Visual evoked potentials in migraine patients: alterations depend on pattern spatial frequency

Rieke Oelkers,¹ Konrad Grosser,¹ Eberhard Lang,² Gerd Geisslinger,¹ Gerd Kobal,¹ Kay Brune¹ and Jorn Lotsch¹

¹Department of Experimental and Clinical Pharmacology and Toxicology and ²Department of Neurology, University of Erlangen-Nuernberg, Germany

Correspondence to: Rieke Oelkers, MD, Department of Child and Adolescent Psychiatry, University of Heidelberg, Blumenstrasse 8, D-69115 Heidelberg, Germany
E-mail: rieke_oelkers@med.uni-heidelberg.de

Summary
Visual information is conducted by two parallel pathways (luminance- and contour-processing pathways) which are thought to be differentially affected in migraine and can be investigated by means of pattern-reversal visual evoked potentials (VEPs). Components and habituation of VEPs at four spatial frequencies were compared between 26 migraineurs (13 without aura, MO; 13 with aura, MA) and 28 healthy volunteers. Migraineurs were recorded in the headache-free interval (at least 72 h before and after an attack). Five blocks of 50 responses to chequerboards of 0.5, 1, 2 and 4 cycles per degree (c.p.d.) were sequentially averaged and analysed for latency and amplitude. Differences in VEPs were dependent on spatial frequency.

Keywords: migraine; visual evoked potential; pattern spatial frequency; habituation; pathophysiology

Abbreviations: c.p.d. = cycles per degree; d.f. = degrees of freedom; MA = migraine with aura; MO = migraine without aura; VAS = visual analogue scale; VEP = visual evoked potential

Introduction
Visual symptoms and photophobia are common features of migraine, but are not exclusively confined to attacks. Hypersensitivity to environmental light (Hay et al., 1994) and grating patterns of definite spatial frequency (Wilkins et al., 1984; Marcus and Soso, 1989) have been demonstrated to persist even between attacks. Hypersensitivity to visual stimuli might be related to the faster low-level visual processing that has been described in migraineurs with aura (Wray et al., 1995). Differences in information processing are not limited to the visual system. In current research, migraine is regarded as a cerebral information-processing disorder associated with central hypersensitivity, which might be at least partly inherited (Gerber and Schoenen, 1998). This is supported by biobehavioural studies in children with migraine (Bille, 1962; Lucas, 1977; Gerber, 1987; Andrasik et al., 1988) and neurophysiological findings using transcranial magnetic stimulation, evoked and event-related potentials (Diener et al., 1989; Kropp and Gerber, 1993; van der Kamp et al., 1996, 1997).

One important aspect of information-processing dysfunction is reduced habituation to stimuli, which has been found, for example, for visual evoked potentials (VEP) and contingent negative variation (Schoenen et al., 1986, 1995; Afra et al., 1998). Deficient habituation in migraineurs, i.e. the absence of a decrement in amplitude over time, might partly account for the increased amplitudes reported in previous VEP studies (Gawel et al., 1983; Diener et al., 1989; Shibata et al., 1997). Although several studies have investigated VEPs in migraineurs, results remain controversial (Kennard et al., 1978; Winter and Cooper, 1985; Polich et al., 1986; Mariani et al., 1988; Drake et al., 1990; Ristanovic et al., 1990; Moreira and Dantas, 1994). This might be due to methodological differences with regard to stimulated field, contrast, spatial and temporal frequency of the patterns used. Check size, i.e. spatial frequency, influences the components and habituation behaviour of pattern-reversal VEPs (Harter and White, 1968, 1970; Peachey et al., 1994).
This is linked to the different involvement of two parallel pathways, the luminance-processing Y system and the contour-processing X system. Affection of these two pathways in migraine has been proposed (Diener et al., 1989). Clinical evidence for this hypothesis has come from psychophysical tests in which migraineurs showed reduced performance in precortical and temporal visual processing (Coleston et al., 1993, 1994). Pathway affection has yet not been investigated using electrophysiological methods, since all previous VEP studies have been performed using only a single check size for stimulation. The aim of the present study was therefore to clarify the affection and interaction of the X and Y systems in migraine by means of pattern-reversal VEP. For this purpose, VEP components and habituation behaviour at four spatial frequencies were compared between migraineurs and healthy controls.

