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CRITICAL REVIEW AND INVITED COMMENTARY

Methodology of photic stimulation revisited: Updated European algorithm for visual stimulation in the EEG laboratory

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Summary

Intermittent photic stimulation (IPS) is a common procedure performed in the electroencephalography (EEG) laboratory in children and adults to detect abnormal epileptogenic sensitivity to flickering light (i.e., *photosensitivity*). In practice, substantial variability in outcome is anecdotally found due to the many different methods used per laboratory and country. We believe that standardization of procedure, based on scientific and clinical data, should permit reproducible identification and quantification of photosensitivity. We hope that the use of our new algorithm will help in standardizing the IPS procedure, which in turn may more clearly identify and assist monitoring of patients with epilepsy and photosensitivity. Our algorithm goes far beyond that published in 1999 (*Epilepsia*, 1999a, 40, 75; *Neurophysiol Clin*, 1999b, 29, 318): it has substantially increased content, detailing technical and logistical aspects of IPS testing and the rationale for many of the steps in the IPS procedure. Furthermore, our latest algorithm incorporates the consensus of repeated scientific meetings of European experts in this field over a period of 6 years with feedback from general neurologists and epileptologists to improve its validity and utility. Accordingly, our European group has provided herein updated algorithms for two different levels of methodology: (1) requirements for *defining photosensitivity* in patients and in family members of known photosensitive patients and (2) requirements for *tailored studies* in patients with a clear history of visually induced seizures or complaints, and in those already known to be photosensitive.

KEY WORDS: Standardization, Intermittent photic stimulation, Photoparoxysmal response, Guidelines, European.

Why Photic Stimulation?

Intermittent photic stimulation (IPS) is used as one of the activating methods in electroencephalography (EEG) recordings in the investigation of patients with suspected or known epilepsy. Although photic stimulation is the provocation technique that can most easily be standardized, great diversity in methodology has occurred. When performed in an efficient, standardized and safe way with attention to details, much valuable information for the patients can (repeatedly) be gathered, for example, in diagnosing syndromes (**1**) and monitoring of treatment (**2**):

1 Paroxysmal photosensitive responses (PPRs) occur in several epileptic syndromes with generalized and/or focal seizures. Relating photosensitivity to definite epileptic syndromes is possible, taking into account other signs and symptoms like myoclonia, absences, eyelid fluttering, intellectual decline, and so on (Kasteleijn-Nolst Trenité et al., 1987, 2001). Specific syndromes have been recognized also, that is, idiopathic occipital photosensitive epilepsy with PPRs confined to the occipital area or with secondarily generalization after occipital onset (Guerrini et al., 1995; Yalcin et al., 2000; Panayiotopoulos, 2002). In 1994 Panayiotopoulos stressed the co-occurrence of headache and visual symptoms in occipital epilepsies, and later studies have confirmed that migraine can be a

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symptom of visually induced occipital epileptiform discharges (Parisi et al., 2007; Parisi, 2009). Especially in families with both migraine and epilepsy, headache can be the sole manifestation of an epileptic event or be the remaining complaint after antiepileptic drug (AED) treatment (Piccioli et al., 2009). Another specific syndrome strongly connected with photosensitivity is Jeavons syndrome (Viravan et al., 2011).

2 Quantification of the response to IPS (upper and lower flash frequency thresholds eliciting a PPR) and tailored studies with pattern and TV testing can help in advising lifestyle restraints (video games, disco lights, TV programs, and so on) (Rubboli et al., 2004) and in choice and evaluation of treatment. Prescription of blue-colored glasses (Capovilla et al., 2006) are useful in a variety of clinical situations, for example, in pregnancy, to avoid antiepileptic therapy or polytherapy. There are, however, indications that the colors selected individually to reduce visual discomfort may offer an effective alternative in patients who do not respond to blue lenses or who do not accept them (Wilkins et al., 1999).

