Photic- and pattern-induced seizures: a Review for the Epilepsy Foundation of America Working Group

by

Robert S. Fisher [1], Graham Harding [2], Giuseppe Erba [3], Gregory L. Barkley [4], Arnold Wilkins [5]

[1] Department of Neurology and Neurological Sciences, Stanford Medical Center, Stanford, CA

[2] Clinical Neurophysiology Unit, Aston University, Birmingham, England, UK

[3] Department of Neurology, University of Rochester, New York

[4] Henry Ford Comprehensive Epilepsy Program, Henry Ford Hospital, Detroit, MI

[5] Department of Psychology, University of Essex, Colchester, Essex, England

CORRESPONDING AUTHOR:

Robert S. Fisher, M.D., Ph.D.
Maslah Saul MD Professor of Neurology
Stanford Medical Center, Room A343
300 Pasteur Drive
Stanford, CA 94305-5235
650-725-6648
rfisher@stanford.edu

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ABSTRACT

Purpose: This report summarizes background material presented to a consensus conference on visually-provoked seizures, convened by the Epilepsy Foundation of America.
Methods: A comprehensive review of literature was performed.
Results: Photosensitivity, an abnormal EEG response to light or pattern stimulation, occurs in approximately 0.3 – 3% of the population. The estimated prevalence of seizures from light stimuli is approximately 1 per 10,000, or 1 per 4,000 individuals 5-24 years old. People with epilepsy have a 2-14% chance of having seizures precipitated by light or pattern. In the Pokemon cartoon incident in Japan, 685 children visited a hospital in reaction to red-blue flashes on broadcast television. Only 24% who had a seizure during the cartoon had previously experienced a seizure. Photic or pattern stimulation can provoke seizures in predisposed individuals, but such stimulation is not known to increase the chance of subsequent epilepsy. Intensities of 0.2 – 1.5 million candlepower are in range to trigger seizures. Frequencies of 15-25 Hz are most provocative, but the range is 1-65 Hz. Light-dark borders can induce pattern-sensitive seizures, and red color also is a factor. Seizures can be provoked by certain TV shows, movie screen images, videogames, natural stimuli (e.g, sun on water), public displays, and many other sources.
Conclusions: Recommendations on reducing risk of seizures have been developed by agencies in the UK, Japan, and the International Telecommunications Union, affiliated with the UN. The Epilepsy Foundation of America has developed a consensus of medical experts and scientists on this subject, reported in an accompanying work.

I. Introduction

On 8/31/04, the Epilepsy Foundation of America held a workshop to bring together expert knowledge about photic or pattern-induced seizures (PPIS). The purpose was to begin to develop a foundation in the United States for considering how best to describe and to reduce the risk of seizures provoked by certain types of visual stimuli. A companion paper (1) presents the expert consensus recommendations. This paper reviews background literature on photic and pattern-induced seizures.

II. History of photosensitivity

Apulius is said to have reported a seizure induced by watching a potter's wheel in 125 AD (2). However, since the potter's wheel was solid at this date the seizure could not have been due to photosensitivity from flashing spokes (3). Gowers first described PPIS in 1885, with reference to a girl who had seizures when going into bright sunshine (4). In 1932, Radovici (5) described eyelid myoclonias and absence seizures in response to eyelid closure while looking at bright light. Livingston described seizures in response to flickering on TV (6). General reviews can be found in several works (2, 7-15).

Gastaut (16) studied 35 patients who had seizures while watching television. They distinguished patients who had seizures from those who had fainting episodes, and those who had frequent seizures likely to be coincidently related to watching television. In the remainder, they believed that there was some relationship to watching television, and they documented abnormalities on the patients' EEGs. Pattern sensitivity in photosensitive subjects was first reported by Bickford and associates in 1953 (17).

