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Evaluation of Electroencephalogram Using Exact Low-Resolution Electromagnetic Tomography During Photic Driving Response in Patients with Migraine

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Keywords
Migraine · Electroencephalogram · Photophobia · Photic driving · Low-resolution electromagnetic tomography

Abstract
Background: Photophobia is a common feature of migraine, which may involve abnormal cortical information processing. In electroencephalograms (EEG), photic driving is known as a reaction to visual stimulation. Both photophobia and photic driving response are present during light stimulation. We hypothesized that cortical response to photic stimulation would differ between migraine patients with and without aura. ***Methods:*** We recruited 50 migraine patients (migraine with aura [MWA] = 21; migraine without aura [MWOA] = 29). Spontaneous eyes-closed resting EEG from 20 electrodes on the scalp during the interictal phase was recorded. After recording, each photic stimulation was separately selected. We analyzed EEG by fast Fourier transform and observed the spectrum frequency peaks and topographies in response to photic stimulation. Exact low-resolution electromagnetic tomography (eLORETA) was used to compute the 3-dimensional intracerebral distribution of EEG activity. ***Results:*** Photic stimulation at frequencies 5, 8, 15, and 20 Hz showed significant differences between migraine patients with and without aura. MWOA patients consistently had a stronger response to photic stimulation than MWA patients. In all patients, the differential response was located in the visual cortex, except for the stimulation at 20 Hz, where the difference at subharmonic 10 Hz was located in the parietal cortex (Brodmann Area 7). ***Conclusion:*** We confirmed high incidences of photic hypersensitivity and photic driving responses in migraine patients. We suggest that repeated occurrences of cortical spreading depression in MWA may suppress cortical function, thus contributing to a weaker visual cortical response to photic stimulation in MWA patients compared with MWOA patients.

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Introduction

Migraine, a common disabling disease with a 1-year prevalence of 8.4% in Japan [1], is characterized by severe pulsatile headache accompanied by nausea, vomiting, and photophobia, leading to great impairment of daily life. Photophobia is a common feature of migraine, which aggravates attacks of migraine headache. The presence of photophobia is also important in migraine diagnosis [2]. Photophobia may involve abnormal cortical information processing and cortical hypersensitivity. During the premonitory phase of migraine, activations of dorsal pons, including the locus coeruleus, which has modulatory effects on cortical excitability, and bilateral occipital cortices have been implicated in producing photophobia [3]. In the electroencephalogram (EEG), the existence of photic driving response is known as a reaction to light stimulus. The photic driving response and the photic hypersensitivity are similar as both are induced by light stimulation. The photic driving response in a high-stimulation region of 15 Hz or more (an H-response) is thought to be abnormal, and migraine patients frequently show the H-response during the interictal phase [4]. We evaluated the electroencephalographic changes during photic driving responses in migraine patients using the global field power (GFP) values and found anteriorization in high-frequency peaks of harmonic driving in the long-duration group, along with a positive correlation between the GFP peak values and disease duration [5]. However, the underlying mechanisms of photophobia have yet to be clarified. In this study, we evaluated EEG changes in migraine patients during photic stimulation by EEG-source localization analysis using exact low-resolution electromagnetic tomography.

Methods

Subjects

We recruited 50 patients with migraine (11 males and 39 females; age 20–50 years; 21 migraine with aura [MWA]; 29 migraine without aura [MWOA]). Migraine was diagnosed in accordance to the International Classification of Headache Disorder criteria, 3rd edition (beta version; ICHD-3beta) [2]. Patients with secondary headaches due to brain lesions were excluded by magnetic resonance images. All participants continued the same acute and preventive treatment for migraine during the study.

Ethics Approval

The study protocol was approved by the Human Ethics Review Committee of Dokkyo Medical University. All procedures were handled in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from each patient participating in the study.

EEG Recording and Data Acquisition

The patients' clinical backgrounds, such as the duration of illness, age at onset, and presence of photophobia in the interictal phase, were obtained by the questionnaire. Spontaneous eyes-closed resting EEG during the interictal phase was performed using silver/silver chloride electrodes attached to 20 locations of the international 10/20 system (Fp1/2, Fz, F3/4, F7/8, C3/4, Cz, P3/4, Pz, T3/4, T5/6, O1/2, and Oz) with a ground electrode attached to linked earlobes. A digital electroencephalography system (NeuroFax 1518; Nihon Kohden Corp., Tokyo, Japan) with a band pass filter of 0.53–120 Hz was used, and sampling was performed at 200 Hz. The resistance of each electrode was set at <5 kΩ. Stroboscope flashes consisting of 3, 5, 8, 10, 13, 15, 18, and 20 Hz were used.

