Characteristics of visual evoked potentials related to the electro-clinical expression of reflex seizures in photosensitive patients with idiopathic occipital lobe epilepsy

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Characteristics of visual evoked potentials related to the electro-clinical expression of reflex seizures in photosensitive patients with idiopathic occipital lobe epilepsy

Running title: Visual system responses and reflex seizures

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Highlights

- Visually induced focal seizures may be related to photo- and/or pattern-sensitivity
- Photosensitive patients have VEP with early components and after discharge of high amplitude
- The increased amplitude suggests higher cortical excitability of the visual system
- After discharge amplitude is greater when EEG anomalies evolves into clinically evident seizure

Abstract

Seizures provoked by visual stimuli may be induced by abnormal responses to light (photosensitivity) and structured patterns (patternsensitivity). In this study, we analysed visual evoked potentials (VEPs) in three different samples: i) 38 photosensitive patients (21 males, 17 females; mean age 10.0 ± 2.9 years) with idiopathic occipital lobe epilepsy and reflex seizures (RS); ii) 13 non-photosensitive patients (6 males, 7 females; mean age 11.7 ± 5.3) with idiopathic occipital lobe epilepsy; 20 healthy controls (12 males, 8 females; mean age 10.0 ± 3.4). After written informed consent, all subjects underwent a standard procedure of visual stimulation with intermittent light and pattern stimulation, under digital video-EEG recording. The EEG signal was processed off-line by averaging analysis for each stimulus to obtain the corresponding VEP. Comparisons among groups showed no significant differences for P100 latency. Higher P100 amplitude as well as higher after-discharge (AD) were found in photosensitive patients with RS. Thirty-seven of these patients had one or more RS during the procedure of stimulation for a total of 66 episodes. Significant increases of P100 amplitude and higher values of AD amplitude were found in relation to the occurrence of photoparoxysmal response (PPR) and/or seizures during full-field pattern stimulation. The increase in amplitude of the AD was higher when PPR was associated with seizures. The high amplitude of early VEP components confirms the abnormal hyperexcitability in the cortex of photosensitive patients with occipital lobe epilepsy. Moreover, the

AD amplitude appears to be related to electro-clinical expression, being greater when PPR evolves into clinically evident seizures.

Key Words: epilepsy, photosensitivity, patternsensitivity, visual evoked potentials, after-discharge

1. Introduction

The international league against epilepsy defines reflex seizure (RS) "…a seizure that is constantly elicited by a specific stimulus…" (Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Berg et al., 2010; Fisher et al., 2014). Visual stimuli are the most common cause of RS (Kasteleijn-Nolst Trenité, 2006; Koepp et al., 2016). Attacks can be induced by abnormal responses to both light (photosensitivity) and structured patterns (patternsensitivity) (Harding and Fylan, 1999; Fisher et al., 2005; Wilkins et al., 2005). About 70-80% of photosensitive patients show patternsensitivity, but both sensitivity can also be found standalone (Brinciotti et al., 1994; Fisher et al., 2005; Radhakrishnan et al., 2005). Photosensitivity is characterized by the typical EEG "photoparoxysmal response" (PPR) with epileptic abnormalities elicited by intermittent light stimulation (ILS). PPR is considered an age-dependent heritable electroencephalographic trait (Stephani et al., 2004; Italiano et al., 2016), often associated with clinical signs and symptoms. Electrophysiological data suggest that PPR is related to an increased cortical excitability (Porciatti et al., 2000; Siniatchkin et al., 2007a, 2007b; Strigaro et al., 2012), generalized or originating from the occipital cortex (Waltz et al., 1992; Stephani et al., 2004). Photosensitive patients have visual evoked potentials (VEP) of high amplitude, first noted by Gastaut and Regis (1964) and then reported in several other studies in generalized epilepsies (Broughton et al., 1969; Cantello et al., 2011; Strigaro et al., 2012) as well as in focal ones (Guerrini et al, 1998; Demirbilek et al, 2000). However, the role of both photosensitivity and patternsensitivity on the electro-clinical expression of seizures is not yet well known. The occurrence of seizures related to PPR may depend on many causes such as the activation of a critical neuronal mass in the occipital cortex, the abnormal discharge propagation along cortico-

cortical and/or cortico-subcortical pathways, and the influence of other epileptic genes predisposing to specific phenotypes (Gastaut and Regis, 1964; Harding and Fylan, 1999; Porciatti et al., 2000; Fisher et al., 2005; Wilkins et al., 2005; Siniatchkin et al., 2007a, 2007b; Lopes da Silva and Harding, 2011; de Kovel et al., 2010; Strigaro et al., 2012; Kasteleijn-Nolst Trenité et al, 2015; Koepp et al., 2016). Recent studies on gamma oscillations provide further contributions to this regard, suggesting an altered control of excitatory and inhibitory processes as causative factor of PPR and seizures (Hermes et al., 2017; Bhatia et al., 2019). Aims of the present study are: i) to analyse VEPs of patients with idiopathic occipital lobe epilepsy and RS in relation to both photosensitivity and patternsensitivity; ii) to correlate VEPs with the PPR electro-clinical expression to better understand the triggering mechanisms of RS.

