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Lack of cortical contrast gain control in human photosensitive epilepsy

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Television and video games may be powerful triggers for visually induced epileptic seizures. To better understand the triggering elements of visual stimuli and cortical mechanisms of hyperexcitability, we examined eleven patients with idiopathic photosensitive epilepsy by recording visually evoked potentials (VEPs) in response to temporally modulated patterns of different contrast. For stimuli of low–medium, but not high, temporal frequency, the contrast dependence of VEP amplitude and latency is remarkably abnormal for luminance contrast (black–white), but not so for chromatic contrast (equiluminant red–green) stimuli. We conclude that cortical mechanisms of contrast gain control for pattern stimuli of relatively low temporal frequency and high luminance contrast are lacking or severely impaired in photosensitive subjects.

Photosensitive epilepsy (PSE) is the most common form of stimulus-induced epilepsy[1]. Its prevalence in children 4–14 years old is substantial (0.5%–0.8%), and its incidence is increasing as a result of the proliferation of television display units and video games, which may act as triggers[2]. During a recent television showing of the 'Pocket Monsters' cartoon in Japan, 685 children experienced epileptic seizures[3,4]. The degree of danger inherent in such seizures ranges from nil to potentially life threatening, in exceptional cases[5]. Epileptic seizures induced by photic stimulation may be primarily generalized (tonic-clonic, myoclonic, absence seizures) or focal (occipital, with or without spreading to other cortical areas). PSE is defined as 'pure' when seizures are exclusively photic induced, and is usually idiopathic (with no other etiology than a genetic background)[6].

Because of the complexity and heterogeneity of video-generated patterns, reports of pattern-induced epilepsies are mainly anecdotal. Oriented lines are considered more powerful than checkerboards in inducing epileptiform EEG changes[7], and oscillating patterns more epileptogenic than static patterns[8]. However, the characteristics of the visual stimulus and the cortical dynamics leading to the hypersynchronous neuronal response underlying PSE are poorly understood. A better knowledge of the triggering elements of visual stimuli might help in devising safer video-generated patterns.

The temporal frequency of an intermittent photic stimulus is crucial for arousing epileptic activity. This suggests that, even for patterned stimuli, the temporal frequency may be critical. However, there is no systematic study on the visually evoked potentials to temporally modulated patterned stimuli in PSE patients. Another crucial parameter of pattern stimuli is spatial contrast (related to the spatial variations in brightness). It is conceivable that contrast is also a critical parameter for cortical excitability.

We studied both control subjects and patients with pure idiopathic PSE whose seizures originated from the occipital lobe[9,10]. VEPs were recorded in response to simple visual patterns (black/white and red/green sinusoidal gratings of different contrast), sinusoidally contrast-reversed at various temporal frequencies. The EEG activity remained in a physiological state throughout the experiment. In patients, the dependence of VEP amplitude on luminance-contrast for stimuli of relatively low temporal frequency (4–10 Hz) was dramatically altered. Specifically, at increasing contrast, the VEPs saturated in amplitude and shortened in phase in controls, whereas in patients there was little saturation or phase shift. These results suggest that cortical mechanisms of contrast gain control were lacking or severely impaired in PSE.

Results

Luminance gratings: effect of temporal frequency

In both controls and patients, steady-state VEPs were recorded as a function of temporal frequency of luminance-contrast gratings. Stimulus contrast (90%) and spatial frequency (2 cycles per degree) were chosen to maximize response amplitude[11,12]. In agreement with previous studies[11,12], the form of the temporal function consistently showed two amplitude peaks (at 3–8 Hz and 16–20 Hz) and a local minimum at 10–12 Hz in normal subjects (**Fig. 1a** and **c**). In PSE patients (**Fig. 1b** and **c**), the high temporal-frequency cutoff was comparable to that of controls. However, the shape of the temporal function was more variable. In particular, low- and high-frequency amplitude peaks were less defined, and in some subjects, substantial activity was present at intermediate frequencies (10–12 Hz), at which controls responded poorly. Overall, VEP amplitude was significantly larger in patients than controls (**Fig. 1c**; two-way ANOVA, $F_{1,271} = 6.2$, $p = 0.012$).