EEG-Source Localization Analysis

We used exact low-resolution brain electromagnetic tomography (eLORETA) to compute the cortical electrical distribution from the scalp electrical potentials measured at the electrode sites [6]. After EEG recordings, for each stimulation frequency separately, 3 artifact-free EEG epochs consisting of 2.56 ms were selected. The selected EEGs were analyzed by fast Fourier transformation, and the frequency-dependent topographies and complex-valued cross-covariances employed for computing the corresponding 3-dimensional cortical distribution of generators of the EEG activity by means of eLORETA [6] (Fig. 1). In detail, for each subject and each stimulation frequency, the 3 EEG files were used for computing the EEG cross-spectrum from 1.17 to 45 Hz at a resolution of 0.390625 Hz. Although these recording conditions do not correspond exactly to those of spontaneous EEG, the classical frequency domain analysis methods are still valid here, due to the maintained periodic nature of the stimuli. Nevertheless, although it was not the aim of the present study, it is noted that higher order spectral analyses might contribute additional information.

All statistical analyses were performed with the non-parametric maximum-statistic randomization methodology, which does not require normal distribution and corrects for all multiple tests. In particular, statistical comparisons of cortical activity between MWA and MWOA patients ("with aura" and "without aura") were performed using an independent sample design. For each stimulation frequency, comparisons were made for the eLORETA cortical localization of the generators of the oscillation at the main photic stimulation frequency and at harmonics and subharmonics between MWA and MWOA patients. To compare the differences in frequencies and continuous variables between MWA and MWOA groups, unpaired t-test and the chi-square test were used, respectively. The 2-tailed p values of <0.05 were considered statistically significant.

Results

Self-conscious photic hypersensitivity was reported in 37 migraine patients (74%). Table 1 shows the clinical characteristics of migraine patients. The average duration of illness in the MWA group was 13.9 ± 8.7 years, and in the MWOA group, it was 15.7 ± 10.7 years. Pho-