2. Material and methods

2.1. Subjects

We studied outpatients with RS who accessed to our epilepsy centre (Neurophysiopathology of childhood and adolescence, Department of Human Neurosciences, *Sapienza* University of Rome) for advanced diagnostic evaluation. Older patients were included if their seizures began in childhood and they had ongoing follow-up at our Epilepsy centre. Selection was based on the following criteria: 1) clinical history of occipital lobe RS induced by visual stimuli; 2) diagnosis of RS confirmed by video-EEG monitoring. Symptomatic epilepsies and poorly cooperative patients due to age or clinical conditions (mental retardation, behaviour disorders) were excluded. The study was conducted in accordance with the Declaration of Helsinki, and according to appropriate ethical standards as required by the Ethic Committee of our Institution. All enrolled subjects or their parents provided written informed consent prior to participation.

2.2. Diagnostic criteria and clinical assessment

Seizures and epilepsies were diagnosed and classified according to the criteria of the Commission on Classification and Terminology Commission of the International League Against Epilepsy

(Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Berg et al., 2010; Fisher et al., 2014). Demographic features, medical and family history, disease course, and treatment were collected from parents during a face-to-face interview. All patients were clinically evaluated by standard general and neurological examinations. CT scan and/or MRI were performed according to the clinical needs.

From a total of 334 patients with documented visually induced seizures, consecutively examined from January 2009 to January 2019, 38 patients fulfilled our selection criteria and were enrolled in this study as sample of RS. Symptomatic photosensitive epilepsies (progressive myoclonic epilepsies, Dravet syndrome, etc,) were excluded from the study. Idiopathic etiology was ascertained according to electro-clinical and neuroimaging data. During the same period, two other groups of subjects comparable for sex and age underwent the same protocol of evaluation, and were used for statistical comparisons: i) non-photosensitive patients without RS suffering from idiopathic occipital lobe epilepsy, according to ILAE criteria (Berg et al., 2010), (epileptic control group = EPI); ii) healthy subjects (control group = C).

2.3. Recording methods

All patients and controls underwent a digital video-EEG recording (21 electrodes) at rest and during a standard procedure of visual stimulation with ILS, PS and at least 30 minutes of TV watching. Patients with RS carried out the study protocol after the diagnosis of RS. ILS was tested, according to internationally recommended guidelines (Kasteleijn-Nolst Trenité et al., 2012), in a darkened room by flash of white light at 30 cm from the patient's eyes (frequency range 1-60 Hz). Each frequency was tested by separate trains of flashes with an inter-stimulus free period of five seconds, during both conditions eye closed and eyes open. Pattern sensitivity was tested by a standard procedure of stimulation, according to recommended guidelines (Wilkins et al., 2005), as reported elsewhere (Brinciotti et al., 2015). Briefly, we used three types of black-and-white full-field pattern (checks, horizontal stripes, vertical stripes), two black-and-white hemi-field pattern (left and right,

horizontal stripes), and one red/blue full-field pattern (horizontal stripes). Stimuli were presented with high contrast (Michelson > 0.8) and different sizes of the constituent elements subtending different spatial frequencies (cycles per degree = c/d = pairs of light-dark elements).

The complete protocol of PS included the following ten stimuli, in total:

PS-1 = black-and-white full-field pattern of checks (1 c/d),

PS-2 = black-and-white full-field pattern of checks (2 c/d),

PS-3 = black-and-white full-field pattern of checks (4 c/d),

PS-4 = black-and-white full-field pattern of horizontal stripes (1 c/d),

PS-5 = black-and-white full-field pattern of horizontal stripes (4 c/d),

PS-6 = black-and-white full-field pattern of vertical stripes (1 c/d),

PS-7 = black-and-white full-field pattern of vertical stripes (4 c/d).

PS-8 = black-and-white right hemi-field of horizontal stripes (4 c/d),

PS-9 = black-and-white left hemi-field of horizontal stripes (4 c/d),

PS-10 = red/blue full-field pattern of horizontal stripes (4 c/d).

Stimulus were presented in reversal mode (1.6 Hz) to ensure a constant total luminance, and any reversal was synchronized with a digital marker to carry out subsequent off-line analysis of the signal. Each pattern was shown for 15 seconds, with a free interval of at least 10 seconds. If any paroxysmal activity appeared, the stimulus was promptly stopped to avoid seizure induction. To ascertain the occurrence of stimulus-related ictal symptoms (hallucinations, micro/macropsias, etc.), at the end of video-EEG recording all patients underwent a semi-structured interview about subjective sensations they experienced during stimulation. We also asked cooperative patients to describe their visual symptoms by drawing.

2.4. Offline EEG analysis

The EEG was processed off-line by averaging of artefact free signal epochs. Although offline analysis is not currently used as a method for standard clinical evaluation, it is suitable for the research purpose of this study. Moreover, morphology and components of the responses are similar to those of VEPs recorded with more traditional techniques. Data recorded from O1 and O2 electrodes (Fz as reference) were adequately filtered (1-100 Hz) and averaged (epochs of 500 ms) for each stimulus to obtain the corresponding VEP. An automatic rejection for amplitude (greater than +/− 100 μV) was used to reduce artifacts and PPR-related interferences. Since a "*transient*" VEP can only be recorded at low frequency (< 2 Hz), the average was performed with a stimulation frequency of 2 Hz for ILS and 1.6 Hz for PS, and used for statistical analysis. According to Strigaro et al., (2012) the response was split into two epochs: 1) the ‘‘main complex’ (from 50 to 200 ms after the stimulus) which included the main positive peak (P100); 2) the late response or “after-discharge” (AD) (from 200–500 ms after the stimulus). The ‘‘main complex’’ was evaluated by latency and peak-to-peak amplitude of the P100 wave, whereas the polyphasic AD was quantified in terms of root mean square (RMS) values.