Methods

Subjects

Fifty-four subjects (43 females, 11 males) participated in the study: 28 healthy volunteers (controls; 18 females, 10 males; mean age ± SD, 27.1 ± 4.1 years) and 26 migraineurs (25 females, 1 male; mean age ± SD, 29.1 ± 5.9 years). Thirteen had migraine without aura (MO, code 1.1) and 13 had migraine without aura (MA, code 1.2) (Headache Classification Committee of the International Headache Society, 1988).

Patients were included who reported having episodes of migraine headaches for at least 2 years (mean ± SD, 6.9 ± 4.1 years) and had suffered at least two attacks per month in the last quarter-year. They were recorded in the headache-free interval, i.e. at least 72 h before and after an attack. Only patients who had not taken preventive therapy for migraine during the preceding 6 months were included. Occasional use of common analgesics, ergotamine, sumatriptane and antiemetics was permitted for acute treatment. Patients and controls had normal or corrected normal vision [patients: right eye 103.6 ± 12.1, left eye 103.4 ± 12.6 (mean ± SD); controls: 105.1 ± 11.2 and 102.2 ± 12.5, respectively] and were free of other neurological, ophthalmological or systemic disease known to cause abnormalities in VEP. Visus and contrast sensitivity at a spatial frequency of 4 cycles per degree (c.p.d.), assessed using the Cambridge Low Contrast Gratings (Wilkins et al., 1988), were not significantly different in MA, MO and controls. Only subjects reporting no recurrent migraine-like headaches or ongoing medication were included in the control group. The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects (Tokyo amendment) and the protocol was approved by the University of Erlangen Ethics Review Committee. All subjects were instructed about the study and written informed consent was obtained.

Experimental design and recordings

Black-and-white chequerboard patterns (contrast >99%, reversal frequency 1 Hz) were binocularly presented on a video screen subtending 12×15° of visual angle. Subjects were instructed to fixate on a red point 1.5 cm below and in the middle of the upper border of the screen, as described by Diener and colleagues (Diener et al., 1989). Spatial frequencies (0.5, 1, 2 and 4 c.p.d.) were applied in increasing order, i.e. proceeding from large to small checks. Each spatial frequency was presented in five consecutive blocks of 50 responses each. Presentation of different spatial frequencies was separated by at least 3 min (time for psychophysical rating) to allow recovery from visual stimulation. During the experiment the subjects were comfortably seated, and white noise via headphones (50 dB SPL) was used for acoustic shielding. EEG was recorded from one position of the international 10/20 system (Oz), referenced to linked earlobes (A1 + A2) using surface Ag–AgCl electrodes. After analogue-to-digital conversion, stimulus-linked EEG segments (sampling time 350 ms, prestimulus baseline 100 ms, sampling frequency 250 Hz, band-pass 0.01–30 Hz) were evaluated off-line and automated artefact rejection (single responses contaminated by eye-blinks or muscle artefacts >40 µV) was applied before averaging. Possible eye-blink artefacts were registered from Fp2(A1 + A2). The five consecutive blocks of each spatial frequency were analysed for peak latencies (P0, N1, P1, N2) and peak-to-peak amplitudes of the maximal negative or positive deflections (N1P1, P1N2) were determined by visual inspection of each averaged recording. In addition, subjects had to rate (visual analogue scale,VAS) (i) the visual discomfort provoked by each pattern; (ii) the acoustic discomfort provoked by the white noise used for acoustic shielding; (iii) aversive effects (eye-ache, queasy feeling, headache, nausea, dizziness); and (iv) the number of illusions (colours, shadows, grids, etc.) after each block.