In addition, repeated quantification of the responses to IPS make it possible to evaluate the individual antiepileptic effect of AEDs (and its change in dosages) and prevent patients from possible AED-withdrawal seizures (Pavlović et al., 2011).

Because the presence or absence of an epileptiform EEG response to visual stimulation has many implications for the patient, we propose a photic stimulation method that gives the maximal information on susceptibility to visual stimuli and is relatively safe when performed systematically with attention to details.

Two different levels of methodology are advised:

The first level comprises requirements for *defining photosensitivity* in patients and in family members of known photosensitive patients. The purpose is to obtain an answer as to whether the patient is photosensitive or not (high sensitivity, low specificity). The procedure can also be repeated in the same patient for evaluation of pharmacologic treatment. If the patient is photosensitive under methodology 1, the patient can be invited at a later time for a more extensive EEG (see methodology 2) to define his/her sensitivity to various visual stimuli with a higher level of precision. The protocol can be performed in the same hospital or the patient can be referred to other centers that specialize in visual stimulation in patients with epilepsy.

The second level comprises requirements for *tailored studies* in patients with a clear history of visually induced seizures or complaints, and in those already known to be photosensitive. The patient will be stimulated with a variety of visual stimuli in order to give a tailor-made estimate of the personal risks that are encountered in daily life by the various visual stimuli (TV screens, video games, striped patterns, and so on), as well as evaluation of the effect of nonpharmacologic treatment (type of glasses; which covered eye is most effective).

Proposed Methodology

What one needs to know before starting *any* IPS procedure

A. Get sufficient clinical information

For risk assessment one needs to know whether the patient—between 10 and 20 years of age (age range of maximum sensitivity)—is drug naive (AEDs diminish risk of provocation of generalized tonic–clonic seizures, GTCS); had a short night sleep (increased of risk of PPRs); had seizures provoked by TV, sunlight, or computers; or has a history of visually induced seizures in family members.

Comment: Several general factors, known to be activating in generalized epilepsies, such as sleep deprivation, alcohol abuse, and drug withdrawal, can influence the degree of photosensitivity (Scollo-Lavizzari & Scollo-Lavizzari, 1974; Ambrosetto & Tassinari, 1987).

Although we do not know exactly how great the risk for the individual patient will be, all the preceding factors have been shown to increase the likelihood of occurrence of a stronger reaction to visual stimulation with the potential risk of eliciting a tonic–clonic seizure.

The proposed methodology diminishes risk of provoked seizures greatly, but with the above-mentioned information, technicians are better prepared to further reduce the risk.

B. No special requirements are needed for the patient before arriving at the EEG department

No special requirements are needed; do not stop any medication the day before the EEG is recorded. If the patient is known to be visually sensitive (PPR or clinical history), advise the patient to avoid long duration of (extreme) visual stimulation with lack of sleep, for example, night-long video gaming and discotheque dancing the night before.

Comment: For diagnostic purposes, it is most informative to register an EEG in a drug-naive state. However, when the patient is already on AEDs, changing the medication shortly before the EEG registration will create a withdrawal situation with increase of PPRs and risk of seizures.

C. Organize Informed Consent

Consent is especially important when performing a second-level EEG in patients with known photosensitivity. Informed consent is necessary not only from the patients (or legal representatives), but also from family members, who will be present in the room during the IPS procedure.

Comment: IPS is by nature a provocation method. Although the risk of evoking a seizure will be very small when the IPS procedure is performed with care and with determination of thresholds, unexpected findings can nevertheless occur, whether causally related to the flashing lights

or not. Small children can be stimulated while sitting on the lap of the parent or with the parents sitting nearby. Therefore, the parent will receive high intensity flashing lights as well. An EEG laboratory has in any case rescue medication at hand, such as midazolam or diazepam, in the event that a seizure occurs.

D. Perform IPS at least 3 min after hyperventilation (HV) or before HV

Comment: After HV patients usually become drowsy and more relaxed. In adults and adolescents this might lower their anxiety for IPS. IPS at the end of the EEG and with HV at the beginning maximizes the chances of obtaining a spontaneous sleep recording, especially in children (Kaleyias et al., 2006).

