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Altered neuromagnetic responses to pattern reversal visual stimulation in patients with migraine

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Abstract. Thirteen migraine patients underwent visual stimulation with left hemifield checkerboard reversals, with their right eye covered. Single dipole modelling of the right visual cortical activation at ~100 ms (P100 m) after stimulus onset demonstrated a significantly shorter peak latency and a trend for increased amplitude in migraine patients than their sex- and age-matched controls. Our findings add evidence to the visual dysmodulation of migraine sufferers.

Keywords: Migraine; Magnetoencephalography (MEG); Visual evoked magnetic field (VEF); Pattern reversals

1. Introduction

Migraine attack is characterized by the development of photophobia. During interictal ("headache-free") state migraine patients may report higher sensitivity to light [1] and intense illusion to grating patterns [2]. Despite above visual disturbances of migraine, earlier VEP studies did not show consistent abnormality in migraine [3]. MEG has strengths over EEG in higher spatial resolution and avoidance of conduction volume effect. MEG

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preferentially records brain current activities tangential to the scalp, in contrast with EEG that detects both radial and tangential current components. We thus use visual evoked magnetic field (VEF) in this pioneer study to investigate if migraine patients present an interictal alteration of the visual cortical processing.

2. Materials and Methods

Thirteen migraine patients (7F6M, age 31.2±7.3 years, 5 with visual aura and 8 without aura) and 13 age- and sex-matched normal controls gave their informed consent and participated in the study. All migraine patients finished a headache questionnaire which collected their demographics and headache profile (frequency, severity, etc.). The enrolled patients reported 2–8 migraine attacks per month in the past 6 months and a family history of migraine; they neither had received preventative therapy for migraine, nor reported histories of neurological, ophthalmologic, and systemic diseases. All subjects had normal or corrected normal vision and reported no headache attacks within 3 days before and after VEF recordings. All subjects except one patient were right-handed.

Pattern reversal checkerboard stimuli (mean luminance 20 cd/m^2, contrast 0.96) were generated using a personal computer and projected onto a screen ~110 cm in front of the subject. With the right eye covered, the subject was asked to gaze at a tiny red fixation point. In separate sessions the pattern was composed of either 30′ or 120′ checks, reversed every second, and presented to subjects' left hemifield with a field size 15°(W)×22°(H). We applied the above two check conditions since they were considerably discrepant in terms of their spatial frequency and both check types elicited clear VEF responses as reported in one of our earlier studies [4].

We used a whole-scalp 306-channel neuromagnetometer (Vectorview™) to record the VEF responses. The signals were bandpass filtered (0.1–130 Hz) and digitized at 500 Hz. Consecutive 200 responses were recorded for both check-size conditions and the whole paradigm was repeated to ensure reproducibility.

We visually searched those channels with signal deflections clearly exceeding the prestimulus background level for further analysis. The single equivalent current dipole (ECD) best describing the measured activities at ~100 ms (P100 m) after stimulus onset was found by a least-squares search using a subset of 32–36 channels around the maximal responses. Goodness-of-fit of the model was calculated and only ECDs explaining >80% of the field variance at selected periods of time over a subset of channels were used for further analyses.

MR imagings of the subject's brain were acquired with a 3-T Bruker Medspec300 scanner. Based on the spherical head model, the 3D locations and orientations of the ECDs calculated from the source analysis were coregistered to MR images of the subject's own brain. The positive *x*-, *y*-, and *z*-axes in our head-coordinate system went towards the right preauricular point, the nasion, and the head vertex, respectively.

The peak latencies, amplitudes, and locations of P100 m sources were computed as the mean of the two repeated recordings. Data comparison within and between groups were dependent upon paired and Student's *t* test; individual differences between means were further evaluated with Bonferroni procedures for repeated measures. The association between headache profile and P100 m source parameters in the migraine group were tested by Pearson's correlation. The *p*-values less than 0.05 were considered significant.

3. Results

In all subjects, the P100 m responses were clearly seen near or around the right striate cortex. The P100 m responses, which were elicited by large checks, showed shorter peak latencies (mean±SEM) than those elicited by small checks (108.0±2.6 vs. 115.0±2.7 ms, $p=0.014$); while the response strength (27.8±2.5 vs. 25.6±2.2 nAm) and locations (22.8±2.0 mm vs. 21.5±2.0 mm, −43.1±2.0 mm vs. −42.2±2.0 mm, and 49.0±1.5 mm vs. 49.0±1.8 mm for *x*-, *y*-, and *z*-coordinate values, respectively) did not differ between large- and small-check conditions (all $p>0.050$).