Data analysis

Statistical analysis was carried out using SPSS for windows, version 7.4. Results were compared by multiway analysis of variance (MANOVA) for repeated measures; the within-subject factor was block [degrees of freedom (d.f.) = 4) and the between-subject factor was group (see below)]. Prior to this, the between-subject factor gender (d.f. = 1) was tested in a separate analysis of variance; no significant influence on VEP parameters and subjective ratings could be detected. After that, the between-subject factor of group was first set to migraine (migraineurs = MA and MO versus controls, d.f. = 1) and then to aura (MA versus MO versus controls, d.f. = 2) to detect differences between the two groups of migraineurs. When appropriate, the number of degrees of freedom was adjusted according to Greenhouse and Geisser. The corresponding ε values and the corrected significance levels are reported. Post hoc analysis was carried out by Scheffe’s test. Habituation was calculated using a relative value, and amplitudes of blocks 2–5 were divided by the amplitude of block 1. Subjective ratings (discomfort VAS, colour illusion VAS, figure illusion VAS and number of
aversive effects) were compared using non-parametric tests (Kruskal–Wallis test, Mann–Whitney U test). The α level was set to 0.05. If not indicated otherwise, group data are presented as mean ± standard error of the mean.

Results

VEP

Latency

Grand means of the VEP recordings of the first block at four different spatial frequencies of MA, MO and controls are presented in Fig. 1.

Migraineurs exhibited longer latencies of the N2 component than healthy controls when small checks were presented, i.e. at high spatial frequency (Table 1, Fig. 1). At 4 c.p.d., latency prolongation was most pronounced in MA patients (first block 186.8 ± 5.3 ms) when compared with controls (first block 167.1 ± 2.2 ms). Differences were significant between the three groups at 2 and 4 c.p.d. [Fig. 2; between-subject factor aura: \(F(2,51) = 3.3, P = 0.046\) at 2 c.p.d. and \(F(2,51) = 3.3, P = 0.006\) at 4 c.p.d.]; post hoc tests revealed differences between MA and controls (\(P = 0.030\) at 2 c.p.d. for block 5 and \(P < 0.01\) at 4 c.p.d. for all blocks). A statistically significant effect of the factor migraine (MA and MO) on N2 latencies was also found for 2 and 4 c.p.d. [between-subject factor ‘migraine’: \(F(1,52) = 6.1, P = 0.017\) and \(F(1,52) = 12.8, P = 0.001\), respectively]. N2 latencies at low spatial frequency (0.5 and 1 c.p.d.) were not significantly different between groups, either for the between-subject factor migraine or for aura.

Latencies of the early VEP components (P0, N1, P1) also tended to be prolonged in MA patients, but only a few differences between MA, MO and control subjects (between-subject factor aura) reached weak significance. P0 tended to be prolonged in MA patients; differences were significant at 0.5 and 2 c.p.d. [0.5 c.p.d., first block (ms), MA 52.3 ± 4.7, MO 49.5 ± 2.5, controls 50.6 ± 2.5; \(F(2,51) = 3.3, P = 0.046\); 2 c.p.d.: first block (ms), MA 65.9 ± 3.7, MO 56.0 ± 3.5, controls 57.3 ± 2.6; \(F(2,51) = 6.3, P = 0.003\)]. At 2 c.p.d., weakly significant aura × block interaction occurred \([F(4,948) = 2.301, \varepsilon = 0.618, P = 0.049]\), indicating more pronounced latency prolongation in MA over the five blocks. N1 latency was significantly different between groups at 1 c.p.d. [first block (ms): MA 89.2 ± 1.5, MO 80.6 ± 2.9, controls 84.1 ± 1.5; \(F(2,51) = 3.5, P = 0.037\)] and P1 latency at 2 c.p.d. [first block (ms): MA 124.6 ± 1.2, MO 120.0 ± 2.1, controls 120.4 ± 1.4; \(F(2,51) = 3.4, P = 0.041\)]. For the factor migraine, latencies of the early VEP components (P0, N1, P1) were not significantly different.

