Human Lateral Geniculate Nucleus and Visual Cortex Respond to Screen Flicker

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The first electrophysiological study of the human lateral geniculate nucleus (LGN), optic radiation, striate, and extra-striate visual areas is presented in the context of presurgical evaluation of three epileptic patients (Patients 1, 2, and 3). Visual-evoked potentials to pattern reversal and face presentation were recorded with depth intracranial electrodes implanted stereotactically. For Patient 1, electrode anatomical registration, structural magnetic resonance imaging, and electrophysiological responses confirmed the location of two contacts in the geniculate body and one in the optic radiation. The first responses peaked approximately 40 milliseconds in the LGN in Patient 1 and 60 milliseconds in the V1/V2 complex in Patients 2 and 3. Moreover, steady state visual-evoked potentials evoked by the unperceived but commonly experienced video-screen flicker were recorded in the LGN, optic radiation, and V1/V2 visual areas. This study provides topographic and temporal propagation characteristics of steady state visual-evoked potentials along human visual pathways. We discuss the possible relationship between the oscillating signal recorded in subcortical and cortical areas and the electroencephalogram abnormalities observed in patients suffering from photosensitive epilepsy, particularly video-game epilepsy. The consequences of high temporal frequency visual stimuli delivered by ubiquitous video screens on epilepsy, headaches, and eyestrain must be considered.

Seizures provoked by video games or television viewing are commonly experienced by photosensitive epileptic patients.[1] The visual attributes eliciting these seizures, for example, the video-screen flicker, are not always consciously perceived. In fact, many events processed by the human brain are not accessible to consciousness, even if they may influence brain activity. High temporal frequency visual stimuli, although not consciously perceived when their frequency is over the perceptual critical fusion frequency, evoke phase-locked responses on the electroretinogram[2,3] and on scalp recordings in humans.[4,5] This kind of periodic response called steady state visual-evoked potentials (SSVEPs)[6] also has been described in neuronal recordings of cat retina and lateral geniculate nucleus (LGN).[7] In humans, it is not known which cortical or subcortical structures are involved in the generation of SSVEPs. Scalp studies do not allow a precise topographic analysis of signals, and other methods are necessary to reach a better spatial precision.

During presurgical evaluation of three epileptic patients, we had the opportunity to study electrophysiological responses in human LGN and cortical visual areas. VEPs to pattern reversal checkerboard and faces were recorded using intracranial multicontact depth probes.

Patients and Methods

Patients
Three female patients (Patients 1–3, aged 27, 48, and 20 years, respectively) suffering from drug refractory epilepsy were included in this study. All three were deprived of medication during the study. The structures to be explored were defined on the basis of clinical, electroencephalogram (EEG), and neuroimaging studies. Visual fields and acuity were normal. None of the subjects presented a light intermittent stimulation sensitivity. Subjects gave fully informed consent.

Implantation of Electrodes
The electrodes were implanted perpendicularly to the midsagittal plane using Talairach's stereotactic grid. Depth probes were 0.8mm in diameter and had 5, 10, or 15 recording electrode contacts. Contacts were 2.0mm long, and successive contacts were separated by 1.5mm. Electrode locations were measured on x-ray images obtained in a stereotactic frame and registered on structural magnetic resonance imaging (MRI). The accuracy of the registration procedure

was approximately 2mm, estimated on another patient's MRI obtained just after electrode explantation with still visible electrode tracks. By convention, the deepest contact is numbered "1."

In Patient 1, depth electrodes were implanted in the left hemisphere. The tip of an electrode aiming the tail of the left atrophic hippocampus was actually lying in the geniculate body, 3mm above the defined target. Its deepest contact (G1) was located in the lateral border of the median geniculate body, whereas the laterally adjacent contacts G2 and G3, respectively, lied within the LGN and optic radiation. The lingual gyrus, the fusiform gyrus, the external temporal neocortex, the temporal pole, the hippocampus, the amygdala, and the insula also were explored in this patient.

In Patient 2, the right superior calcarine bank, as well as the right fusiform gyrus, external temporal neocortex, temporal pole, hippocampus, amygdala, insula, anterior cingulate cortex, and orbital and dorsolateral frontal cortex were explored.