Table 1 shows the comparison of P100 m responses between the migraine and the control groups. P100 m peaked earlier in migraine patients, both in large-check (100.1 vs. 115.9 ms, $p=0.001$) and small-check (108.1 vs. 121.9 ms, $p=0.010$) conditions. Migraine patients tended to have a stronger P100 m (large checks: 29.1 vs. 26.5 nAm, $p=0.599$; small checks: 28.2 vs. 22.9, $p=0.233$) but the difference was not significant. P100 m localization was otherwise comparable.

The patient group reported a migraine history of 15.4±7.8 (mean±SD) years, with a frequency of 6.8±5.0 attacks per month. Neither the length of history nor the frequency of migraine correlated with the peak latency and amplitude of P100 m. P100 m of the patients with migraine aura showed trends for shorter peak latency (for large checks, 99.5 vs. 100.5 ms; for small checks, 102.2 vs. 111.8 ms) and larger amplitude (for large checks, 35.5 vs. 25.2 nAm; for small checks, 30.9 vs. 26.6 nAm) when compared with patients without aura (all $p>0.050$).

4. Discussion

The present study on P100 m shows a significant shortening in the peak latency and a possible trend for an increase in amplitude in migraine patients; this alteration pattern seems more prominent in those patients with migraine aura. Some earlier VEP studies also demonstrated a shorter latency [5,6] and a larger amplitude [6–8] in migraine patients than controls, in line with our current observation. Notably, the P100 response showed inconsistent findings across previous VEP studies in migraine patients. The discrepancy between various reports might be related to a difference in stimulus methods (e.g., check size, stimulation fields), the patient's state during experiment (e.g., the time interval to last attack, menstrual

Table 1
Comparisons of P100 m parameters [mean (SEM)] between migraine patients ($n=13$) and normal controls (NC, $n=13$) in responses to left hemifield checkerboard reversals in different check-size conditions

	Large checks (120′)			Small checks (30′)		
	Migraine	NC	p*	Migraine	NC	p*
Peak latency	100.1 (2.7)	115.9 (3.0)	.001	108.1 (4.0)	121.9 (2.9)	.010
Strength	29.1 (3.8)	26.5 (3.3)	.599	28.2 (3.2)	22.9 (2.9)	.233
x coordinate	21.7 (2.5)	23.8 (3.0)	.602	21.2 (2.6)	21.8 (3.3)	.883
y coordinate	−44.1 (3.5)	−42.1(2.0)	.614	−43.1 (3.0)	−41.3 (2.6)	.640
z coordinate	48.2 (2.4)	49.8 (1.7)	.597	49.4 (2.3)	48.5 (2.9)	.793

*p-value for comparison between migraine patients and control groups (Student's t test).

phases), and the nosological diversity (e.g., with or without aura, duration of migraine history) [3,8]. To elucidate the impact of migraine upon visual processing, this preliminary study thus applied MEG (without the conduction volume effect of EEG) and hemifield pattern reversals (as a standard stimulation for clinical VEP studies) upon a homogenous patient population (all have an ICHD-II diagnosis, a positive family history, and a similar attack frequency of migraine; none received a preventative treatment of migraine prior to the present study).

The shortened latencies and increased amplitudes of P100 m in migraine patients might reflect a dysmodulation of sensory input leading to facilitated visual processing, which renders the migraine patients a lowered threshold for migraine attacks. A VEP study using sine-wave modulated light suggested an increased excitability of neurons and neuronal transmission in the visual system of migraine patients [9]. Psychophysically, migraine patients demonstrated response time advantages in low-level vision tasks [10]. Plasma analysis also showed an elevated excitatory amino acid level in migraine patients [11]. Taken together, it is proposed that migraine patients have an interictal hyperexcitability in the visual cortical pathway.

Intriguingly the shortening of P100 m latency seemed to be more explicit in the large-check condition. Further studies of check size effect upon P100 m would help elucidate whether the magno- and parvo-cellular pathways are symmetrically involved in migraine.

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