Amplitude

The peak-to-peak amplitudes (N1P1, P1N2) were consistently higher in migraineurs at all spatial frequencies tested, N1P1 ranging from 23.3 to 29.9 µV in MO patients and from 19.2 to 30.9 µV in MA patients compared with a range from 17.8 to 26.0 µV in controls. Amplitude augmentation in migraineurs was marked at low spatial frequencies. P1N2 differences reached statistical significance at 0.5 c.p.d. for the between-subject factor migraine [first block (µV): MA 22.2 ± 3.4, MO 22.4 ± 3.6, controls 17.4 ± 1.4; \(F(1,51) =

Fig. 1 Grand means of the VEP recordings (first block) at 0.5, 1, 2 and 4 c.p.d. in migraine with aura (MA), migraine without aura (MO) and controls (CO).
**Table 1** Latencies of the late VEP component N2 (mean ± SEM) for the four spatial frequencies each with five subsequent blocks in migraine patients with aura (MA) and without aura (MO) and in healthy controls

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Groups were significantly different at 2 and 4 c.p.d. [between-subject factor aura: $F(2,51) = 3.3, P = 0.046$ at 2 c.p.d. and $F(2,51) = 9.3, P = 0.000$ at 4 c.p.d.; between-subject factor migraine: $F(1,52) = 6.1, P = 0.017$ at 2 c.p.d. and $F(1,52) = 12.8, P = 0.001$ at 4 c.p.d.].

**Fig. 2** Latencies of the N2 component (mean ± SEM) at 2 and 4 c.p.d., each with five consecutive blocks in migraine with aura (MA), without aura (MO) and controls (CO). Asterisks indicate significant differences between groups: *2 c.p.d.: between-subject factor aura: $F(2,51) = 3.3, P = 0.046$; between-subject factor migraine: $F(1,52) = 6.1, P = 0.017$; **4 c.p.d.: between-subject factor aura: $F(2,51) = 9.3, P = 0.000$; between-subject factor migraine: $F(1,52) = 12.8, P = 0.001$. 
Habituation
Habituation was calculated using a relative value [amplitude (block 2–5)/amplitude (block 1)]. In migraineurs and controls, amplitude decreased over blocks when the smallest check size was presented, indicating habituation at high spatial frequency (4 c.p.d.). When large checks were presented (0.5 c.p.d.), amplitude tended to increase over blocks in MA patients whereas MO patients and controls showed stable or slightly declining responses. However, group differences did not reach statistical significance at any spatial frequency either for the between-subject factor migraine (d.f. = 1) or for aura (d.f. = 2) (Fig. 3).

Psychophysical rating
Illusions
Migraineurs reported more colour and figure illusions at all spatial frequencies (Fig. 4). Group differences were significant at all spatial frequencies (grouping factor migraine: Mann–Whitney U test, d.f. = 1, P = 0.030, P = 0.019, P = 0.001, P = 0.043 at 0.5, 1, 2 and 4 c.p.d., respectively, for colour illusions and P = 0.027, P = 0.046, P = 0.036, P = 0.037 at 0.5, 1, 2 and 4 c.p.d. for figure illusions). The number of illusions increased in both groups when small checks were presented, i.e. at high spatial frequency. A statistically significant effect of the factor aura was also found at 1 and 2 c.p.d. for colour illusions (grouping factor aura: Kruskal–Wallis test, d.f. = 2, P = 0.011 and P = 0.005, respectively) and at 2 and 4 c.p.d. for figure illusions (P = 0.007 and P = 0.029).

Aversive effects
The percentage of subjects reporting one to three aversive effects was augmented at high spatial frequencies in migraineurs but not in control subjects. Differences were statistically significant at 2 and 4 c.p.d. (Mann–Whitney U test, grouping factor migraine: d.f. = 1, P = 0.002 and P = 0.001, respectively; Kruskal–Wallis test, grouping factor aura: d.f. = 2, P = 0.005 at 2 and 4 c.p.d.).

Discomfort of visual and acoustic stimulation
MA patients tended to experience more visual discomfort at 2 and 4 c.p.d. (data not shown), but group differences were not statistically significant either for the factor migraine (Mann–Whitney U test, d.f. = 1) or for aura (Kruskal–Wallis test, d.f. = 2). Rating of the white noise used for acoustic shielding, however, revealed significantly higher discomfort in migraineurs at high spatial frequencies (Mann–Whitney U test, grouping factor migraine: d.f. = 1, P = 0.011 at 2 c.p.d., P = 0.012 at 4 c.p.d.; Kruskal–Wallis test, grouping factor aura: d.f. = 2, P = 0.036 at 2 c.p.d., P = 0.015 at 4 c.p.d.).