In Patient 3, the right superior calcarine bank was explored, as well as the ipsilateral fusiform gyrus, hippocampus, amygdala, insula, and occipitoparietal cortex.

Stimuli and Procedures

During a first procedure, pattern reversal VEPs were recorded using a black and white checkerboard reversing every 910 milliseconds. The checkerboard and square angular sizes were 10.4×14.1 degrees and 31×47 minutes, respectively (distance, 110cm). Contrast was 90% and the mean luminance of the checkerboard was $95cd \cdot m^{-2}$. The refresh rate of the noninterlaced video display was 70Hz. Subjects passively looked at a central red cross. Two blocks of 100 trials were recorded. Moreover, to explore the functional integrity of Patient 3's calcarine banks, we presented stimuli in each of the four quadrants of the screen (50 trials per quadrant).

During a second procedure, subjects looked at static grayscale faces of men and women depicting five emotional expressions.[8] The digitized size-, brightness-, and contrast-adjusted images were presented on the computer screen with a visual angle of 4×5 degrees. They were presented during 400 milliseconds and followed by a black screen during 1,600 milliseconds. A central white cross was continuously displayed as a fixation point. With these stimuli, the video-screen refresh rate was lower (60Hz). Twelve blocks of 40 stimuli were delivered. The subject had to mentally count a target, that is, a type of face according to its expression or to its gender. This task initially had been designed to study the processing of human facial emotional expressions.[9] In this study, gender and facial expression conditions are averaged in a "face condition."

Recordings and Signal Averaging

The patients were comfortably seated in a sound- and light-shielded recording room. Continuous intracranial EEG was amplified and recorded with a 64-channel EEG device (SynAmps; Neuro Scan Labs, El Paso, TX). A bipolar electrooculogram was recorded from the supraorbital ridge and outer canthus of the right eye. The nose was used as the reference site, and the ground was located on the mediofrontal scalp. Only binocular stimulation was performed.

EEG was recorded continuously with a 500Hz sampling rate through a bandpass of 0.1 to 70Hz for Patients 1 and 2 and with a 1,000Hz sampling rate through a bandpass of 0.1 to 200Hz for Patient 3. A prestimulus 100-millisecond baseline correction was performed. Epochs with eye blink artifacts greater than 100μV on electrooculogram and epileptic transient activities greater than 300μV were rejected.

Time-frequency Transformation of the Data

We used a time-frequency representation based on a wavelet transform of the signals[10] and applied it to the averaged evoked potentials obtained at each electrode contact. This provides a time-frequency representation of the spectral power $E(t, f_0)$ of the evoked responses, that is, responses that are phase-locked to the stimulus onset. The time-varying energy $E(t, f_0)$ of the evoked potential in a frequency band around f_0 is the squared norm of the result of the convolution of a complex Morlet's wavelet $w(t, f_0)$ with the signal $s(t)$: $E(t, f_0) = |w(t, f_0) * s(t)|^2$.[11] To obtain a time-frequency representation of the signal, we used a family of wavelet with f_0 ranging from 30 to 70Hz in 1Hz step. A Morlet's wavelet $w(t, f_0)$ has a gaussian shape both in the time domain (standard deviation, σt) and in the frequency domain (standard deviation σ_f) around its central frequency f_0: $w(t, f_0) = A. \exp(-t^2/2\sigma_t^2).\exp(2i\pi f_0 t)$, with $\sigma f = 1/2\sigma t$ and $A = (\sigma_t \sqrt{\pi})^{-1/2}$.

Results

Visual Response Sites

Pattern reversal VEPs were recorded in the vicinity of LGN and optic radiation in Patient 1. The first peak latency was 42 milliseconds in the LGN. VEPs also were recorded in the occipital cortex, that is, Brodmann area (BA) 17 (V1) in Patients 2 and BA17 to 18 (V2d) in Patient 3. The first peak latency was 62 milliseconds in V1.