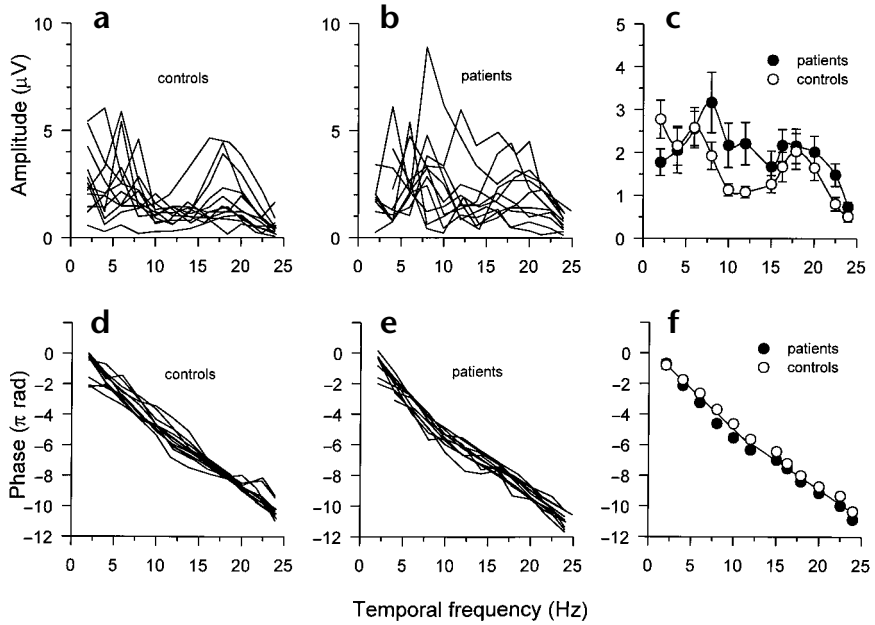

Fig. 1. Luminance-contrast gratings: effect of temporal frequency. VEP amplitude and phase plots of individual control subjects (**a**, **d**) and patients (**b**, **e**). (**c**, **f**) Average (± s.e.) VEP amplitude and phase of control subjects and patients are shown superimposed.

The VEP phase progressively lagged with increasing temporal frequency. Both raw data (**Fig. 1d** and **e**) and averaged data (**Fig. 1f**) indicate that the phase plots were similar in controls and patients. The response latency (in seconds) can be obtained from the slope of the phase plot (π rad / Hz) divided by 4 (modulo = 2 π rad * 2nd harmonic; see ref. 12). The average latencies, evaluated from individual phase plots, did not significantly differ between controls and patients (106.7 ± 2.5 ms, s. e., versus 107.7 ± 2.2 ms).

Luminance gratings: effect of contrast

For each subject, contrast functions were evaluated at the low- and high-frequency peaks of the individual temporal functions (**Fig. 1**). In agreement with previous reports[13], the average VEP amplitude of controls progressively increased with increasing contrast, and saturated at about 20% contrast (**Fig. 2a**). In patients, the average contrast function was virtually identical to that of controls in the low contrast range (3–20%; **Fig. 2a**), indicating comparable contrast threshold and contrast dependence at low contrast. Unlike controls, however, the response did not saturate with increasing contrast above 20%, and reached abnormally higher-amplitude values at maximum contrast (two-way ANOVA, $F_{1,236} = 17.6$, $p < 0.001$).

The difference in shape of the contrast function between the two groups was evaluated from individual curves (see below). At higher temporal frequencies (**Fig. 2b**), the VEP contrast function was comparable in controls and patients, and did not show amplitude saturation.

Average VEP phase showed contrast dependence in the low temporal-frequency range (**Fig. 2c**). Because VEPs were recorded at different temporal frequencies in individual subjects, data were normalized by transforming original phase values into latency values. Phase data were first divided by 4 (modulo = 2 π rad * 2nd harmonic) and then multiplied by the stimulus period in milliseconds. Latency values of responses to maximum contrast were normalized to zero-latency lag, and latencies for all other contrasts were expressed as relative changes. Normalization of latency for responses to maximum contrast was possible, as VEPs of controls and patients showed comparable latencies at high contrast (see above). The VEP latency of controls progressively lagged with decreasing contrast (**Fig. 2c**). In patients, however, the response latency did not slow down with decreasing contrast in the medium- to high-contrast range (10–90%). The different latency dependence between controls and patients was evaluated from individual curves (see below).