E. Perform IPS for the first time always while the patient is awake after a normal night sleep. If this registration does not reveal photosensitivity and the patient has a history of visually induced seizures or if the influence of night sleep deprivation (NSD) is of importance (JME patients), IPS can be performed in the early morning after a scheduled partial NSD. If possible, perform IPS near the time of the day in which the patient had his/her evoked seizures.

Comment: Although photosensitive patients are mostly found in an epilepsy population, a PPR can be found unexpectedly in patients with other neurologic diseases and disease states (migraine, Parkinson, head trauma, alcohol or drug withdrawal, dementia) or simply because of genetic predisposition (Kasteleijn-Nolst Trenité et al., 2011).

Most patients with a clear recent history of visually induced seizures and without AED treatment will show a PPR in a routine registration with standardized IPS. IPS during sleep does provoke PPRs only in rapid eye movement sleep; sleep deprivation is the most provocative state (Scollo-Lavizzari & Scollo-Lavizzari, 1974).

JME patients are particularly likely to show a PPR in the early morning and even more pronounced after NSD (Labate et al., 2007). Variations in daytime biologic rhythms in photosensitivity do exist, however.

F. Use dim room lighting, an upright position of the patient, and when a tailored study is performed also simultaneous video recording

Comment: During IPS the patient should be observed for detection of clinical signs for safety and diagnostic reasons, to help discover artifacts and notice change in eye conditions. At least dim room lighting is necessary to be able to see the subtle clinical manifestations, that often accompany PPRs. It has been demonstrated that the likelihood of finding a PPR is more or less equal with dim surrounding lights and darkness (Van Egmond et al., 1980). Only in patients with suspected fixation-off and scotosensitive epilepsy, additional registration in darkness is useful as well (Panayiotopoulos, 1998).

If the patient is sitting (or standing with extra security measures taken to prevent any possible harm), clinical signs like subtle myoclonic movements in limbs and face can be noticed during IPS. Simultaneous video images are helpful and mandatory for precise detection of clinical signs.

In order to get the patient to sleep and relaxed with a minimum of artifacts, routine EEG recordings usually are done with the patient lying on a bed with eyes closed. However, both HV and IPS with different eye conditions can be more easily performed by patients, while sitting (or standing); modern EEG technology helps reduce artifacts. For capturing self induction with hand waving and eyelid movements, patients necessarily need to be in an upright position.

G. Record before the actual IPS procedure starts at least 2.5 min with eyes open and 2.5 min with eyes closed

Comment: This is to enable discrimination between spontaneous and IPS-evoked discharges and to detect fixation-off sensitivity (Panayiotopoulos,1998). If the alpha-rhythm shows a lower amplitude and less spindling, then it will be more likely that the patient is photosensitive (Brazzo, 2010; Kasteleijn-Nolst Trenité, 1989).

H. Use a lamp with circular reflector that delivers flashes with an intensity of at least 0.70 Joule. Use a viewing distance of 30 cm

Comment: To achieve a maximum level of sensitivity, uniform stimulation of the whole retina is essential. This is better achieved by round stimulators than oblong ones, because the visual angles of stimulation for the latter are different (Harding & Jeavons, 1994). Grids should be avoided to prevent combining pattern and light stimulation (Kasteleijn-Nolst Trenité et al., consensus 1999a,b), unless no PPR is found and the patient has a consistent history of TV- or video game–induced seizures, in which case pattern might play a predominant role. The energy output conveyed by the stimulator must ideally be close to 1 Joule, as many patients will show sensitivity only with higher light intensity (Specchio et al., 2010). The lamp at 30 cm from the nasion of the patient diminishes photomyoclonic responses and most importantly the patient's face, and thus evoked clinical signs, e.g., eyelid movements and eye deviations can be observed.