Face-related VEPs were recorded (1) in the vicinity of LGN and optic radiation in Patient 1; (2) in occipital cortex BA17 (V1) in Patients 2 and 3 and BA17 to 18 (V2d) in Patient 3; (3) in the fusiform gyrus BA37 in Patient 2, BA19 in Patient 3, and BA20 in Patient 1; (4) in the parahippocampic gyrus BA35 in Patient 1; (5) in the amygdala (Patients 1, 2, and 3); and (6) in the insula (Patients 1 and 2) and in orbitofrontal cortex (Patient 2).

Electrophysiological Confirmation of the Lateral Geniculate Nucleus Implantation

In another study of Patient 1,[12] auditory potentials were selectively recorded on the deep contact G1 (Fig 1) located in the medial geniculate nucleus. Moreover, visual potentials but no auditory potentials were recorded on the very close G2 and G3 contacts (see Fig 1). This double dissociation confirms the respective locations of G1 in thalamic auditory structure (medial geniculate nucleus) and G2 and G3 in visual structures, LGN, and optic radiation, respectively.

Steady State Visual-Evoked Potentials

A periodic sinusoidal activity was recorded in Patient 1 at contacts lying in the LGN and optic radiation vicinity (G2 and G3) in the checkerboard reversal paradigm (see Fig 1). Its frequency was 70Hz, identical to video-display refresh rate. This activity was not detected at any of the other contacts implanted in Patient 1. Whereas the mean energy on the G2 and G3 thalamic contacts in the 60 to 70Hz range during the 400 to 800-millisecond time interval was approximately $50\mu V^2$, it was less than $4\mu V^2$ on all the other recording contacts (Fig 2).

In the same checkerboard paradigm, a similar periodic sinusoidal activity was recorded in Patients 2 and 3 at occipital electrode contacts (O1 to O6) exploring the calcarine area. It was not present in the other explored structures, especially not in the fusiform gyrus (contacts F1 to F6 in Patients 1, 2, and 3; see Fig 2). Whereas the maximum energy at the O contacts was $70\mu V^2$ for Patient 2 and $110\mu V^2$ for Patient 3, it did not exceed $1.8\mu V^2$ and $7\mu V^2$ at their other contacts, that is, a ratio greater than 15.

In Patient 3, the checkerboard was presented separately in each of the four visual quadrants. The energy of the signal recorded at the supracalcarine occipital contacts was maximal when the stimulus occurred in the contralateral inferior quadrant (Fig 3). This is consistent with the retinotopic properties of the calcarine area.

In the face paradigm, a periodic activity was observed in Patient 1 at G2 and G3 contacts. Its frequency was 60Hz, which was the video refresh rate for this paradigm. The oscillations were present only when the face stimulus was on, and they disappeared during the black screen period (Fig 4). They were not observed at the adjacent contacts. As represented on the time-frequency maps during the face paradigm, the oscillations begin after the transient response to the stimulus. The off transient response occurred between 400 and 500 milliseconds.

Several arguments demonstrate that these SSVEPs correspond to the neural response to the monitor flicker. First, video display terminals create a periodic visual stimulus. Indeed, the refresh rates of the screen (60 and 70Hz in this study) imply that the electron beam, once every 1/60 or 1/70 second, sweeps across the screen from the top left corner to the bottom right corner. Thus, each square of the checkerboard can be considered as a stimulus flickering at 60 or 70Hz. Second, the two different frequencies of the evoked oscillations were identical to the flicker frequencies of the monitor, demonstrating that the recorded brain signal (see Fig 4) is related to the screen rate. Third, the absence of oscillations when the screen was still on but black (see Fig 4) proves that the oscillations were driven by the stimulus through the visual pathways: it
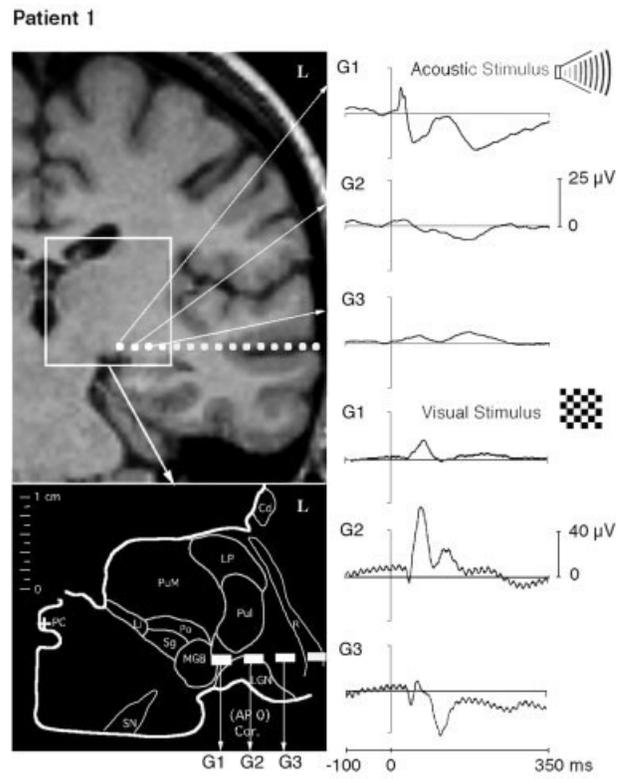