Discussion
Up to now, no study has systematically investigated VEPs at different spatial frequencies in migraine. Most studies have focused on latencies of the stable early components and patterns of low spatial frequencies, i.e. <=1 c.p.d. (Kennard et al., 1978; Gawel et al., 1983; Winter and Cooper, 1985; Polich et al., 1986; Mariani et al., 1988; Diener et al., 1989; Drake et al., 1990; Ristanovic et al., 1990; Moreira and Dantas, 1994; Shibata et al., 1997). The present VEP study was performed using patterns of four spatial frequencies to investigate two parallel visual pathways (the X and Y systems), which might be differentially affected in migraine. Results suggest that migraineurs have prolonged N2 latencies when small check sizes are applied. In contrast, no differences were found at low spatial frequencies, i.e. when large check sizes were used.

VEP parameters vary as a function of check size. Two visual pathways are involved to different degrees: the X system and the Y system (Harter and White, 1968, 1970). Large patterns (i.e. low spatial frequency, 0.5 and 1 c.p.d.) are mainly conducted by the Y system, which processes movement and luminance. In contrast, the X system processes contrast and contour. For small patterns both the X system and the Y system are involved (Kulikowski, 1977, 1978). These two pathways have properties equivalent to two spatiotemporal filters (ST1 and ST2) on visual stimuli. ST1 is linked to the X-type mechanism and is stimulated by spatially modulated background gratings with a peak response at 4–8 c.p.d. and low temporal frequency (non-flickering). ST2 has low-pass properties for spatial frequencies (peak 1 c.p.d.) and band-pass properties for temporal frequencies (peak 10–20 Hz) like the Y-type mechanism (Holliday and Ruddock, 1983). The Y system receives input mainly from the retinal periphery via the magnocellular pathway (dorsal layers of lateral geniculate nucleus, lateral geniculate nucleus) and is very sensitive to contrast (Kubova et al., 1995). The X system receives input mainly from foveal and perifoveal areas via the parvocellular pathway (ventral layers of the lateral geniculate nucleus) and requires higher luminous intensities.

The P1 component of pattern-reversal VEPs is attributed to the X system. In contrast, the N2 component is ascribed mainly to the Y system (Kubova et al., 1995). Latencies of all VEP components increase with increasing spatial frequency, but prolongation of N2 is partly compensated for by the appearance of an earlier contour-specific negative component called N130 (Wenzel, 1984). This component interferes with the Y-dependent N180, and the resulting N2 is a superposition of N130 and N180. N130 is characteristic of potentials evoked by small checks and might be ascribed
R. Oelkers et al.

Fig. 3 Habituation expressed as relative amplitude changes of N1P1 and P1N2 [amplitude (block 2–5)/amplitude (block 1), mean ± SEM] in five sequential blocks at 0.5, 1, 2 and 4 c.p.d. in migraine with aura (closed circles), without aura (closed triangles) and controls (open squares). Habituation was not significantly different between groups.

to the X system (Wenzel, 1984). In healthy subjects, N130 predominates when small checks are presented and is therefore important for ‘normal’ N2 latencies at high spatial frequency. Delayed N2 latency for these check sizes in migraineurs may be due to an attenuated or absent N130 and/or a relatively predominant N180 (Fig. 5). This might reflect an imbalance of the two visual pathways with relative predominance of the luminance-dependent Y system. Intrinsic abnormalities in the connectivity of the magnocellular (Y) and parvocellular (X) precortical visual pathways (Coleston et al., 1994), possibly due to impairment of GABAergic inhibitory interneurons (Chronicle and Mulleners, 1994) and/or altered dopaminergic transmission, may be responsible.