I. Explain to the patient what procedure will be followed and what precautions will be taken to prevent a seizure.

Comment: Flashing lights of high luminance are potentially provocative and thus need to be administered with the utmost care. Several patients do not like to be subjected to IPS, especially after bad previous experiences such as an IPS-evoked generalized seizure. To gain confidence, it is very helpful to explain the stimulation procedure, that is, threshold stimulations and the cessation of stimulation as

soon as generalized epileptiform discharges are seen in the EEG.

J. Instruct the patient to look at the center of the lamp and to close their eyes when asked.

Comment: Stimulation of the central part of the retina is most effective in provoking a PPR (Wilkins et al., 1980). Eye closure on command, especially at the onset of the train of flashes, is most provocative. Eye closure not only sets the brain in a more excitable state (as seen in normal records in the alpha squeak phenomenon), but also provokes a diffusion of light over the entire retina. Flashing during the eyes-open condition is the least effective in evoking a PPR (Kasteleijn-Nolst Trenité, 1989). The red filter effect of the eyelids probably plays a role in this. Stimulation with a diffuser (a translucent paper in front of the patient's eyes) has been proposed as a highly efficient technique in simulating the eye closure and eyes closed condition (Leijten et al., 1998). It can be very useful in noncooperative patients, but has the disadvantage that the face is no longer visible.

Infants are usually attracted by flashing light and look into the lamp; otherwise the child's attention could be attracted by holding a toy behind and above the lamp.

In children <4 years of age, or with conditions that limit cooperation (i.e., intellectual disability, behavioural disturbances, and so on), eyes can be kept closed by the parent or by the technician.

IPS procedure on the basic level

The purpose is to gather as much information as possible and in a concise way for clinical purposes; it is not a goal to lower the epilepsy threshold but simply to assess whether there is a susceptibility to visual stimuli in daily life. Confirmation and exclusion of photosensitivity are equally important.

A. Stop the visual stimulus immediately as soon as generalized epileptiform discharges occur during any flash frequency, regardless of whether the discharges stop at the end of the stimulus or continue after that (i.e., they are self-sustaining).

Comment: Although some older studies (Reilly & Peters, 1973) have suggested that only self-sustaining PPRs are associated with epilepsy and seizures, later studies have shown that also non–self-sustaining generalized discharges can have the same impact (Puglia et al., 1992; Nagarajan et al., 2003). Waiting for self-sustaining PPRs is thus not appropriate.

B. Determine IPS sensitivity in three eye conditions with separate trains of flashes of 5 s duration each during eye closure, eyes closed, and eyes open.

If there is not enough time, choose the eye closure condition (closure of the eyes on command at the start of a flash train) and stimulate for 7 s per flash frequency

Comment: Eye closure is by far the most provocative eye condition. Ten percent of photosensitive patients are detected exclusively with performance of eye closure during IPS (Kasteleijn-Nolst Trenité, 1989). Children older than 4 years of age are usually capable of performing eye closure.

If recording time is limited, choose eye closure only and expand the flash duration to 7 s. In doing so eye closure is partly combined with eyes closed with diminishment of the total duration of IPS to 2 min max, in case there is no PPR at any flashfrequency. The disadvantage is that, both conditions are hard to disentangle.

To know whether patients react to IPS during eye closure is relevant, because these will occur during the watching of TV or in sunshine, and so on. See Fig. 1 as an example of IPS during eye closure on demand.