2.5. Experimental design

- Phase 1. Since some patients were taking antiepileptic drugs at the time of the examination, a preliminary analysis was performed to compare the differences of response between treated and untreated patients.

- Phase 2. Comparisons among groups (RS, EPI, C) for ILS and PS. Both conditions of the eyes were considered separately for ILS (eyes open = ILS-EO; eyes closed= ILS-EC); the black-and-white full-field pattern with checks of 1 c/d (PS-1) was used for PS.

- Phase 3. Comparison within the RS group, to analyze changes of the response in relation to the type of stimulus (ILS-EO, ILS-OC, and each item of PS) and to the electro-clinical expression (PPR *vs* PPR associated with seizures).

2.6. Statistical analysis

The analysis was performed by dedicated software (STATISTICA 9.1 - © *StatSoft, Inc*., Tulsa, OK, USA). All values were expressed as means ± SD or percentages, and means and limits were calculated adopting tolerance limit of 99% with a confidence of 95%. Comparisons were performed using ANOVA and $\chi 2$ with Yates correction when appropriate. Since data were not distributed normally in some cases, nonparametric tests were adopted (Kruskal-Wallis, U Mann-Whitney) with post hoc test for multiple comparisons. Since VEPs are usually described according to mean values and SD of their components, we reported mean rather than median. Significance was set at $p < 0.05$ with Bonferroni corrections of the p-values applied throughout.

3. Results

Demographic data of the selected samples were as follows: i) RS = 38 photosensitive patients (21 males, 17 females; mean age 10.0 ± 2.9 years); ii) EPI = 13 non-photosensitive patients (6 males, 7 females; mean age 11.7 ± 5.3) with idiopathic occipital lobe epilepsy; C = 20 healthy subjects (12 males, 8 females; mean age 10.0 ± 3.4).

3.1. Electro-clinical features of the study group (RS)

All patients had focal seizures of the occipital lobe (focal to bilateral tonic–clonic seizures in 4 cases). In 23 patients, the electro-clinical features met the diagnostic criteria for idiopathic photosensitive occipital lobe epilepsy (Guerrini et al., 1995); the remaining 15 cases had only RS. PPRs were recorded in all patients: 18 (47%) with closed eyes, 11 (29%) with open eyes, and 9 (24%) with both conditions. The table 1 shows PPRs evoked by ILS according to eye condition and stimulus rate.

3.2. Phase 1

At the time of the recordings, 17 patients (7 RS, 10 EPI) were treated with valproate while the others were not taking any therapy. Since the preliminary comparison of the responses did not show significant differences between treated and untreated patients (Table 2), they were considered together in the subsequent analysis.

3-3. Phase 2

Comparisons among groups showed no significant differences for P100 latency in the three stimulus conditions (ILS-EO, ILS-EC, PS), while higher P100 amplitude as well as higher RMS values of AD were found in RS (Table 3).

3.4. Phase 3

Even if the stimulus was promptly stopped at PPR occurrence, as per the protocol, thirty-seven patients of the studied group had one o more RS during the procedure of stimulation (24 cases to both ILS and PS, 7 ILS, 6 PS) for a total of 66 episodes (Table 4).

Table 5 shows the responses of patients with RS in relation to each stimulus and its effect. No significant differences of the P100 latency were found in relation to the occurrence of PPR and/or seizures for all stimuli. No significant changes of P100 amplitude were noted during ILS and hemi-field PS. Significant increases of P100 amplitudes and higher RMS values of AD were found during full-field PS in relation to the occurrence of PPR and/or seizures (Figure 1), with variations related to spatial frequency and orientation of the stimuli (Figure 2). The increase in amplitude of AD was higher when PPR was associated with clinical manifestations (Table 5).

4. Discussion

4.1. Comparisons among groups

Photosensitive patients with RS did not show differences in VEP latencies compared with both controls and non-photosensitive epileptic patients. Moreover, VEP latencies showed no significant

changes in relation to the occurrence of PPR or seizures. These observations agree with previously reported data on a normal conduction velocity along the visual pathway in idiopathic photosensitive patients (Genç et al., 2005; Siniatchkin et al., 2007b). In the present study, we found higher amplitude of early VEP component and higher RMS values of AD in patients with RS compared to both non-photosensitive epileptic patients and healthy controls. These differences were noted with both types of stimuli, flash and pattern. During pattern stimulation, VEP amplitudes were influenced by orientation and spatial frequency of the constituent elements. Moreover, the increase in amplitude was evident with full-field stimuli, whereas it did not appear with hemi-field stimuli. According to experimental and clinical data (Soso et al., 1980; Haider et al., 2010; Hermes et al., 2017), these findings might be explained by the different extension of stimulated cortical area, smaller for hemi-field pattern, and consequently with more circumscribed effect.