In the higher temporal-frequency range (**Fig. 2d**), the contrast dependence of average VEP phases was virtually identical in controls and patients. The abnormal dependence of VEP amplitudes and phases on contrast in the low temporal-frequency range was very consistent among patients. We plotted individual response curves for both controls and patients (**Fig. 3**). The individual curves of most controls showed amplitude saturation at high contrasts (**Fig. 3a**), whereas this was not observed in the majority of patients (**Fig. 3b**). To provide a quantitative evaluation of saturation, a saturation index[14] was derived for the individual amplitude curves. The saturation index is defined as

$(1 - c_{1/2})/c_{1/2}$

where $c_{1/2}$ is the contrast that elicits responses with half the amplitude of the response at maximum contrast. A value of one corre-

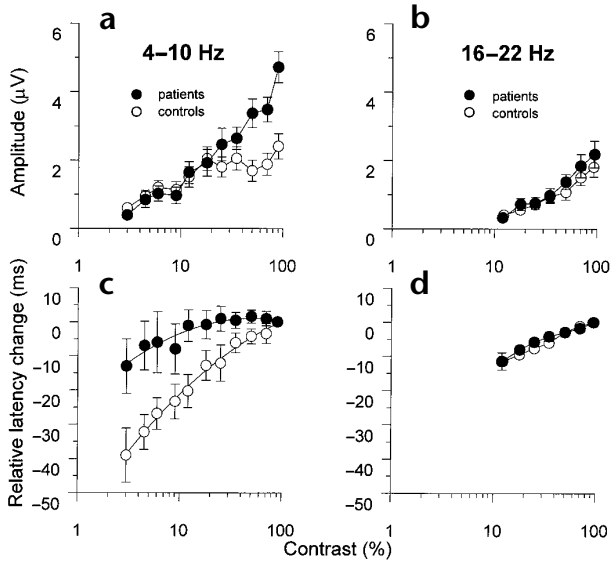

Fig. 2. Luminance-contrast gratings: effect of contrast. Average (± s.e.) amplitude (**a**, **b**) and latency (**c**, **d**) for two different ranges of temporal frequencies. In the 4–10 Hz range, the contrast dependence differed remarkably between controls and patients at medium–high contrast. In the 16–22 Hz range, the contrast dependence of amplitude (**b**) and phase (**d**) was virtually identical in control subjects and patients.

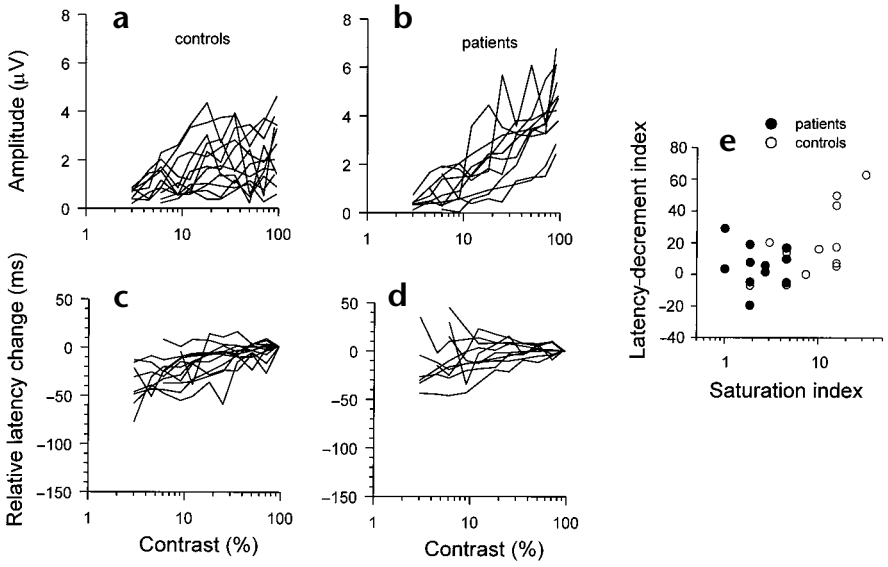

Fig. 3. Luminance-contrast gratings of 4–10 Hz temporal frequency: effect of contrast in individual subjects. Amplitude and latency plots of control subjects (**a** and **c**) and patients (**b** and **d**). (**e**) Scatter plot of saturation and latency indices (see text) for control subjects and patients.

sponds to lack of saturation. The average saturation index was much higher in controls than in patients (13.45 ± 2.39 versus 2.8 ± 0.63; $t_{21} = 3.91$, $p = 0.0008$). To provide an index of latency decrement with increasing contrast, the individual curves (**Fig. 3c** and **d**) were linearly interpolated between 20% and maximum contrast. The average slope of the regression line (ms per unit contrast) was found to be significantly steeper in controls than in patients (19.52 ± 6.18 versus 1.64 ± 5.15; $t_{21} = 2.16$; $p = 0.04$). In a scatter plot of saturation index and latency decrement (**Fig. 3e**), there was little overlap between the two groups, with patients showing less saturation and lower latency decrement than most controls. Interestingly, the two indices were correlated in controls ($R = 0.72$, $p = 0.008$) but not in patients ($R = 0.12$, $p = 0.73$). The correlation between saturation and latency decrement is consistent with proposed models of contrast gain control[14–16].