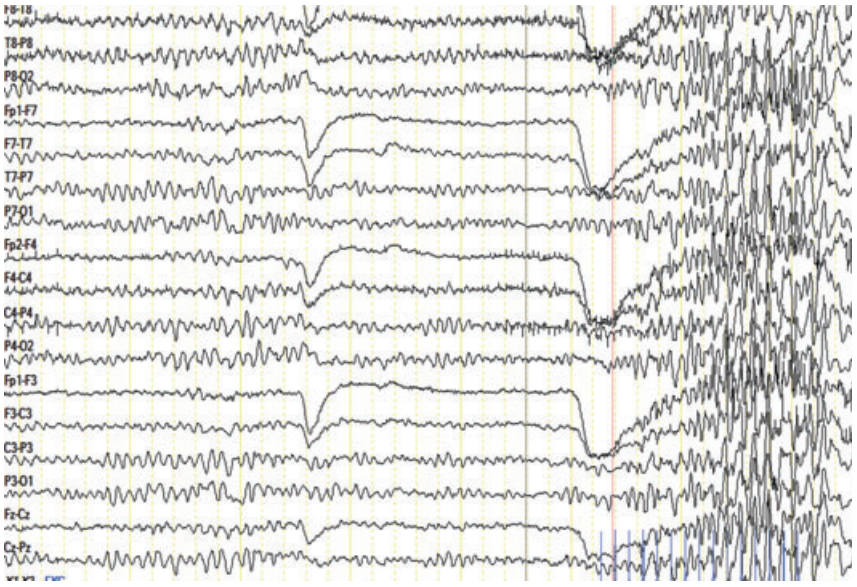

Figure 1.
IPS at 8 Hz during eye closure on demand evokes a generalized photoparoxysmal response in a 23-year-old woman with twice-daily 50 mg lamotrigine. EEG registration was performed at 30 mm/s with sensitivity 10 μV, high frequency filter 70 Hz, and low frequency filter 0.3 s.
Epilepsia © ILAE

C. Use the following flash frequencies separately and in this order: 1 – 2 – 8 – 10 – 15 – 18 – 20 – 25 – 40 – 50 – 60 Hz. If there is a generalized response at a certain frequency (lower threshold), skip the remainder of the series and start again with 60 Hz and go down in frequencies (60 – 50 – 40 – 25 Hz- …) until again a generalized PPR occurs (upper threshold). When in doubt if a particular frequency has provoked a generalized PPR, repeat the frequency after a rest of 10 s or give a frequency of 1 Hz difference.

Comment: The low frequencies of 1 and 2 Hz are for detection of progressive myoclonic epilepsies (Rubboli et al., 1999). The patients who are sensitive specifically to the higher frequencies are more sensitive to fluorescent lighting and TV. Most patients are sensitive between 10 and 30 Hz (Harding & Jeavons, 1994). In order to prevent seizure occurrence, lower and upper thresholds of sensitivity are determined as described earlier.

The number of flash frequencies is diminished by 5 (five times 30 s per flash frequency, all eye conditions included = 150 s; 30%) compared to the first methodology proposal of 2001 in order to shorten the IPS recording time. The current proposal takes 5 min of IPS at maximum (5 s IPS and 5 s rest times three eye conditions = 330 s) when the patient is either not sensitive or sensitive to only one frequency; in this case all frequencies are done only once and when arriving at 60 Hz the stimulation can be stopped. Otherwise, the duration will be shorter; the more sensitive a patient, the less time it will take, because stimulation stops at the lower and upper threshold frequencies (Kasteleijn-Nolst Trenité et al., 1999a,b). If a patient shows a generalized PPR at, for example, 8 Hz (lower threshold) and at 40 Hz (upper threshold), the total number of stimulations has been six frequencies with a total duration of stimulation of 3 min (six times 30 = 180 s).

By following this strategy a sensitivity range can be determined that is individual, is related to the liability to seizures in daily life, and changes with age and use of AEDs.

If only 18 Hz is used, about 15% of patients will not be detected as being photosensitive because they are sensitive at other frequencies, as has been seen in a population of 70 patients (age range 13–73; average 31 years) with a generalized PPR in one or more eye conditions (personal data DKNT).

In most laboratories, traditionally a mix of even and uneven frequencies are given; although no controlled trials or published peer-reviewed data are available, patients appear to react stronger to even than odd frequencies. Repetition of the same frequency within a time frame of seconds might change the type of response (silent period; Forster et al., 1964). One can thus take another close flash frequency or wait longer before repeating the same frequency.

See Table 1 as an example; the emptied form can be used for clinical purposes also.