Early VEP components of higher amplitude were frequently found in photosensitive patients with generalized epilepsy (Broughton et al., 1969; Cantello et al., 2011; Strigaro et al., 2012) as well as in those with focal epilepsy (Guerrini et al, 1998; Demirbilek et al, 2000). In our sample, the greater amplitude of both flash and pattern VEPs indicates an involvement of the magnocellular (M) and parvocellular (P) pathways. As widely documented, these pathways originate in two types of retinal ganglion cell, and maintain their separation at the level of lateral geniculate nucleus and primary visual cortex (Hubel and Wiesel, 1972; Harding and Fylan, 1999). M cells respond preferentially to low-spatial-frequency and high-temporal-frequency stimuli, whereas P cells best respond to stimuli of high contrast, high spatial frequency, and low temporal frequency. The increased amplitude of VEPs confirms the hyperexcitability in the visual system of these patients, as previously reported (Guerrini et al, 1998; Demirbilek et al, 2000; Siniatchkin et al., 2007b).

4.2. Comparison within the RS group

In photosensitive patients, VEP elicited by PS showed a significant increase in AD amplitude related to the occurrence of PPR, in contrast to the responses of the same patient during ineffective

stimuli. No comparison was made for ILS as no PPRs were recorded at the low frequencies used to average (2 Hz). This point represents a methodological limit of the work; further studies on larger samples would allow collecting an adequate number of data to be analyzed.

In animal models, experimental data identified the thalamus as the origin of AD (Ishikawa et al., 2008), and these late components may be involved in the thalamus-cortical circuit activated by photic stimulation (Bigler and Eidelberg, 1976). Although this study was not designed to investigate subcortical structures, AD changes allow to theoretically hypothesize an involvement of the thalamus, as supported by experimental and clinical studies (Redecker et al., 1997; Lin et al., 2009). Furthermore, relays from the occipital cortex to the thalamus and from the thalamus to the frontoparietal areas were noted in the evolution of photoparoxysmal responses into generalized tonic-clonic seizures (Moeller et al., 2013). Thalamo-cortical abnormalities were reported in IGE, and a loss of feed-forward inhibition between the thalamus and its neocortical connections may have epileptogenic effect, as suggested by Paz and Huguenard (2015). Vaudano et al. (2017) documented that the cortical-subcortical network generating the alpha oscillation at rest is different in photosensitive patients, due to reduced inhibition. Moreover, they found an abnormal connectivity of the occipital, sensory-motor, anterior cingulate, and supplementary motor cortices with the visual thalamus, whereas these abnormalities were not present in non-photosensitive epileptic patients. Recently, Wang et al., (2019) studied a sample of patients with generalized epilepsy via resting-state fMRI connectome analysis. They found abnormalities in cortical and thalamic connectivity that could reflect the tendency to engage in recursive thalamocortical loops, contributing to hyperexcitability. Although all these data concern patients with generalized epilepsies, our observations suggest a more widespread structural and functional involvement also in photosensitive patients with occipital lobe epilepsy, and agree with the current pathophysiological hypothesis of the epilepsy as a network disorder (Avanzini et al., 2012).

In our sample, the increase in AD amplitude was even more pronounced when PPR was associated with clinical manifestations. This aspect is particularly interesting and suggests that the transition of

PPR towards the appearance of clinical signs may be due to a possible "threshold effect" which modifies the expression from "EEG tract" to clinically evident seizure.

Seizure triggering in photosensitive patients may depend on many factors such as abnormal excitability of the visual cortex with defective contrast gain control mechanisms, activation of a critical neuronal mass in the occipital cortex, abnormal discharge propagation along cortico-cortical and/or cortico-subcortical pathways, and many others (Gastaut and Regis, 1964; Harding and Fylan, 1999; Porciatti et al., 2000; Fisher et al., 2005; Wilkins et al., 2005; Siniatchkin et al., 2007a, 2007b; Strigaro et al., 2012; Koepp et al., 2016; Bhatia et al., 2019). An altered control of excitatory and inhibitory processes has been supposed as causative factor of PPR and seizures, and recent studies on gamma oscillations provide further contributions to this regard (Hermes et al., 2017; Bhatia et al., 2019). Lopes da Silva and Harding (2011) reported an enhancement of phase synchrony in the gamma-band preceding the stimulation trials that evolved into PPR. These features differed significantly from that recorded in trials not followed by PPR or in controls. Based on these data, they suggested that “recruitment or dynamic capture of neurons into larger assemblies precede the epileptic chain reaction (ictal cascade) that leads to the transition to an epileptic seizure". Moeller et al. (2009) reported a photosensitive patient in whom ILS accidentally caused a generalized tonic-clonic seizure during simultaneous recordings of EEG and functional magnetic resonance imaging. PPR was associated with increase in blood oxygen level dependent (BOLD) signal in the visual cortex, the thalamus, and both superior colliculi. Koepp et al. (2016), in their recent review, speculate that “cortico-cortical and cortico-subcortical visuomotor pathways can be recruited differentially: bursts of generalized photoparoxysmal responses with no motor output might preferentially imply a corticocortical transmission, while a seizure-specific combination of corticocortical and corticosubcortical connections might underlie the occurrence of seizures with myoclonic or tonic-clonic components.” In our sample, the greater increase in AD amplitude during PPRs associated with seizure occurrence, especially eyelid myoclonia, seems to support this hypothesis also in photosensitive patients with idiopathic occipital lobe epilepsy.