Chromatic gratings: temporal frequency and contrast

We explored whether steady-state VEPs to chromatic gratings were abnormal in PSE patients. Previous studies report failure of equiluminant red/green stimuli to induce paroxysmal EEG activity[7]. Temporal and contrast functions were evaluated for equiluminant red/green gratings (see Methods), and the results were summarized (**Fig. 4**). The temporal function for high contrast chromatic gratings (**Fig. 4a**) had a simple profile with an amplitude peak at about 5 Hz and rapid attenuation at higher frequencies[11,17]. Both the shape of the temporal function and the high-frequency cutoff were similar in PSE and controls, differing mainly in amplitude (two-way ANOVA, $F_{1,197} = 20.9$, $p < 0.001$; PSE > controls). The average amplitude curves actually showed a slight difference in bandwidth (half-height width), but there was no significant temporal-frequency × group interaction ($F_{1,197} = 1.55$, $p = 0.14$), possibly because of the larger variability of patient data. The VEP phase (**Fig. 4c**) lagged as a function of temporal frequency, with a comparable slope in controls and patients. Average latencies, evaluated from individual phase plots, tended to be longer in controls (142.2 ± 7 ms) than in patients (129.3 ± 6 ms). However, the difference was not significant.

Contrast functions were evaluated at individual peak temporal frequencies (range, 3–6 Hz). In both controls and patients (**Fig. 4b**), the VEP amplitude progressively increased with increasing contrast, and tended to saturate at the highest (70%–90%) contrasts. The average saturation index of individual response curves was not significantly different between controls (2.1 ± 0.32) and patients (1.81 ± 0.34; $t_{21} = 0.61$, $p = 0.54$). The variation in response latency (after normalization of phase data; see above) was contrast dependent (**Fig. 4d**). As for luminance-contrast stimuli, the VEP latency progressively lagged with decreasing contrast, with a somewhat steeper slope for controls than for patients. Latency decrement indices were obtained by linearly interpolating between 20% and maximum contrast individual curves. The average slope of the regression line (ms per unit contrast) did not significantly differ between controls and patients (27.3 ± 11.4 versus 8.0 ± 8.9; $t_{21} = 2.3$; $p = 0.2$).

Discussion

Intermittent photic stimulation using a stroboscope is exploited in the EEG laboratory to trigger photoparoxysmal responses in PSE patients, with 11–20 flashes per second representing the most

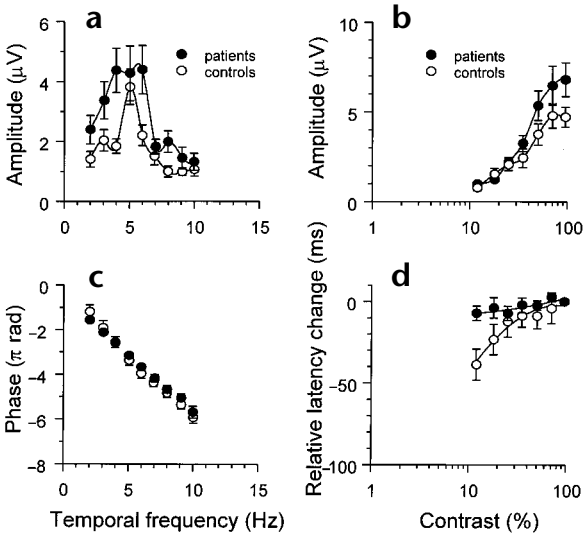

Fig. 4. Chromatic-contrast gratings: effect of temporal frequency and contrast. Average (± s.e.) VEP amplitude and phase as a function of temporal frequency (**a**, **c**) and contrast (**b**, **d**). The shape of the temporal and contrast functions (**a**, **b**) was comparable in control subjects and patients. The slopes of the phase and latency plots (**c**, **d**) tended to be steeper in controls than in patients.

effective frequencies[2,18]. Photoparoxysmal activity may also be provoked by viewing a striped black/white pattern[19]. Contrast values above 40%, a spatial frequency of 2–4 cycles per degree and 10–20 Hz reversal frequency are most epileptogenic[19].