Fig 1. Confirmation of lateral geniculate nucleus (LGN) implantation (Patient 1). In the top left panel, left hemisphere coronal magnetic resonance imaging scan of Patient 1 at the level of electrode G lying in the LGN shows the 15 contacts (G1 being the deepest one). In the bottom left panel, the contacts are registered to an atlas of the thalamus.[33] In the right part, recordings at G1, G2, and G3 contacts showing an evoked potential after acoustic stimulation exclusively at G1, and after visual stimulation at G2 and G3. This functional duality is consistent with the localization of G1 in the median geniculate body (auditory thalamic relay), and G2 and G3, respectively, in LGN and optic radiation. Note that oscillations are observed at contacts G2 and G3 in our visual study.

excludes an electromagnetic interference noise, because the electricalmagnetic characteristics of the monitor do not change during the presentation of the black screen centered by the fixation white cross. Moreover, this signal was not widely recorded at all electrode contacts but selectively in the LGN, optic radiation, and occipital cortex (V1–V2 complex). Finally, larger oscillations were evoked in the superior calcarine bank by contralateral inferior quadrant stimulation (see Fig 3); this is consistent with the retinotopy of the posterior occipital cortex and confirms that the oscillations were evoked by a visual stimulus.

In the face paradigm, no oscillations were found in the fusiform gyrus despite the occurrence of large evoked potentials, as illustrated in Figure 5.
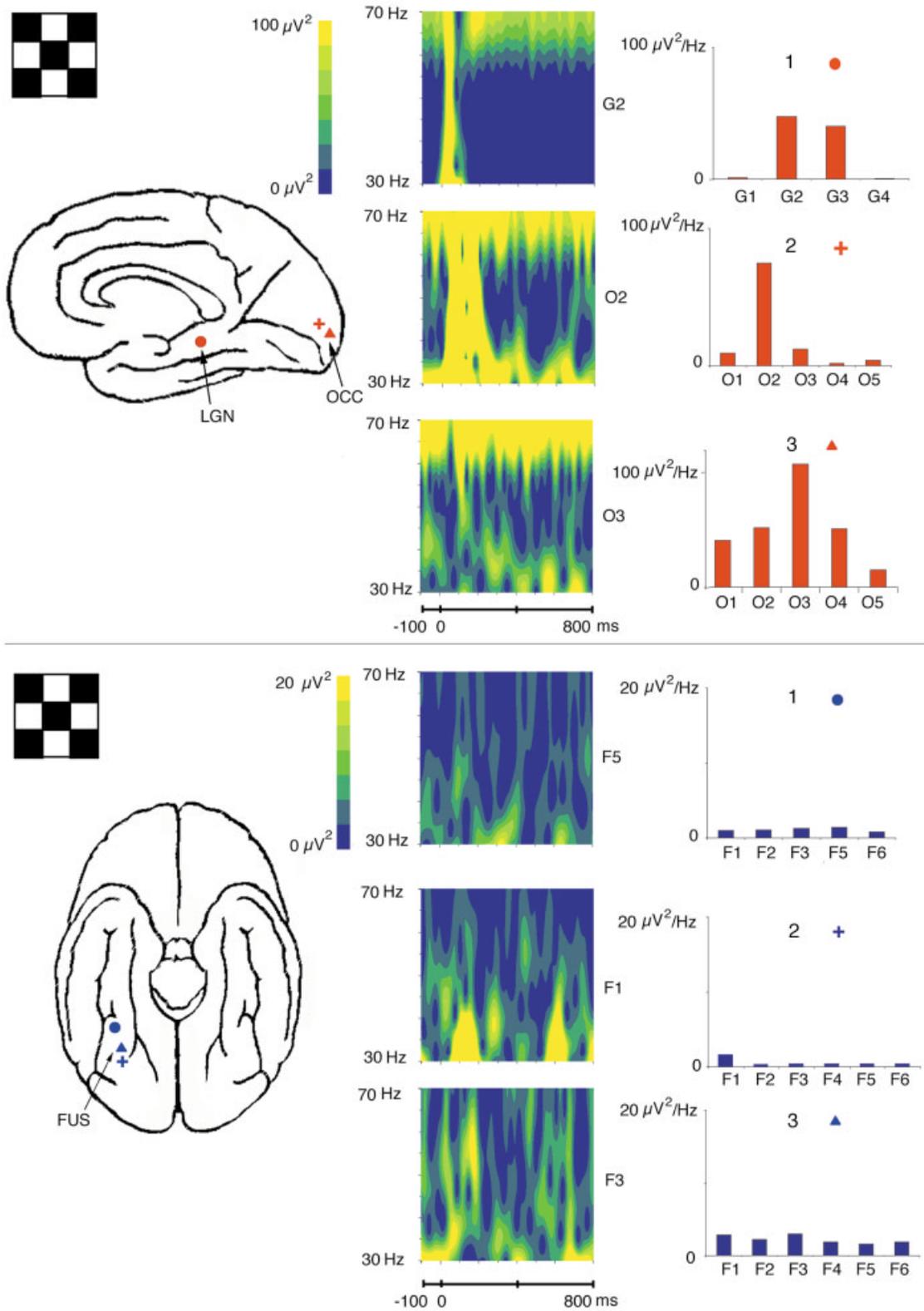
Figure 2.

Discussion