Finally, from a clinical perspective, some VEP characteristics found in the present study could contribute to the clinical evaluation; for example, an asymmetric amplitude of the AD could suggest focal rather than generalized photosensitive epilepsy, with possible repercussions on therapy. This study was not designed to answer these questions directly, but the results suggest further research to understand the clinical significance of the observed anomalies.

5. Conclusions

Photosensitive patients with idiopathic occipital lobe epilepsy and RS show abnormal reactivity of the visual system well documented by VEPs. The increased amplitude of early components confirms the hyperexcitability of the cortex, while the increase in AD amplitude theoretically suggests a possible involvement of the thalamus. Furthermore, these changes appear to be related to the electro-clinical expression, being greater when PPR evolves into clinically evident seizure. Further studies are needed on physiopathological mechanisms of PPR and its transition to an epileptic seizure, to better understand the significance of the abnormal visual system responsiveness of photosensitive patients.

Declaration of interest

None

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Figure 1

Examples of generalized (A) and focal (B) PPR recorded by video-EEG during pattern stimulation (left side) and related VEPs (right side). In B, note the asymmetry of the VEP amplitude, with AD higher in O2 (black arrow), in the same hemisphere of the EEG abnormalities (right occipital lobe, red arrow). VEP: upper trace = left occipital; lower trace = left occipital; amplitude = 2 μV/division; time window = 500 ms; * P100

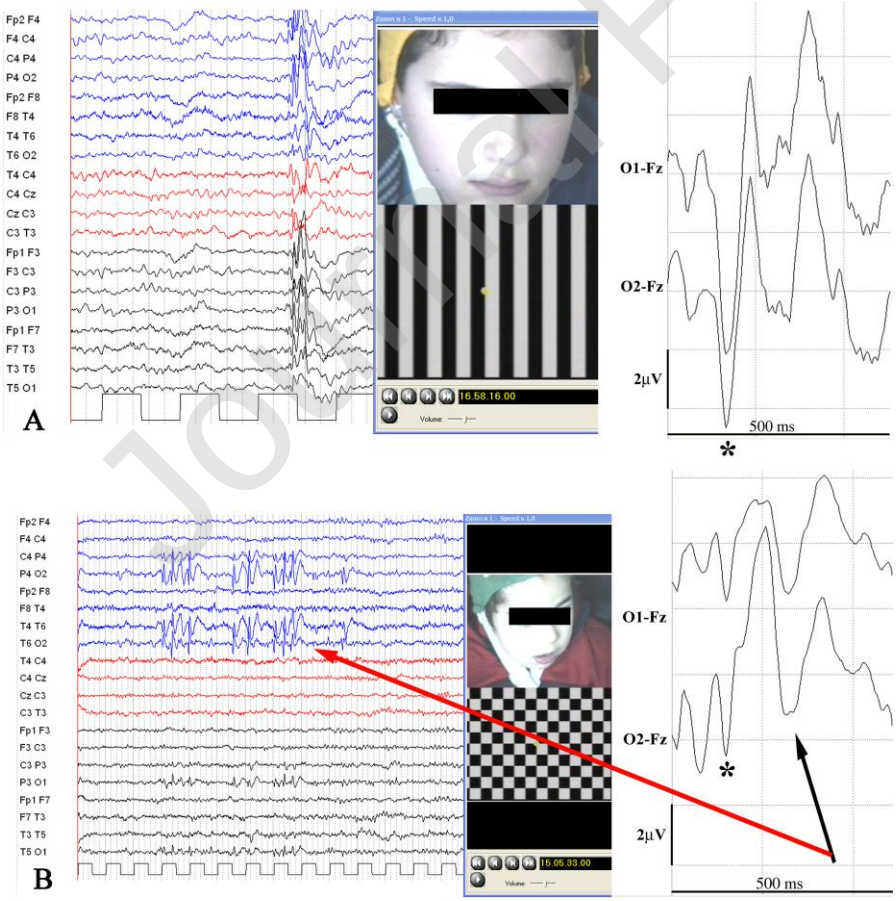

Figure 2

VEPs recorded in the same patient during each pattern in relation to PPR elettroclinical expression. Only EEG epileptic abnormalities occurred during PS-2, PS-4, PS-6, and PS-7. PS-3 shows an abnormal increase of amplitude related to PPR associated with an occipital seizure (arrow). VEP: upper trace = left occipital; lower trace = left occipital; amplitude = 2 μV/division; time window = 500 ms. PS = Pattern stimulation (for numbers, see medoths)