Human photosensitivity is a form of reflex epilepsy arising in the visual cortex, with high tendency toward generalization[19]. The efficacy of the triggering stimulus depends on its ability to elicit action potentials in a hyperexcitable visual cortex, on synchronizing effects and on the size of the neural population activated[8].

The present findings, obtained with patterned stimuli of high contrast sinusoidally modulated in time, show that a range of relatively low temporal frequencies may be critical for cortical hyperexcitability. Indeed, the VEP responses of the patients in this temporal frequency range tend to be higher in amplitude in comparison with controls, in spite of most patients being treated with antiepileptic drugs, which may reduce the size of the VEPs[2,21].

To investigate the origin of the different VEP responses of patients and controls, we measured the amplitude and phase dependence of VEPs on stimulus contrast at two temporal frequency ranges, 4–10 Hz and 16–22 Hz. Whereas the VEP dependence on contrast is comparable for patients and controls at higher temporal frequency, there is a clear difference at the lower temporal frequency. The amplitude saturation at high contrasts and the phase advance with increasing contrast typically found in normal subjects[22] were absent or much reduced in patients. Interestingly, the contrast threshold and the contrast dependence in the low contrast range were not affected in PSE. The critical range of reversal of square-wave patterns reported to elicit epileptic EEG activity (10–20 reversals per second)[19]corresponds to a fundamental temporal frequency of 5–10 Hz, in agreement with our findings of sine-wave temporal modulation.

Single cells of the primary visual cortex of the cat and monkey show response saturation and phase advance in response to drifting sinusoidal gratings of increasing contrast[14,23]. These nonlinear response properties could result from a contrast gain control stage that scales the input contrast taking into account the average contrast in the surround[16] or the average activity of a large population of surrounding cells[14,24]. In the cat visual cortex, removing inhibitory effects by local application of bicuculline abolishes VEP response saturation and reduces phase shift, suggesting that a mechanism normally responsible for contrast gain control has been suppressed[25]. Our VEP data do not allow us to advance suggestions about the site and nature of the gain-control mechanism[14–16,26]. Note, however, that the pattern ERG in response to both luminance and chromatic gratings does not show significant saturation and phase shift with increasing contrast[27]. The average saturation index of VEP amplitudes and the average latency decrement with increasing stimulus contrast in controls are in agreement with data obtained from simple cortical cells under similar stimulus conditions[14]. This encourages us to interpret the control data as indicating a mechanism of contrast gain control and to speculate that such a mechanism is defective or absent in the visual system of PSE patients. VEP responses at the higher temporal frequencies, at which normal subjects did not show amplitude saturation, were unaffected in PSE.

VEPs to high-contrast red/green equiluminant gratings tended to be larger than normal and showed a smaller phase advance in PSE, although saturation indices were not different from those for controls. The present findings do not contradict the previous report that stationary equiluminant patterns are ineffective in inducing photoparoxysmal EEG activity[7].

In conclusion, our results indicate that pattern stimuli of relatively low temporal frequency and high contrast may be particularly effective in uncovering cortical hyperexcitability in PSE, possibly because of an impairment of contrast gain-control mechanisms normally present at these temporal frequencies. High-contrast stimuli endowed with such temporal characteristics are common in TV images and in video games, and may be important in triggering the abnormal cortical response underlying visually induced epileptic seizures.

Methods

Subjects. Subjects were 12 normal volunteers (mean age, 15.2 ± 3.2 years; $n = 6$ males) and 11 adolescents and young adults (mean age, 18 ± 3 years; $n = 3$ males) with PSE[9] (**Table 1**). All patients showed high-amplitude VEPs (with normal waveform) to both bright flashes and checkerboard patterns[21]. Nine patients were being treated with antiepileptic drugs during the study. Antiepileptic drugs (especially VPA) attenuate the photoparoxysmal response and may reduce the VEP amplitude[2,21]. These effects are interpreted as resulting from reduced spread of cortical activity rather than alteration of mechanisms responsible for its generation[28]. EEG monitoring throughout the VEP sessions did not show epileptiform

Table 1. Details of the 11 photosensitive patients.