An oscillatory activity related to the computer screen flicker was recorded in crucial human visual structures, that is, LGN, optic radiation, and V1/V2 cortex of nonphotosensitive epileptic patients. Despite previous electrophysiological investigations of the thalamus,[13–15]

such visual responses have not been described in the literature.

Temporal and retinotopic properties developed above confirmed that this oscillating signal is evoked by the screen flicker and is not an electromagnetic artifact. This signal presents the electrophysiological characteristics of the SSVEPs usually evoked by repeated flashed stimuli. Indeed, these oscillations are phase-locked to the periodic stimulus, as they are best observed on the averaged evoked potentials. Our data show that this kind of high temporal frequency oscillating signal is evoked by a commonly experienced visual stimulus, that is, a computer screen. Recordings of stimulus-phase-locked oscillations in the retina and LGN of animals[16,17] and electroretinogram studies in humans[2] suggest that this signal is partly driven by ganglion cells. Recordings in animal visual cortex[17,18] and scalp data in humans[4,19–21] demonstrate that visual cortical neurons also generate such oscillations in response to high temporal frequency stimuli. Our results show that these oscillations are present in the human LGN, optic radiation, and V1/V2 complex, and that they are driven along the retinogeniculostriate pathway. Two temporal properties of the evoked responses suggest that SSVEPs in the LGN mainly correspond to magnocellular (M) neurons activity. First,
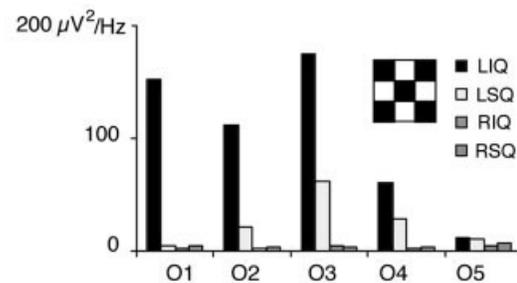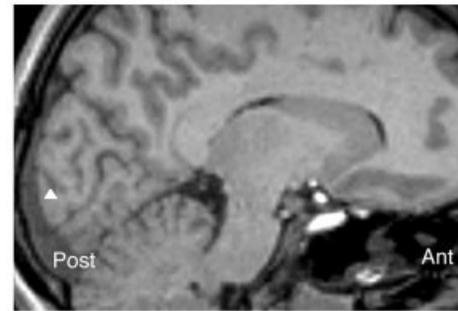