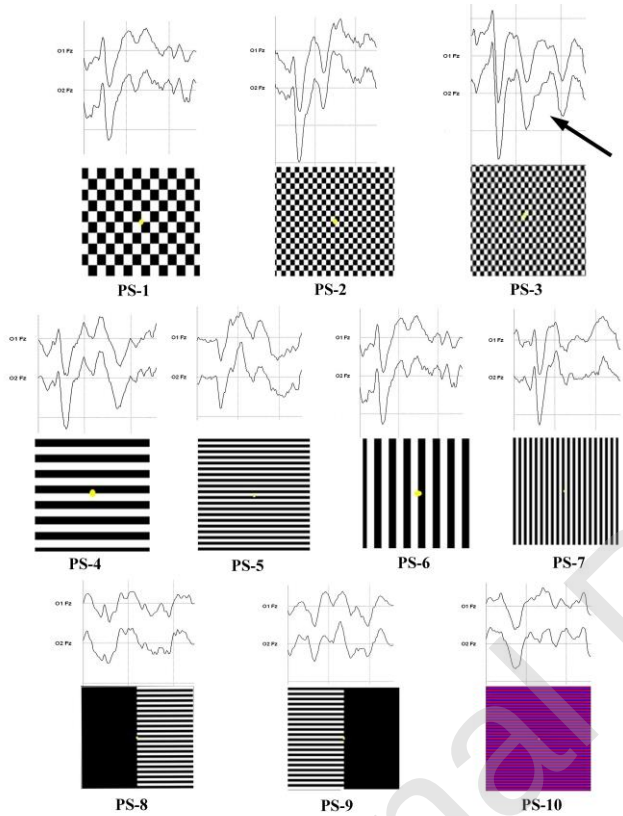

Table 1

PPRs evoked by ILS according to eye condition and stimulus rate

	PPRs *							
ILS frequency Hz	**Eye closed**		**Eye open**		**Both**		**Total**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
< 10	10	(28)	3	(19)	7	(29)	20	(26)
11-30	15	(42)	7	(44)	9	(38)	31	(41)
> 30	11	(30)	6	(37)	8	(33)	25	(33)
Total	**36**	**(47)**	**16**	**(21)**	**24**	**(32)**	**76**	**(100)**

PPR= photoparoxysmal response; ILS = intermittent light stimulation; * some patients were sensitive to more than one frequency range; p = NS

Table 2

VEP comparison between treated and untreated patients

Stimuli	**Group**	**O1**			**O2**		
		P 100 Latency ms	**P 100 Amplitude µV**	**A-D RMS μV^2**	**P 100 Latency ms**	**P 100 Amplitude µV**	**A-D RMS μV^2**
ILS EO	**RS**						
	AEDs	94.50 ± 7.90	24.91 ± 8.09	4.22 ± 1.21	92.33 ± 7.17	25.35 ± 9.32	0.85 ± 0.35
	No	101.07 ± 9.72	26.61 ± 13.02	5.07 ± 2.56	101.97 ± 9.85	28.29 ± 15.22	2.96 ± 0.55

	EPI						
	AEDs	101.75	20.21	3.21	105.12	21.52	3.67
		± 9.51	± 6.65	± 1.49	± 10.15	± 4.55	± 1.55
	No	103.25	26.61	4.60	106.00	25.14	3.84
		± 5.32	± 10.73	± 2.56	± 11.02	± 15.32	± 2.00
ILS EC	**RS**						
	AEDs	111.33	27.82	6.57	99.43	28.21	7.16
		± 12.82	± 6.33	± 1.27	± 32.61	± 6.60	± 1.59
	No	109.48	29.11	7.77	107.12	30.64	7.58
		± 11.61	± 18.22	± 3.45	± 19.43	± 17.23	± 3.02
	EPI						
	AEDs	111.86	14.14	4.35	113.75	15.63	4.98
		± 17.11	± 5.85	± 1.63	± 16.70	± 5.98	± 2.23
	No	107.75	15.62	7.99	107.75	20.74	7.82
		± 6.50	± 11.99	± 6.16	± 10.69	± 11.22	± 2.11
PS-1	**RS**						
	AEDs	122.00	12.76	2.56	121.67	14.88	2.13
		± 11.37	± 5.95	± 1.49	± 11.38	± 6.22	± 1.26
	No	121.97	20.71	3.89	122.83	23.85	4.11
		± 8.60	± 11.55	± 2.73	± 11.49	± 13.20	± 3.22
	EPI						
	AEDs	122.00	12.58	2.38	121.25	12.04	2.55
		± 3.85	± 7.03	± 1.30	± 3.58	± 5.09	± 1.72
	No	123.0	17.89	3.30	124.75	22.59	2.95
		± 4.24	± 5.44	± 1.52	± 5.06	± 9.38	± 1.37

Numbers are mean ± SD (Kruscal-Wallis test = NS); RMS = root mean square; ILS-EO = intermittent light stimulation (eyes open); ILS-EC = intermittent light stimulation (eyes closed); PS-1 = pattern stimulus n.1 (black-and-white full-field pattern of 1 c/d checks); RS = reflex seizures; EPI = non photosensitive epileptic patients; AEDs = antiepileptic drugs; No = untreated patients.