D. Observe clinical signs during the PPRs and ask the patient about any complaints he/she might have felt.

Comment: Clinical signs and symptoms give valuable information about the type of seizures and epilepsy the patient has and allow correlation with clinical history data (Trenité, 2006). Patients can be taught to recognize their signs and symptoms during epileptiform EEG activity and use them to prevent seizures induced by visual stimuli in daily life.

IPS procedure on a higher level of sophistication

The purpose is to gather as much information as possible for clinical and research purposes. Thanks to a greater range of visual stimuli tested like pattern and videogames etc., a more precise individualized advice about potential provocative visual stimuli and therapeutic measures can be given.

A. Use electrodes for recording eye movements and surface axial electromyography (EMG) recording to detect subtle myoclonus

Comment: Eye movement recording permits more precise registration and, therefore, discrimination between the different eye conditions and especially the detection of self induction with slow eye closures (Kamp & Lopes da Silva, 1987). For detection and more precise registration of

Table 1. Scoring table photic stimulation

Name: A. K.
Date of birth: 20-12-1992
Medication: none
Date: 7-5-2011
Time: 9.30

Flash frequency (Hz)	1	2	8	10	15	18	20	25	40	50	60
Eye condition											
Eye closure	–	–	+	0	0	0	0	0	+	–	–
Eyes closed	–	–	±	±	+	0	+	±	–	–	–
Eyes open	–	–	–	–	±	+	±	–	–	–	–

In this scoring table, an example is given of determination of the three photosensitivity ranges based on the proposed methodology.
Photosensitivity ranges eye closure: 8–40 Hz; eyes closed: 15–20 Hz; eyes open: 18 Hz. *Explanation of codes* + : generalized epileptiform discharges; ±: epileptiform discharges, not generalized; –: no epileptiform discharges; 0: frequency not tested.

clinical events, including negative myoclonus (Rubboli et al., 2004), EMG is helpful.

B. Test IPS sensitivity in three separate eye conditions (eye closure, eyes closed, and eyes open).

Comment: Eye closure is the most provocative condition. Ten percent of photosensitive patients are detected only with performance of eye closure during IPS (Kasteleijn-Nolst Trenité, 1989). Eye closure at the start of the stimulus train of 5 s duration is different from the eyes closed condition; after eye closure an alpha squeak (Storm van Leeuwen & Bekkering, 1958) occurs and the threshold for a PPR subsequently diminishes. The duration of the flash-train can be longer if thought useful, for example, if there is a history of juvenile myoclonic epilepsy or video game seizures (Appleton et al., 2000; Waltz & Stephani, 2000).

C. Use the following flash frequencies in this order: 1 – 2 – 6 – 8 – 9 – 10 – 13 – 15 – 18 – 20 – 23 – 25 – 30 – 40 – 50 – 60 Hz. If there is a generalized response at a certain frequency, skip the remainder of the series and continue then with 60 Hz and go down in frequencies (60 – 50 – 40 – 30 – 25 Hz- …) until again a PPR occurs.

Comment: Retesting of photosensitive patients gives the opportunity to determine more precisely the photosensitivity range.

D. Stimulation with colored flashes in patients with a history of TV and videogame epilepsy.

Comment: Since the Pokémon incident in Japan (Furusho et al., 2002), much attention has been given to color stimulation emitted through the TV. Color stimulation can be a powerful tool to trigger PPRs at a low-luminance level that may be especially prominent in a subset of patients. It is performed only in the eyes-open condition with a luminance of 20–30 cd/m^2, and it is especially effective at frequencies of <30 Hz, as the stimulation is conveyed mainly by the parvocellular pathway (Takahashi et al., 1999; Parra et al., 2007). Red light of wavelength >600 nm seems to be particularly effective, and it has been argued that this is because it overcomes the antagonistic effects of cone stimulation by providing maximal stimulation to the occipital cortex (Binnie et al., 1984). Alternating red and blue stimulation seems to be an even more provocative stimulus, with a synergistic effect not predictable by the sensitivity to red or blue light alone (Parra et al., 2007). Young teenagers seem to be particularly at risk from these stimuli (Yamasaki et al., 2008). Alternating stimulation with colors far apart in color space might also be very effective in triggering PPRs (Wilkins et al., 2008).