Fig 3. Checkerboard paradigm (Patient 3). The top part shows the location (triangle) of the occipital electrode O lying in the right superior calcarine bank on a sagittal magnetic resonance imaging scan of Patient 3. Histograms represent the power of the oscillatory signal recorded by the occipital electrode O in the 60 to 80Hz band during the 400 to 800-millisecond time interval, for each stimulated quadrant. Note the maximal energy for the LIQ stimulation, consistent with the localization of the deep contacts of the O electrode in the right superior calcarine bank. LIQ = left inferior quadrant; LSQ = left superior quadrant; RIQ = right inferior quadrant; RSQ = right superior quadrant.

Fig 2. Main results in the checkerboard paradigm (three patients). In the left part are displayed the electrode sites for the three patients (Patient 1: circle; Patient 2: cross; Patient 3: triangle). The red symbols referring to the lateral geniculate nucleus (LGN) and occipital contacts are projected on a median sagittal view, whereas the blue symbols referring to the fusiform gyrus are represented on a bottom view. The middle part shows the time-frequency power representations at the contacts having the highest energy. Time zero corresponds to the pattern reversal. The time-frequency analysis covers the 30 to 70Hz band, and power values are color-coded. Note that the upper cutoff frequency was 70Hz and that it does not allow a correct analysis of higher frequencies. In the right part are displayed the histograms of the mean power in a time-frequency window of 400 to 800 milliseconds and 60 to 70Hz at the adjacent contacts of the six electrodes (1 in the LGN, 2 in occipital lobe, and 3 in fusiform gyrus). The three red plots in the top panel show high power of oscillations between 60 and 70Hz in the LGN (Patient 1 and occipital lobes (Patients 2 and 3). The blue plots in the bottom show the absence of oscillations in the fusiform gyrus of the same three patients. Talairach coordinates of electrode contacts (calculated in the Talairach box of each patient), given in millimeters, respectively on x, y, and z axes are −19 to −30, −25, −6 for contacts G1 to G4 in Patient 1; 7 to 22, −80, 13 for contacts O1 to O5 in Patient 2; 1.5 to 15, −86, 10 for contacts O1 to O5 in Patient 3; and −15 to −33; −32; −12 for contacts F1 to F6 in Patient 1, 27 to 47, −56 to −50, −9 for contacts F1 to F6 in Patient 2; and 19 to 36, −53, −5 for contacts F1 to F6 in Patient 3.