Table 3

VEP comparison among groups for ILS and PS

Stimuli	**Group**	**O1**			**O2**		
		P 100 Latency ms	**P 100 Amplitude µV**	**A-D RMS μV^2**	**P 100 Latency ms**	**P 100 Amplitude µV**	**A-D RMS μV^2**
ILS EO	RS	101.46 ± 1.58	26.76 * ± 12.08	5.02 * ± 2.28	101.38 ± 10.77	28.24 * ± 14.04	5.13 * ± 2.69
	EPI	101.54 ± 8.18	22.31 ± 8.02	3.50 ± 1.90	104.46 ± 10.12	22.96 ± 8.63	3.59 ± 1.62
	C	106.40 ± 10.44	16.94 ± 8.03	1.99 ± 1.28	105.75 ± 9.96	17.47 ± 7.59	2.26 ± 1.56
ILS EC	RS	110.43 ± 12.60	28.81 * ± 16.24	7.47 * ± 3.32	106.29 ± 21.49	30.07 * ± 15.46	7.47 * ±2.79
	EPI	110.50 ± 14.21	14.63 ± 7.84	5.56 ± 3.90	111.75 ± 14.74	17.33 ± 7.10	5.93 ± 2.52
	C	109.05 ± 10.20	14.34 ± 7.82	3.2 ± 1.75	107.75 ± 10.80	16.68 ± 8.55	3.04 ± 2.20
PS-1	RS	122.22 ± 8.94	19.20 * ± 11.02	3.64 * ± 2.56	122.86 ± 11.24	22.15 * ± 12.56	3.74 * ± 3.01
	EPI	121.46	15.55	2.65	121.54	16.82	2.64

		± 4.8	± 7.82	± 1.33	± 5.16	± 9.08	± 1.50
	C	118.50 ± 5.50	10.71 ± 5.03	1.60 ± 0.72	118.50 ± 4.64	11.43 ± 5.03	1.66 ± 0.74

Numbers are mean ± SD (* Kruscal-Wallis test = p < .001); RMS = root mean square; ILS-EO = intermittent light stimulation (eyes open); ILS-EC = intermittent light stimulation (eyes closed); PS-1 = pattern stimulus n.1 (black-and-white full-field pattern of 1 c/d checks); RS = reflex seizures; EPI = non photosensitive epileptic patients; C = control group.

Table 4

Seizures recorded during the procedure of visual stimulation

	ILS		**PS**	
Seizures	**N**	**(%)**	**N**	**(%)**
Signs	**19**	**(54)**	**14**	**(45)**
Eyelid myoclonia	14	(74)	8	(57)
Clonic seizures (head)	2	(11)	0	--
Clonic seizures (arms)	0	--	1	(7)
Tonic eye deviation	1	(5)	1	(7)
Oral automatisms	0	--	2	(14)
Atypical absence	2	(10)	2	(14)
Symptoms	**16**	**(46)**	**17**	**(55)**
Visual	10	(63)	13	(76)
Perceptive illusions	6		4	
Hallucinations	3		7	
Micropsia	0		1	
Amaurosis	0		1	

Hemianopsia	1	0
Pain in the eyes	6 (37)	3 (18)
Dizziness	0 --	1 (6)
Total (n. 66)	**35 (53)**	**31 (47)**

ILS = intermittent light stimulation; PS = pattern stimulation

Table 5

Visual responses of patients with RS for each stimulus condition related to electro-clinical expression of PPR

Stimuli	**O1**			**O2**		
Effect	**P 100 Latency ms**	**P 100 Amplitude µV**	**A-D RMS μV^2**	**P 100 Latency ms**	**P 100 Amplitude µV**	**A-D RMS μV^2**
ILS-EO						
EA (11)	103.1 ± 15	28.6 ± 12	5.2 ± 2	102.9 ± 12	29.1 ± 16	5.3 ± 3
None (25)	100.6 ± 10	26.2 ± 12	5.0 ± 2	100.5 ± 10	12.0 ± 14	5.1 ± 3
ILS-EC						
EA (27)	109.3 ± 12	31.0 ± 18	8.1 ± 3	107.2 ± 18	31.8 ± 17	7.8 ± 2
None (9)	114.3 ± 14	23.7 ± 7	5.9 ± 3	104.1 ± 31	26.7 ± 7	6.8 ± 4
PS-1						
EA (21)	124.3 ± 10	23.3 ± 11 [a) b)]	4.7 ± 3 [a b]	126.6 ± 10	27.4 ± 13 [a b]	5.0 ± 3 [a b]
None (15)	119.3 ± 7	13.5 ± 9	2.1 ± 1	117.6 ± 10	14.8 ± 8	1.9 ± 1