E. Stimulation with black-and-white evenly striped patterns (gratings that are circular in outline and centrally fixated) with spatial frequency between 2 and 4 cycles per degree, Michelson contrast >0.8, and a mean luminance of at least 300 cd/m in a well-lit room or on an LCD monitor with a steady backlight. Patterns of increasing size are presented in succession having radii of 3, 6, 12, and 24 degrees, and the series is terminated if a PPR occurs. In one series the stripes are black and white and in a second series they are red and blue.

Comment: Potentially epileptogenic visual stimuli are commonplace in the modern urban environment. They include not only geometric patterns, but also to a lesser extent more complex designs, even works of modern art. It is important to know whether a patient is likely to be sensitive to visual stimuli that do not flicker. In nature, images have a particular power spectrum in which the luminous contrast energy decreases with increasing spatial frequency as the reciprocal of the frequency, that is, a graph of log contrast energy against log spatial frequency is linear with a slope of about −1. Images in which the power spectrum departs from this simple relationship are uncomfortable to view (Juricevic et al., 2010). Those images with an excess of contrast energy at mid-range spatial frequencies relative to the energy expected are particularly uncomfortable (Fernandez & Wilkins, 2008). If an image has all its energy at mid-range spatial frequencies, it is not only uncomfortable but is also epileptogenic. This can be examined in the laboratory using nonflickering patterns with the above-mentioned parameters. The purpose of increasing the radius is to determine thresholds for evaluation of drug effects and age as well as to reduce the risk for seizures.

F. Video games and cartoons on TV and computer screens.

Comment: When patients have a history of seizures or complaints while playing or viewing a specific video game or cartoon, ideally these are presented in the laboratory with concurrent video-EEG recording.

Testing different TV sets in the EEG lab would provide the patient and family with a good understanding of one of the most provocative settings that might trigger seizures in the home environment and learn techniques to avoid the risk of seizures. This test would be available in only a few EEG labs dedicated to this specific field. Several minutes of recording may be necessary to elicit PPR in this situation.

The new developments in the field of television screens including three-dimensional (3D) devices as well as the increasing popularity of video games among youth (the segment of the population most sensitive to seizures triggered by visual stimuli) will warrant more research oriented to the properties of these devices and the peculiarities of the stimuli they will be able to convey. Although some specific research will undoubtedly be centered in specific programs with an unusual power to trigger seizures (like the Pokémon episode or the footage of the London Olympic games), we believe that the analysis of these programs and video game-scenes should be done from the perspective of the fundamental properties of the visual system rather than

focusing on individual properties of the image itself. Currently commercial devices like the Graham Harding pattern analyzer of Cambridge Research can analyze video sequences and detect those segments with features able to trigger seizures (See http://www.hardingfpa.com).

> G. Observe clinical signs with precision during the PPRs and ask the patient about any complaints he/she might have felt (Note: Recording of eye movement/myoclonus or of axial myoclonus is fundamental.)

Comment: Clinical signs and symptoms provide valuable information about the type of seizures and epilepsy the patient has and allows correlation with clinical history data. The clinical signs and symptoms might be different for the various types of stimuli, being focal or generalized, although in most cases the signs will be similar (Piccioli et al., 2005). Headache can even be the only symptom during a PPR, and EEG recording with photic stimulation as described above helps in discriminating between migraine and epilepsy (Parisi, 2009; Kasteleijn-Nolst Trenité et al., 2010). Patients can be taught to recognize this feeling and use it for prevention of seizures induced by visual stimuli in daily life.