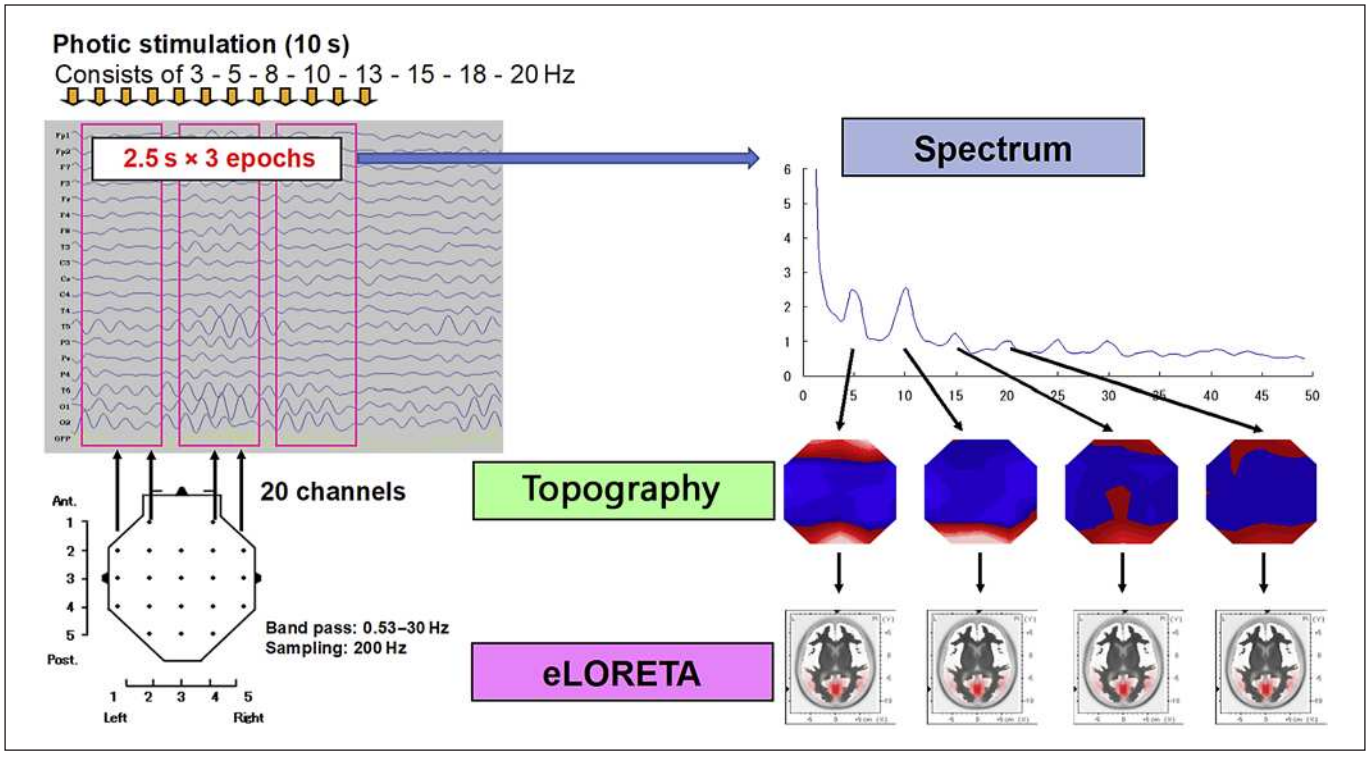

Fig. 1. Schematic illustration of data acquisition and analysis methods. eLORETA, exact low-resolution electromagnetic tomography.

Table 1. Clinical characteristics of migraine patients

	MWA group (n = 21)	MWOA group (n = 29)	p value
Gender, male/female	4/17	7/22	0.74
Age, years	32.9±9.1	35.7±10.5	0.33
Disease duration, years	13.9±8.7	15.7±10.7	0.53
Photophobia, n (%)	16 (76.2)	21 (72.4)	1.0

MWA, migraine with aura; MWOA, migraine without aura.

tophobia was observed in 16 patients (76.2%) in the MWA group and 21 patients (72.4%) in the MWOA group. In any frequency range, the main activity area during photic stimulation was the occipital lobe on eLORETA. In comparison with migraine subtypes, there was no significant difference in most frequency ranges (e.g., 3, 10, 13, 18 Hz; Table 2). However, a significant difference was observed between the subtypes MWA and MWOA of the following drivings: harmonic driving of 15 Hz with 5-Hz photic stimulation, harmonic driving of 16 Hz with 8-Hz photic stimulation, fundamental driving of 15 Hz with 15-Hz photic stimulation and subharmonic driving of 10 Hz with 20-Hz photic stimulation. Photic stimulation at frequencies 5, 8, 15, and 20 showed a significant difference between the subtypes with and without aura. MWOA consistently had a stronger response to photic stimulation than MWA (Table 2). In all cases, the differential response was located in the visual cortex, except for 20 Hz stimulation, where the difference at subharmonic 10 Hz was located in the parietal cortex (BA 7; Fig. 2).

Discussion

Photic hypersensitivity was observed in 74% of migraine patients in our study, which was slightly lower compared to previous studies that reported a photic hypersensitivity prevalence of 76.4–93.9% in patients with migraine [7, 8]. The photic driving response, which is a concurrent reaction relevant to vision, was first reported in 1934 [9]. It is a rhythmic activity elicited over the posterior regions, consisting of rhythmic EEG activity. The difference in photic driving to light stimulation between healthy and epileptic patients, schizophrenia, and dementia has been reported [10–13]. Photic driving by

