosen due to the limited number of participants (non-matched age), thus this results study has to be interpreted as preliminary.

We obtained the approval of the ethical committee of Warsaw Medical University as required for this study and modified in accordance with the Declaration of Helsinki. A written consent was signed by all participants.

Image acquisition

Routine MRI scans were obtained using standard equipment (3 T Siemens Magnetom Trio Tim MR) and a standard protocol. fMRI data collected between attacks of migraine were acquired by an experienced physician with no knowledge of the diagnosis.

Image analysis

The fMRI study included standard anatomical 3D T1-weighted images of the whole-brain analyses (3D MP-RAGE sequence, TR = 1,900 ms, TE = 2.26 ms, 0.9 × 0.9 × 0.9 mm voxels), 172 slices in total (TA = 6 min 32 s), and gradient of Echo-Planar Imaging (EPI) sequences [TR = 3,000 ms, TE = 30 ms, flip angle = 90°, FOV 192 × 192 mm Matrix size was 96 × 96, each volume consisted of 47 axial slices, 3 mm thick (no gap, 2 × 2 × 3 mm voxel), pixel bandwidth = 1,532Hz/pix, iPAT = 2] obtained using 12-channel matrix head coil and MR compatible goggles (Nordic NeuroLab Visual system) in the Bioimaging Research Centre of the Institute of Physiology and Pathology of Hearing in Warsaw, Poland. The images were analysed using Statistical Parametric Mapping (SPM12b, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and adjusted for motion correction and spatial normalisation (a least squares approach and a six parameter spatially normalized, reference to the first scan) to the standard Montreal Neurological Institute (MNI) template in SPM 12b (resampling voxel size = 2 × 2 × 2 mm). Static and flickering checkerboard test results were individually preprocessed (first level analysis). Cortical activation was separately analysed and compared for both groups using the two sample t test.

Results

There were no demographic differences in terms of age and gender between the MwA and MWA patients. Significant ($p < 0.001$, uncorrected) similar bilateral activations were located predominantly in the occipital lobe, in the cuneus and the lingual gyrus as well as in various regions of the frontal cortex (presented in Figs. 1 and 2 and in Tabs. 2 and 3). Increased fMRI activity in the right brainstem, the left part of the cerebellum and in the right middle temporal gyrus (Fig. 3, Tab. 4) was found in the MWA group. There were no statistically significant differences in those regions during the flickering checkerboard

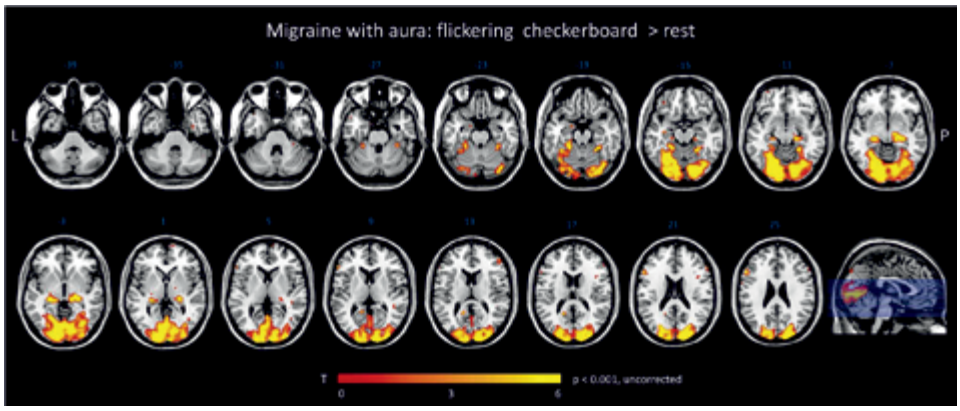

Figure 1. Activations in response to a flickering checkerboard in migraine with aura