the oscillations driven by high temporal frequency visual stimuli reflect an activity mostly related to the M system.[16] Second, despite the difficulty to compare human data with animal data and to compare latencies in different experiments, the latency of the pattern reversal VEP earliest component in the human LGN (42 milliseconds) is intermediate between those of similar VEPs recorded in the M (~35 milliseconds) and the parvocellular (P) (~45 milliseconds) layers of the macaque LGN.[22–24] This strengthens the hypothesis of a M system participation in the responses recorded in the LGN. The cortical oscillations appear to be restricted to posterior occipital areas, that is, V1/V2 complex, because we did not find them in the other recorded intracranial sites. Of particular interest is the absence of oscillations in the inferior extrastriate occipitotemporal visual areas, especially in the fusiform gyrus, despite large Event Related Potentials (ERPs) to human faces (see Fig 5). This can be explained by the mild implication of the ventral visual stream in the processing of
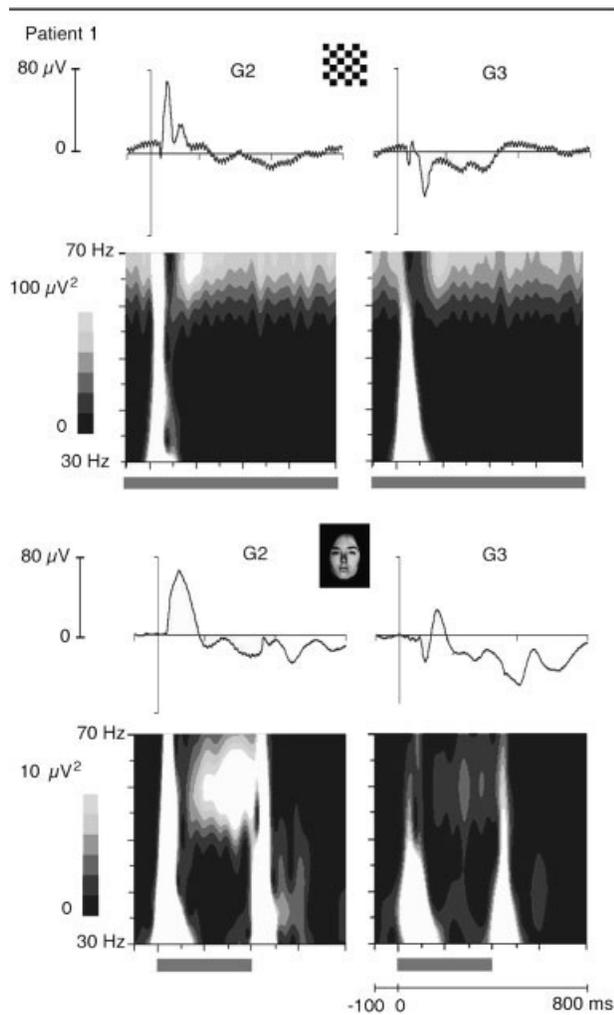
Fig 4. Visual responses in lateral geniculate nucleus (LGN) and optic radiation (Patient 1). Evoked potentials to checkerboards and faces and the corresponding time-frequency representations of the gray-coded power (in the 30–70Hz band) recorded at G2 and G3 contacts of the LGN electrode. The gray horizontal bar below each time-frequency plot shows the presentation time of the stimulus. The steady state activity at approximately 70Hz for checkerboard and 60Hz for faces appearing at G2 and G3 contacts during the stimulation is a response to the flicker of the screen. Latencies of potentials to checkerboard were 42 milliseconds for the first negative peak and 68 milliseconds for the first positive peak in the LGN (contact G2) and 46 milliseconds for the first negative peak and 60 milliseconds for the first positive peak in optic radiation (contact G3). Latencies of responses to faces were 62 milliseconds for the first peak and 70 milliseconds for the second peak in the LGN (G2); they were 70 milliseconds for the first peak and 84 milliseconds for the second in optic radiation (G3).

high temporal frequency stimuli.[25] However, the limited number of electrode contacts in the occipitotemporal region do not allow certification of the absence of high temporal frequency signals in the visual ventral stream. Besides, a study combining source analysis of the SSVEPs waveforms and functional MRI found different generators of SSVEPs to much slower temporal frequency stimuli (~10Hz) in ventral and lateral extrastriate visual cortex.[26] High temporal frequency signals are best processed by cortical areas located in the dorsal visual stream. Nevertheless, no oscillations were detected on an electrode implanted at the frontier between occipital and parietal lobes (Patient 3). We cannot assess that SSVEPs are not present in the dorsal visual stream because the occipitoparietal areas were not consistently explored in this study. Moreover neurons in extrastriate areas have large receptive fields compared with those of LGN and striate cortex neurons. Thus, they integrate larger parts of the monitor screen including black and white squares, which can no longer be considered as flickering stimuli and no longer elicit an oscillating signal. It would be interesting to test if a whole-field visual flicker would generate such oscillations in extrastriate areas.