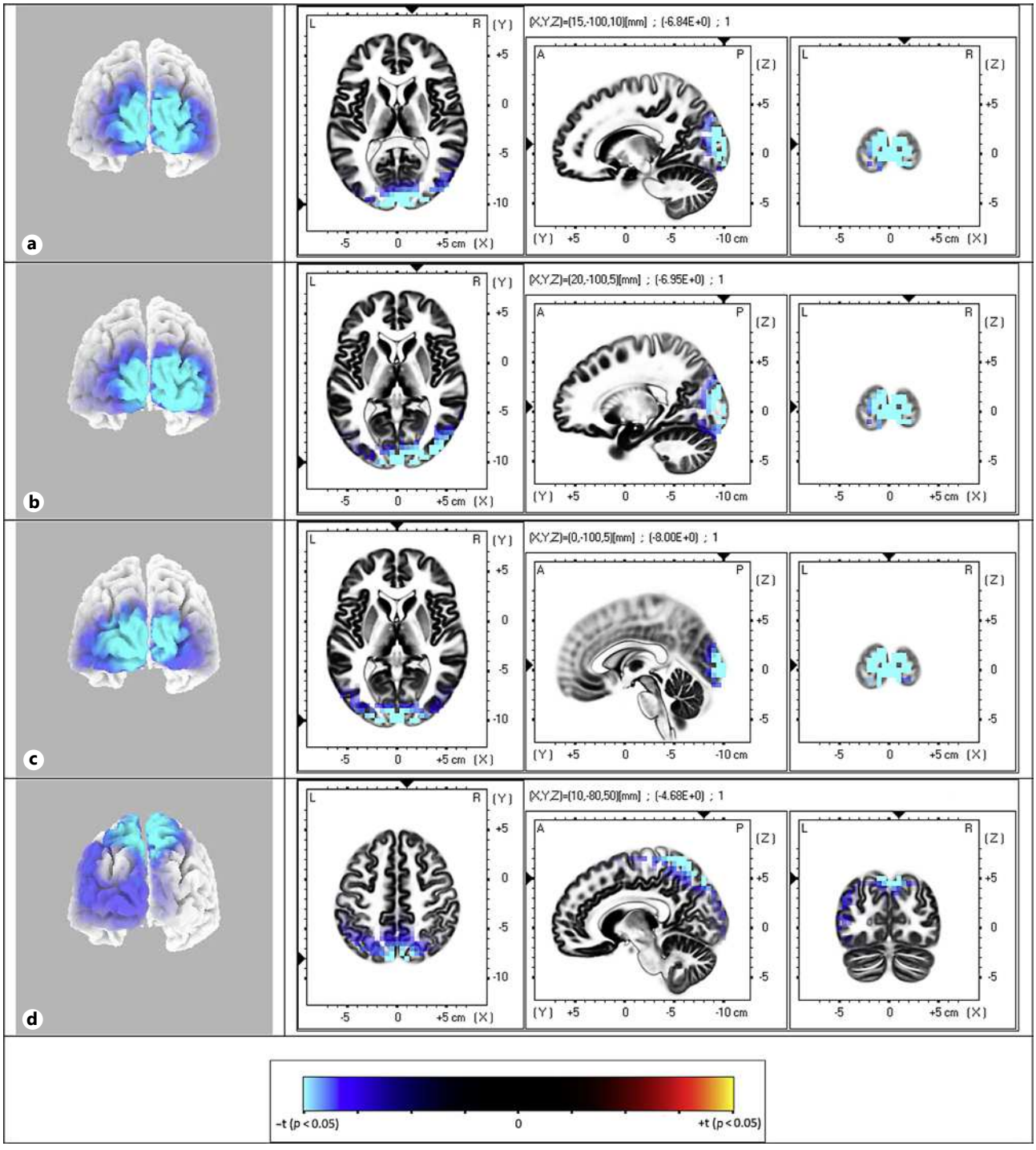

Fig. 2. Statistical (non-parametric randomization) comparison for "MWA minus MWOA," of the generators of oscillatory activity. Only significant results at $p < 0.05$ are shown with color scale in bottom row. Blue color indicates significantly more activity for MWOA as compared to MWA. **a** Occipital regions, 5 Hz PS, 15 Hz harmonic response. **b** Occipital regions, 8 Hz PS, 16 Hz harmonic response. **c** Occipital regions, 15 Hz PS, 15 Hz fundamental response. **d** Parietal regions, 20 Hz PS, 10 Hz subharmonic response. First column corresponds to a posterior view of a 3D rendered cortex; second, third, and fourth columns correspond to 2D slices (axial, sagittal, and coronal, respectively). MWA, migraine with aura; MWOA, migraine without aura; PS, photic stimulation.