Sz (9)	124.0 ±10	24.8 ± 9	4.9 ± 3 [a b]	126.7 ±12	29.3 ± 12 [b]	5,2 ± 4 [a b]
None (27)	121.6 ± 8	17.3 ±11	3.2 ± 2	121.6 ±11	19.8 ± 12	3.2 ± 3
PS-2						
EA (22)	127.8 ± 10	20.4 ± 10 [a]	3.8 ± 2	127.4 ± 11	22.0 ± 14	4.3 ± 3 [a]
None (10)	131.4 ± 11	12.8 ± 8	2.6 ± 2	128.4 ± 11	13.9 ± 8	2.4 ± 1
Sz (12)	132.3 ± 10	16.4 ± 9	4.5 ± 3	133.2 ±12	16.0 ± 9	4,8 ± 3 [a]
None (19)	131.8 ± 12	15.6 ± 11	4.2 ± 3	131.3 ± 7	16.8 ± 13	2,6 ± 4
PS-3						
EA (23)	131.1 ± 10	16.3 ± 9	4.6 ± 3	132.2 ± 10	16.8 ± 11	4.5 ± 3
None (8)	134.6 ± 13	14.5 ± 11	4.2 ± 4	133.1 ± 13	15.6 ± 13	4.9 ± 5
Sz (15)	123.9 ± 9	19.8 ± 14	2.8 ± 2	123.1 ±10	19.4 ± 13	2.8 ± 2
None (17)	125.5 ±10	19.4 ±13	3.2 ± 2	125.5 ± 9	22.5 ± 15	3.3 ± 2
PS-4						
EA (13)	121.2 ± 10	16.9 ± 11	3.7 ± 2 [b]	122.7 ± 9	18.7 ± 13	3.6 ± 2 [b]
None (19)	126.9 ± 9	21.4 ± 14	2.6 ± 2	125.5 ± 10	22.6 ± 15	2.7 ± 1
Sz (7)	143.1 ± 20	15.9 ± 8	6.0 ± 2 [a b]	144.7 ± 20	16.0 ± 8	5.4 ± 2 [a b]
None (25)	130.6 ±13	17.0 ± 11	2.9 ± 2	129.7 ±17	17.0 ± 11	2.8 ± 2
PS-5						
EA (21)	134.6 ± 16	16.7 ± 10	3.9 ± 2	135.6 ± 20	17.2 ± 9	3.7 ± 2
None (11)	131.0 ± 14	16.9 ± 11	3.0 ± 2	127.8 ± 14	18.0 ± 14	2.7 ± 3
Sz (10)	130.7 ±19	12.8 ± 6	3.5 ± 2 [a]	134.0 ± 21	12.6 ± 7	2.4 ± 1 [a]
None (21)	124.4 ± 18	12.1 ± 7	2.7 ± 1	124.9 ± 17	10.0 ± 5	1.5 ± 1

PS-6						
EA (16)	125.7 ± 21	11.6 ± 5	3.3 ± 2	125.8 ± 19	10.5 ± 6	3.6 ± 2
None (15)	127.3 ± 16	13.2 ± 8	2.5 ± 1	130.0 ± 17	11.2 ± 5	2.4 ± 1
Sz (8)	137.5 ± 27	7.0 ± 4	2.3 ± 1	136.6 ± 23	9.3 ± 3	2.5 ± 1
None (23)	129.8 ± 17	11.0 ± 6	2.2 ± 1	126.4 ± 20	11.3 ± 7	2.2 ± 1
PS-7						
EA (12)	133.7 ± 16	8.5 ± 5	2.3 ± 1	132.4 ± 22	10.2 ± 8	2.2 ± 1
None (19)	130.5 ± 18	10.9 ± 6	1.9 ± 1	126.8 ± 21	11.2 ± 5	2.1 ± 1
Sz (6)	142.2 ± 17	8.2 ± 4	2.7 ± 1	146.2 ± 21	8.7 ± 4	2.6 ± 1
None (25)	129.2 ± 16	10.4 ± 6	2.1 ± 1	124.9 ± 19	11.3 ± 6	2.2 ± 1
PS-8						
EA (19)	136.1 ± 17	11.6 ± 8	4.3 ± 2 [a b]	127.8 ± 32	13.1 ± 9	4.9 ± 3 [b]
None (12)	142.2 ± 18	12.3 ± 6	2.6 ± 3	143.1 ± 17	16.0 ± 12	3.4 ± 4
Sz (13)	133.5 ± 16	13.4 ± 8	4.8 ± 2 [a b]	122.1 ± 35	15.0 ± 9	5.5 ± 3 [a b]
None (18)	141.1 ± 17	10.7 ± 6	3.2 ± 3	142.1 ± 18	13.7 ± 11	3.4 ± 3
PS-9						
EA (16)	123.4 ± 7	17.9 ± 10	2.9 ± 1 [b]	124.1 ± 8	19.9 ± 12	2.9 ± 1 [b]
None (16)	118.2 ± 6	20.2 ± 14	2.2 ± 1	117.9 ± 7	19.7 ± 12	2.5 ± 1
Sz (6)	125.8 ± 7	22.2 ± 11	3.9 ± 1 [a b]	126.0 ± 8	23.4 ± 13	4.1 ± 1 [a b]
None (26)	119.6 ± 6	17.2 ± 11	2.2 ± 1	119.4 ± 8	19.4 ± 12	2.4 ± 1
PS-10						
EA (25)	127.8 ± 10	16.1 ± 10	3.0 ± 2 [b]	127.9 ± 9	18.3 ± 13	3.5 ± 2 [b]

None (7)	135.1 ± 10	13.1 ± 12	2.5 ± 2	138.4 ± 9	13.7 ± 12	2.4 ± 1
Sz (9)	131.1 ± 11	18.1 ± 12	4.3 ± 1 [a b]	132.6 ± 10	21.8 ± 14	5.2 ± 2 [a b]
None (23)	128.7 ± 10	14.4 ± 11	2.4 ± 1	129.3 ± 10	15.6 ± 12	2.6 ± 1

Numbers are mean ± SD (in brackets = number of patients); EA = epileptic abnormalities, Sz = seizure; PS = pattern stimulation (for numbers, see methods); a) EA or Sz *vs* None < p .05; b) EA *vs* Sz < p .05