This concept of X–Y imbalance also makes it clear why marked latency group differences are limited to the presentation of small patterns that stimulate both pathways. Our results are in line with those of others that suggest normal N2 latencies for migraineurs under Y-stimulating conditions, i.e. when large checks are applied (Winter and Cooper, 1985; Polich et al., 1986; Mariani et al., 1988; Drake et al., 1990; Ristanovic et al., 1990). One study using small checks showed normal latencies (Schoenen et al., 1995), but the stimulating conditions in that study addressed the Y system to a greater extent than did the conditions used in our design (lower pattern contrast, higher temporal frequency). In general, direct comparisons of VEP studies are difficult because of the heterogeneity of stimulating conditions with regard to contrast, stimulated visual field, and spatial and temporal frequencies.

The barely changed latencies of the early VEP components P0, N1 and P1 in migraineurs may be explained by the generally greater stability of the early VEP components...
Fig. 4 Subjective ratings (visual analogue scales, mean) of VEP recordings at 0.5, 1, 2 and 4 c.p.d. in migraine with aura (MA), migraine without aura (MO) and controls (CO). Asterisks indicate significant differences between groups. *Grouping factor migraine: Mann–Whitney U test, P < 0.05; **grouping factor migraine: Mann–Whitney U test, P < 0.01; † grouping factor aura: Kruskal–Wallis test, P < 0.05; ‡ grouping factor aura: Kruskal–Wallis test, P < 0.01.

Fig. 5 Model of VEPs at high spatial frequency (4 c.p.d.). N2 can be regarded as a superposition of N130 and N180 with strong predominance of N130 in normal subjects. In migraineurs, attenuation or absence of a contour-specific N130 may cause a delayed N2 consisting mainly of the luminance-dependent N180.

affected primarily by morphological changes in the optic nerve and the central pathways (Ellingson et al., 1973). Our results are basically in accordance with those of other authors (Winter and Cooper, 1985; Polich et al., 1986; Mariani et al., 1988; Drake et al., 1990; Ristanovic et al., 1990; Schoenen et al., 1995; Tagliati et al., 1995).

Different involvement of the X and the Y systems is also proposed to play a role in habituation behaviour with respect to pattern-reversal stimulation. In normal subjects, clear habituation is found only when small checks are presented. In contrast, nearly stable responses are characteristic of low spatial frequencies, i.e. Y-stimulating conditions (Peachey et al., 1994). This is consistent with our findings. No statistically significant differences were found between MA, MO and control subjects. This is in contrast to previous studies describing deficient habituation in migraineurs at high spatial frequency (Schoenen et al., 1995; Afra et al., 1998).

The discrepancy might be explained by the different stimulating conditions, with a greater proportion of Y stimulation compared with our design due to higher temporal frequency and lower pattern contrast. Low pattern contrast is known to increase habituation effects (Thompson and Spencer, 1966). As normal subjects fail to habituate under Y-stimulating conditions, the previously described deficient
habituation to pattern stimuli in migraineurs (Schoenen et al., 1995; Afra et al., 1998) might be linked to the proposed predominance of the Y system. This would also be consistent with the statistically non-significant tendency to increasing amplitude that we found in MA patients at 0.5 c.p.d.

Habituation behaviour in migraine seems to be affected in a complex way, depending on stimulating conditions, rather than being generally impaired. A predominant Y system might contribute to altered habituation behaviour under specific stimulating conditions. Further research in which these conditions are varied (contrast, spatial and temporal frequency, time course of repeated series of habituation) is necessary for clarification.

Spatial frequency also influenced the psychophysical ratings in our study, so subjective discomfort and aversive effects similar to symptoms of migraine attacks (eye-ache, queasy feeling, headache, nausea, dizziness) are particularly reported at high spatial frequencies in the migraineur group. At present, it is not evident how these subjective perceptions are related to the prolongation of N2 latency. However, the parallelism of objective and subjective findings might indicate that X–Y imbalance plays a role in migraine pathophysiology and is probably involved in triggering migraine attacks.

In summary, for the first time a prolongation of N2 latency in migraineurs was shown at high spatial frequencies, i.e. when small checks were presented. Habituation behaviour was not different between groups. The prolongation of N2 latency argues in favour of an imbalance of the luminance-processing Y system and the contour-processing X system. Interictal Y predominance might increase sensitivity to visual stimuli and thereby be relevant in migraine pathophysiology.

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