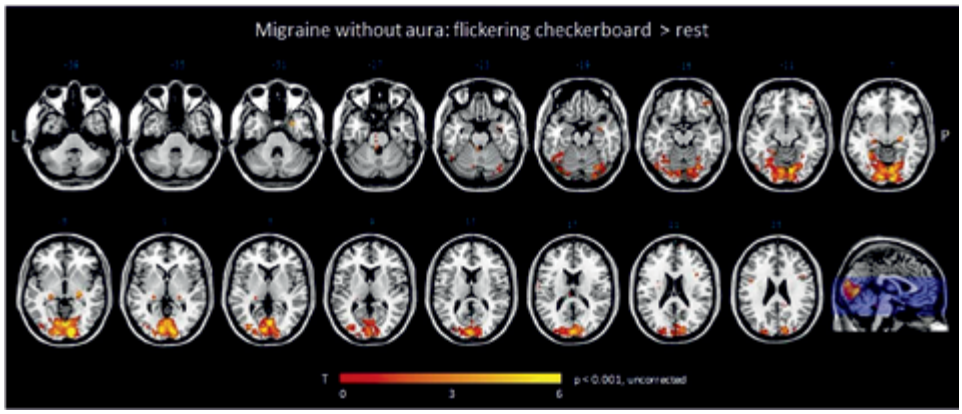

Figure 2. Activations in response to a flickering checkerboard in migraine without aura

Table 2. Brain areas (MNI coordinates, number of voxels and z scores, p < 0.001, uncorrected) activated in the flickering checkerboard block in migraine with aura

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	Z statistics
Occipital lobe	L + R	18, 19	-20 -62 -2	8,333	5.15
Brainstem	R	-	-24 -26 -4	320	5.36
Hippocampus	L	-	-26 -30 -2	172	4.32
Cerebellum	R	-	-24 -46 -18	127	4.54
Cerebellum	L	-	-22 -40 -18	150	4.14
Precuneus	L	7	-4 -84 -46	64	4.34
Middle frontal gyrus	L	45	-54 -22 -24	48	3.69

L — left; R — right

block test (Figs. 4–5, Tabs. 5–6). At the same time, increased bilateral activity was observed in the brainstem, in the right part of the cerebellum, and in the left medial frontal gyrus of the MwA patients (Fig. 6, Tab. 7).

Discussion

The preliminary data indicates a substantial difference in BOLD-fMRI response patterns between MWA and MwA patients.

In the MWA group, increased response in the right part of the brainstem, the left hemisphere of the cerebellum, and the right middle temporal gyrus corresponds (minor remark) with hyperresponsiveness within the primary visual cortex and the lateral geniculate nuclei. Greater activation of the primary visual cortex of migraneurs and differences in the activation of lateral geniculate nuclei between MWA and MwA patients were also reported in a recent prospective case-control study [20, 21]. We also found a difference between the MWA and

Table 3. Brain areas (MNI coordinates, number of voxels and z scores) activated in the flickering checkerboard block in migraine without aura ($p < 0.001$, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	Z statistics
Occipital lobe	L + R	17,18	-12 -92 -6	1,247	3.87
Lingual gyrus					
Cuneus					
Cuneus	R	18	14 -86 -16	53	3.45
Lingual gyrus	R	18	26 -72 -14	24	3.41
Superior frontal gyrus	R	9	-18 -48 -48	25	4.71

L — left; R — right

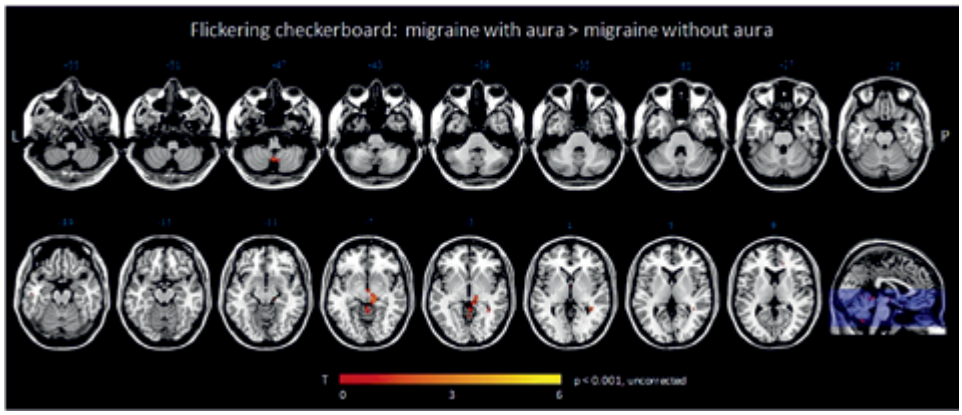

Figure 3. Activations elicited by a flickering checkerboard in contrast: migraine with aura *vs.* migraine without aura patients