Our results were obtained in the context of patients with partial epileptic seizures. The cortex of some patients with generalized photosensitive seizures can show an increased excitability, particularly in response to high temporal frequency visual stimuli. This phenomenon has been widely studied in patients presenting video-game epilepsy, which is known as a type of photosensitive epilepsy. However, it was not the case of

Fig 5. Face responses in fusiform gyrus (Patient 2). The evoked potentials to faces and the corresponding time-frequency representations of the gray-coded energy (in the 30–70Hz band) recorded at the F1 contact of the fusiform electrode. No oscillatory signal is detected. This figure demonstrates an absence of strict relationship between the existence of a transient evoked response to stimuli and the presence of an oscillatory signal.
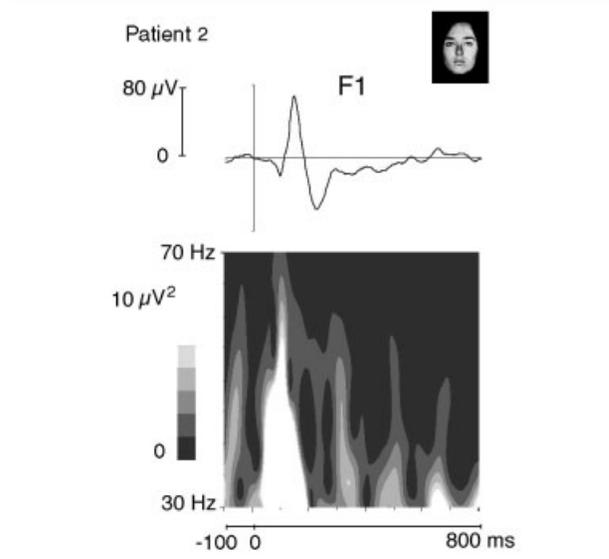
our patients who had temporal lobe seizures without hypersensitivity to intermittent photic stimulation. This suggests normal or close to normal visual processing in the patients of this study.

Two main types of abnormalities are described in photosensitive epileptic patients: the photoparoxysmal responses and the scalp occipital spikes (OSs). The photoparoxysmal responses are essentially elicited by patterned photic stimuli with high spatial frequency mostly stimulating P cells.[27] The OSs generally produced by 8 to 20 flickering stimuli are phase-locked to the stimulus and mostly processed by M cells.[24] High temporal frequency steady state oscillations observed in subcortical (LGN and optic radiation) and cortical (V1/V2 complex) areas in our three nonphotosensitive epileptic patients share the following essential properties with OSs. They are mostly driven by M cells, they are recorded in occipital areas, and they are phase-locked to the stimulus. Thus, scalp OSs may reflect physiological steady state responses to flicker, larger at relatively lower temporal frequencies (8–20Hz). However, the relationship between OSs and epilepsy is still unclear.[28] The increase of EEG abnormalities when using low-frequency flickering video screens[4,21,29] suggests a relationship between steady state activities, possibly OSs, and the genesis of photosensitive epilepsy. The high sensitivity to video games in visual reflex epilepsy may be linked to the simultaneous stimulation of the two main visual systems along the retinogeniculostriate pathway. On the one hand, cortical neurons connected to P layers of the LGN best responding to high spatial frequency stimuli and, on the other hand, cortical neurons connected to M cells best responding to high temporal frequency stimuli may generate both photoparoxysmal responses and steady state oscillations, respectively. Moreover, these high temporal frequency cortical activities, because they are focused in the V1/V2 complex, are not communicated by volume conduction, but rather reflect cortical neurons activity. Monkey studies appear to confirm this hypothesis.[18] That brings a new argument for a role of these activities to induce seizures photically .

The high temporal abilities of the brain shown by SSVEPs are surprising, because they are related to a nonphysiological stimulus, the monitor screen flicker. Why can the human brain process such high temporal frequency visual stimuli, whereas they do not access consciousness? It has been demonstrated that LGN and cortical neurons of anesthetized cats oscillate in the 30 to 80Hz range in response to drifting gratings.[30] These very high temporal resolution capacities of visual neurons needed for detection and analysis of movement may allow the generation of the oscillating signal that we have observed in human LGN and visual cortex.

This oscillating activity also may provide discomfort, pain, and functional alteration. Indeed, behavioral studies have demonstrated that high temporal flashed flickers can provoke glare, eyestrain, and headaches.[31] Moreover, intermittent illumination from visual display units affects saccades during text reading.[32] The oscillations may be considered as an excess of activity affecting the signal to noise ratio of information in the retinogeniculostriate pathway. Because 100Hz frame rate screens provide less damage,[29] they should become more commonly used.

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