Gender/age	Seizure types	AEDs at VEPs examination	Reported enviromental triggers	Photosensitivity range (frequency) IPS	Pattern (reversal rate)
M/19	CPS	VPA	bright sunlight	10–30 Hz	2–20 Hz
F/20	CPS	no	TV	18–25 Hz	NP
F/22	SPS + II gen	CBZ	TV, computers	15–25 Hz	10–18 Hz
F/21	SPS + II gen	CBZ	TV	15–18 Hz	NP
F/13	SPS	VPA	TV, bright sunlight	12–30 Hz	NP
F/21	CPS + II gen	VPA, PB	TV, bright sunlight, video games	15–40 Hz	2–18 Hz
M/19	SPS + II gen	no	video games	12–21 Hz	10–20 Hz
F/21	CPS	VPA, CBZ	TV, bright sunlight	5–15 Hz	5–20 Hz
F/19	CPS	VPA	TV	13–18 Hz	10–18 Hz
F/14	SPS + II gen	VPA	TV	15–21 Hz	10–20 Hz
M/15	CPS	VPA	TV, highly contrasted patterns	4–50 Hz	4–18 Hz

AEDs, antiepileptic drugs; VEPs, visual evoked potentials; Y, years; IPS, intermittent photic stimulation; M, male; CPS, complex partial seizure; VPA, valproic acid; Hz, hertz; F, female; TV, television; NP, not performed; SPS, simple partial seizure; II gen, secondary generalization; CBZ, carbamazepine; PB, phenobarbital.

activity. Experiments followed the tenets of the Declaration of Helsinki. Informed consent was obtained after the nature of the technique and the aim of the research were explained.

Visual stimuli. Methods for generating luminance contrast (black–white) and chromatic contrast (red-green) stimuli are reported in detail elsewhere[17,29]. Briefly, stimuli were horizontal sinusoidal gratings of 2 cycles per degree and different Michaelson contrast (3–90%, in half-octave steps), sinusoidally reversed in contrast at 3–24 Hz. Both luminance and chromatic gratings were generated by a VSG/2 graphic card (Cambridge Research System, Cambridge, UK) and displayed on a gamma-corrected color monitor (Barco CCID 7751, Kortrijk, Belgium). To establish equiluminance, subjects viewed a red/green grating of 50% contrast alternating at 15 Hz, and adjusted the relative luminance of red and green[30] to minimize perception of flicker. Chromatic patterns were viewed through yellow filters (Kodak Wratten 16, Rochester, New York) to attenuate wavelengths lower than 500 nm. CIE coordinates (evaluated by a Minolta Chromameter CS 100, Osaka, Japan) were $x = 0.637$, $y = 0.362$ (red); $x = 0.416$, $y = 0.582$ (green). Visual stimuli had a mean luminance of 14 cd per m^2 and subtended an area of 14° × 14° at the viewing distance of 100 cm. Subjects monocularly fixated a black spot at the center of the screen.

Stimuli in a comparable spatiotemporal range provoked abnormal EEG activity under diagnostic investigation (**Table 1**). To prevent triggering abnormal EEG activity during the experiment, we limited stimulation to one eye and to a relatively small area of the visual field. Moreover, abrupt changes in retinal stimulation were avoided using sine-wave contrast reversal and horizontal gratings that reduced the effects of saccadic eye movements.

VEP recording. Steady-state VEPs were recorded from scalp electrodes (resistance < 5 kΩ) placed over the occipital (Oz) and frontal (Fz) cortices, and referenced to the vertex (Cz). The left mastoid was grounded. Signals were filtered (0.3–100 Hz, –6 dB per octave) amplified (50,000-fold), digitized (2 kHz, 12-bit resolution) and averaged (at least 160 sums), with rejection of signals exceeding a threshold voltage. This assured that single sweeps occasionally contaminated by epileptiform spikes did not contribute to the averaged records. To reduce patients' exposure time to the patterns, the stimuli were presented for a short time (corresponding to 20 sweeps) and intermingled with brief interruptions. Partial averages (20 sums) of the total averages were used to evaluate response consistency[11]; these were of the same order in patients as in controls. Averaged VEPs were submitted to DFT analysis to evaluate the second-harmonic (major response component) amplitude and phase[11]. Responses to patterns of zero contrast were frequently recorded to obtain a measure of residual noise (average, 0.3 μV). Responses recorded simultaneously from Fz were close to the noise level and are not shown.

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