Table 4. Brain areas (MNI coordinates, number of voxels and z scores) involved in a flickering checkerboard perception for contrast: migraine with aura *vs.* without aura patients ($p < 0.001$, uncorrected)

Region	Side	MNI coordinates (x, y, z)	No. of voxels	z statistics
Brainstem	R	10 -20 -6	172	4.03
Cerebellum	L	-2 -62 -46	37	3.77
Middle temporal gyrus	R	38 -44 2	29	3.66

L — left; R — right

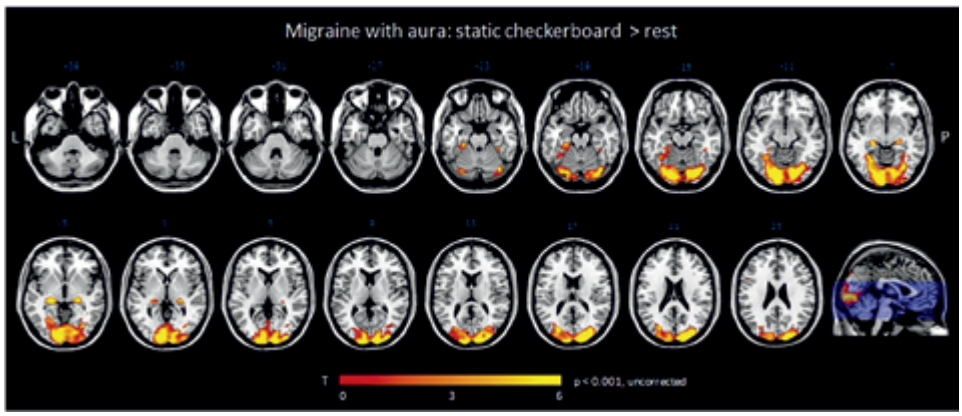

Figure 4. Activations in response to a static checkerboard in migraine with aura

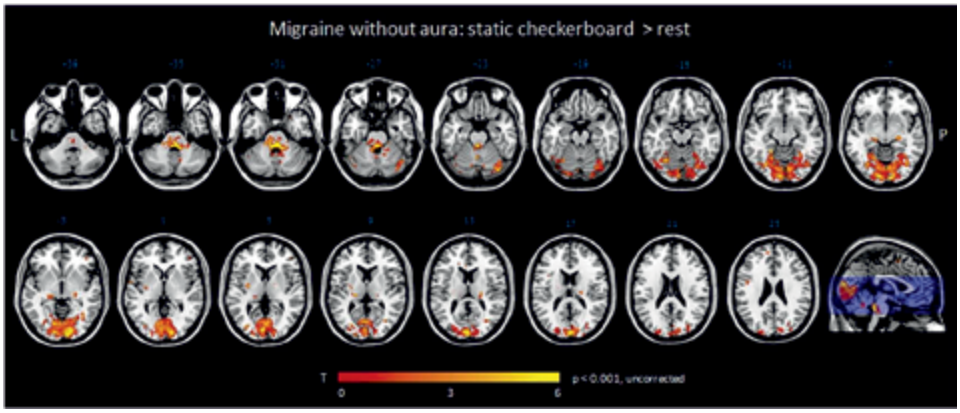

Figure 5. Activations in response to a static checkerboard in migraine without aura

Table 5. Brain areas (MNI coordinates, number of voxels and z scores) activated in the static checkerboard block in migraine with aura (p < 0.001, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	Z statistics
Occipital lobe	L + R	18, 19	-8 -92 0	5,626	4.99
Lingual gyrus					
Cuneus					
Cerebellum					
Hippocampus	L	-	-26 -28 -4	124	6.19
Parahippocampa gyrus	L	36	-26 -28 -22	39	4.17
Thalamus	R		24 -26 -2	86	4.30

L — left; R — right

Table 6. Brain areas (MNI coordinates, number of voxels and z scores) activated in the static checkerboard block in migraine without aura (p < 0.001, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	z statistics
Occipital lobe	L	17,18	-30 -62 -18	752	3.98
Lingual gyrus					
Cuneus					
Occipital lobe	R	17	8 -96 -4	230	3.82
Lingual gyrus					
Brainstem	L + R	-	4 -36 -30	311	4.66
Cerebellum	R		34 -80 -26	76	3.75
Inferior occipital gyrus	R		40 -68 -8	45	3.62

L — left; R — right

MwA groups that could possibly imply an association between these two variables, the presence of aura and its cortical hyperresponsiveness. This gives potential for further investigation.