Future Developments

Future developments in the study of photosensitivity should address three main issues:

1 *Definition and standardization of methodologic procedures to reliably detect photosensitivity either in the laboratory or in environmental conditions*. Indeed, at present, no known method is recognized as able to fully determine the risks of visually induced seizure precipitation in a highly susceptible person, although proposals for standardized procedures have been made (Kasteleijn-Nolst Trenité et al., 1999a,b). Indeed, additional methodologic studies on standardization of IPS are still necessary to demonstrate the yields provided by using adequate equipment and appropriate procedures to reliably detect photosensitivity (Rubboli et al., 2004; Specchio et al., 2010). Development and implementation of visual evoked potential recordings may also be useful for identifying abnormal susceptibility to light stimuli by using nonprovocative visual stimulation (Vermeulen et al., 2008). Finally, the clear definition of the phenotype Epilepsy with Photosensitivity identified by the methodologies described here will refine the cohorts of patients involved in genetic and other research (Trenité, 2006).

2 *Elucidation of the pathophysiologic mechanisms underlying photosensitivity*. Present knowledge on pathophysiology of epileptic photosensitivity points to two types of mechanisms—mediated by the magnocellular and parvocellular systems—that contribute either synergistically or independently to elicit a PPR. Selective activation of parvocellular or magnocellular divisions has been proposed as triggering different types of PPR: excitation of the parvocellular system by colored stimuli would be more epileptogenic, eliciting a generalized PPR, whereas stimulation of the magnocellular system would result in a milder PPR, represented by occipital spikes (Harding & Fylan, 1999). Moreover, it has been recently demonstrated that color sensitivity depends on two mechanisms: one related to color modulation, intervening at low frequencies, and the other dependent on single-color light intensity modulation and related to white light sensitivity that is activated at higher frequencies (Parra et al., 2007). Further research in this field, by using different techniques [i.e., magnetoencephalography (MEG), visual evoked potentials, functional imaging, optical imaging] (Parra et al., 2003; Schwartz, 2003) to deepen the comprehension of the different pathophysiologic mechanisms of photosensitivity, may provide the information necessary to develop more effective therapeutic measures (drugs, protective lenses) and to define more precisely endophenotypes for genetic research.

Application of specific types of visual-evoked potentials, using special parameters, might contribute to further clarify the role of the parvo and magno systems in generating abnormal visually driven cortical responses (Porciatti et al., 2000) and to define which are the potentially dangerous regions of the visual spectrum, in order to design safer visual stimuli by eliminating hyperactivating features of the visual information, and eventually to test the protective effects of drugs. Investigation of visual habituation in photosensitive patients may permit the identification of imbalances in excitatory and inhibitory cortical processes mediating the abnormal responses to visual stimuli, which may reflect impaired neurotransmission (Shepherd & Siniatchkin, 2009; Brazzo et al., 2011).

Finally, research on photosensitivity should take also into account that photosensitive epilepsy, as the most common form of reflex epilepsy (i.e., epilepsy in which epileptic manifestations can be triggered by external factors), represents a privileged model to investigate in a controlled fashion the brain processes that intervene in the transition from the interictal to the ictal state, opening a window on the mechanisms of ictogenesis and, possibly, epileptogenesis.

3 *Development and implementation of preventive measures and guidelines.* Development and implementation of guidelines to minimize exposure of susceptible populations to provocative stimuli are an important public health issue. In fact, the Pokémon incident in Japan stimulated a debate on the need for regulations and protective measures for video material, particularly for television programs, to prevent seizure precipitation. Since then, guidelines have been indeed implemented in the UK and in Japan; however, an agreement on the application of global homogeneous guidelines has not yet been achieved. Updated

guidelines and recommendations should consider the role of parameters such as modulation depth and stimulus wavelength at provocative frequencies and the increasing availability of modern audiovisual technology that employs large screen without flicker effects but with significant changes of other variables (for instance, luminance of the screen and the separate stimulation of the two eyes). To pursue this goal, sensitization and cooperation from the industry are necessary as well as the involvement of broadcasters and producers.

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