Table 2. Stimulation frequency with a significant difference between migraine subtypes

Stimulation frequency	Results
3 Hz	Not significant at any frequency
5 Hz	15 Hz harmonic driving; significant difference in the occipital cortex (MWOA > MWA)
8 Hz	16 Hz harmonic driving; significant difference in the occipital cortex (MWOA > MWA)
10 Hz	Not significant at any frequency
13 Hz	Not significant at any frequency
15 Hz	15 Hz fundamental driving; significant difference in the occipital cortex (MWOA > MWA
18 Hz	Not significant at any frequency
20 Hz	10 Hz subharmonic driving; significant difference in the parietal cortex (MWOA > MWA)

photic stimulation of high frequency (≥15 Hz) is called the H-response, and is observed in the interictal phase in migraine patients [4]. We have observed the photic driving response at a flashing rate of >15 Hz in migraine patients, and there was a tendency towards more frequent photic driving response in migraine patients with photic hypersensitivity, regardless of the aura status [5]. Additionally, the findings of an anterior shift of the activated area during photic stimulation, which was more marked in patients with longer disease duration, and a positive correlation between GFP values and disease duration [5] suggest central sensitization of the limbic system in migraine patients [14]. In the present study using eLORETA, we observed significant differences in responses to photic stimulations at frequencies 5, 8, 15, and 20 Hz between MWA and MWOA groups. Interestingly, patients with MWOA consistently had stronger responses to photic stimulation than those with MWA, and all the differential responses were located in the visual cortex with 15–16 Hz peak frequency response, except for 20 Hz stimulation, where the difference at subharmonic 10 Hz was located in the parietal cortex (Brodmann Area 7).

Steady state visual stimulation is closely related to photic stimulation, in which case it has been shown that the maximum response occurs at a stimulation frequency of about 15 Hz [15], specifically localized in the visual cortex. This is strongly related to 2 aspects of our results, in which the peak frequency response occurs at approximately 15 Hz for most of the stimulation frequencies, localized to the occipital regions including the visual cortices for the MWOA group.

The aura, which precedes the migraine attacks, consists of various symptoms, such as vision, language, and sensation, and the most common symptoms are visual symptoms presenting as field defects or scintillating scotoma, which move across the visual field of the patient. The aura of migraine has been associated with the phenomenon called cortical spreading depression (CSD), which starts in the visual cortex of the occipital lobe. CSD is a phenomenon in which the electric activity suppression state propagates in the cerebral cortex at a rate of 2–3 mm/min following the transient cerebral cortical neuron over-excitation [16]. CSD has been shown to activate the trigeminovascular systems by inducing c-fos activation of the trigeminothalamic nuclei [17, 18], thereby provoking migraine attacks. CSD may play a role in the pathophysiology of MWOA, similar to MWA [19, 20].

During the interictal phase, cortical hyperexcitability has been reported in migraine patients [20, 21], but Afra et al. [22] reported that cortical hyperexcitability was normalized during migraine attacks. Lights from retinal ganglionic cells activate the thalamic trigeminovascular neurons and a subgroup of light/dura-sensitive neurons mainly located in the posterior hypothalamus, which have a projection to parietal and visual cortices, contributing to enhanced pain and altered responses to visual stimuli [20]. In our study, we analyzed the interictal phase of cortical activities of migraine patients with photic stimulation by using EEG-source localization analysis (eLORETA) and found different cortical responses to photic stimulation between MWOA and MWA, supporting that neuronal excitability may play an important role in the predisposition to develop different forms of migraine [20]. A study using resting state functional MRI images revealed that interictal cortical activity was higher in MWA patients compared to MWOA patients [23]. Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions, especially MWA, has been described [24]. A systematic review on transcranial magnetic stimulation studies of migraine patients supported a hyperexcitability in the primary visual cortex in MWA, but not MWOA [25]. In contrast, a recent study suggested that CSD can cause the destruction of the blood–brain barrier by activation of matrix metalloproteinase-9 [26]. We suggest that in the MWA group, repeated migraine

attacks may cause dysfunction of the occipital lobe cortex, resulting in abnormal photic driving response to light stimulation.

The limitations of this study include a lack of a healthy control group, as well as individual differences in severities in migraine headache, accompanying symptoms and sensitivity to lights.

In conclusion, our study confirmed high incidences of photic hypersensitivity and photic driving responses in migraine patients. We suggest that repeated occurrence of CSD in MWA may suppress cortical function, thus contributing to lower activity in the occipital region.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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