According to Martin et al. [15], the brains of migraineurs demonstrate hyperexcitability of the visual cortex during interictal periods, with more spacious areas of photoresponse due to the paired mechanism: constitutional (defensive) and acquired (sensitisation). Moreover, BOLD alterations during the onset of a migraine attack with visual aura coincided with the onset of the aura and progressed throughout the occipital cortex at the velocity of 3–5 mm per minute and declined after the initial increase [22]. The BOLD signal activation in the brainstem structures, specifically in the red nucleus and substantia nigra, indicates that these structures are also involved in the migraine attack in MWA patients [23, 24]. An altered activation pattern in the migraine phase has also been demonstrated in several subcortical and cortical regions [25].

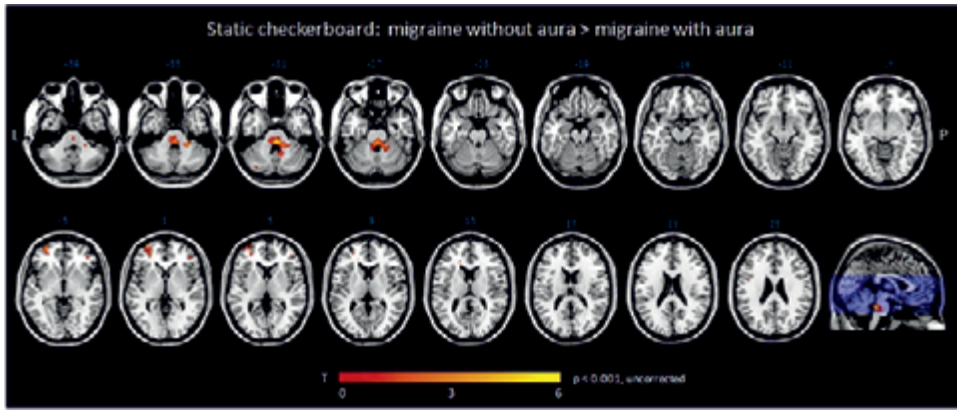

Figure 6. Activations elicited by a static checkerboard in contrast: migraine without aura *vs.* migraine with aura patients

Table 7. Brain areas (MNI coordinates, number of voxels and z scores) involved in a static checkerboard perception for contrast: migraine with aura vs. without aura patients ($p < 0.001$, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	z statistics
Brainstem *Pons*	L + R		-2 -36 -28	431	4.23
Cerebellum	R	-	10 -52 -30	41	3.73
Medial frontal gyrus	L	10	-32 58 -2	118	3.93

L — left; R — right

In our study, we found brainstem activation in patients with MWA during the interictal phase, whereas an increased activation was found in part of the cerebellum and in the left medial frontal gyrus of MwA patients.

It is unclear whether the frequency of migraine attacks affects activation of particular brain regions and if so, it is rather increased frequency and its activity during migraine's attacks. The result of our study indicates a different pathomechanism of the attack in MwA patients compared to MWA patients. The distinct response patterns during brainstem activation observed in our study suggest two separate types of migraine attack. Unfortunately, an insufficient analysis of macro- and microstructural changes, both cortical and subcortical, the absence of a control group, unmatched age, gender and the frequency of migraine attacks in our study are limitations of our study. However, age and gender play insignificant roles in brain activation during attacks. Therefore our results have to be interpreted as preliminary. Further investigation is required for a better understanding of the pathomechanism during a migraine attack.

Nevertheless, the combination of functional and structural techniques to acquire and analyse function and organisation of the CNS in basic migraine studies could provide a more effective approach to propose a unique model of migraine events [12, 26].

Insight into the pain circuits altered in migraine could potentially contribute to the development of a new rs-fMRI-based, noninvasive migraine indicator. More accurate classification, and analysis of long term migraneurs, could potentially indicate that the duration of the disease plays a crucial role in the "reorganization of brain circuitry" [27, 28].

Compliance with ethical standards

There were no conflicts of interest and commercial relationships including grants, honoraria, speaker's lists, significant ownership, and/or support from pharmaceutical or other companies, during our study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee.

Informed consent was obtained from all individual participants included in the study.

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