PPIS from television program content (as opposed to the flicker from the refresh rate of the raster scan of the screen) came to public awareness only gradually, on the basis of a series of publicized events. In the 1980's, frequent flashes from targets and guns in a US television show called "Captain Powers" induced a seizure in a young male viewer (18). In 1993, an advertisement for "Golden Wonder, Pot Noodle" was shown in the UK. This commercial employed rapidly flashing contrast changes, and induced three seizures on its first showing. The UK regulatory commission for television (Independent Television Commission or ITC) solicited guidelines for photic stimulation on TV commercials (18). Subsequent violation of these guidelines led to 13 further known incidents of TV-induced seizures (18). The "Pocket Monster" incident in Japan, discussed below, was perhaps the most dramatic.

III. Types of Sensitivity to Light

Terminology relevant to photic- or pattern-induces seizures (PPIS) is often imprecise. Discussions may refer to photosensitivity, to seizures provoked by photic or visual pattern stimulation, to a "photomyoclonic" response with no seizures, to "photoconvulsive" or "photoparoxysmal" EEG changes in the absence of clinical manifestations, or to the development of long-term epilepsy. Each of these has different clinical significance and possibly different mechanisms. Therefore, definition of terms is in order. Since there is no authoritative compendium for each of these definitions, we operationally will define our terms here.

A. Definitions

Photic induced-seizure: A seizure provoked by visual stimulation. The usual stimulus is a flashing light, but can be patterns of lines, gratings, checkerboards or other configurations.

Photoparoxysmal response (PPR): An abnormal EEG response to light or pattern, consisting of spikes, spike-waves, or intermittent slow waves. To be classified as photoparoxysmal, the spikes should not be confined to occipital regions and should not be confused with the normal visual evoked response that is phase-locked to the flash.

Photosensitivity: An abnormal response of the EEG to light or pattern stimulation, consisting of a PPR.

Photomyoclonic response: Forehead and muscle twitching in response to light flash, disappearing with eye opening. Photomyoclonic responses are most common in subjects with early alcohol withdrawal and in anxious patients. A photomyoclonic response is considered to be a myogenic component of eye flutter, and not an epileptiform pattern. It is more frequently seen at low frequency stimulation and it disappears when the interval between stimuli is shorter than the eyelid reflex latency

B. Categories of EEG Responses that are Associated with Photosensitivity

When performing routine EEGs, most laboratories measure the response to photic stimulation at flash rates from about 5 to 25 Hz. Response to patterns is not assayed, except in special situations. Kasteleijn-Nolst Trenité and colleagues (19) and Rubboli et al. (20) have recommended systematic parameters for EEG labs to use to test for photic or pattern sensitivity. Response to intermittent photic stimulation (IPS) is considered normal unless the response shows marked asymmetry over the two sides of the head, or spikes. Some authors grade the degree of abnormality of photic stimulation, with spikes outlasting the photic stimuli, and spikes spreading beyond parietal-occipital areas graded more abnormal. Most photoparoxysmal responses do not outlast the stimuli, but still may correlate with epilepsy (21). Absence of photic response to IPS is normal, as is a prominent photic response, provided that it lacks spikes or asymmetry. The view of the current authors, however, is that spikes restricted to occipital regions during IPS are not currently known to have clinical significance.

A widely used EEG classification system was proposed by Waltz (22). In this scheme, Class I represents occipital spikes; II, local parieto-occipital spikes and biphasic slow waves; III, parieto-occipital spikes and biphasic slow waves spreading to frontal regions; IV, generalized spikes or polyspikes and waves.

Jeavons and Harding (9) categorized the type of EEG response to photostimulation into three groups: 1. responses seen only in the anterior regions (photomyoclonic); 2. response seen only in the posterior region (photic driving, visual evoked potentials, occipital spikes); 3. widespread, anterior and posterior, bilateral response (photoconvulsive). In their experience, photomyoclonic responses were extremely rare. In distinction to the scheme of Waltz, responses in category two of the Jeavons and Harding classification were considered normal, including occipital spikes that did not persist or spread (23). Although occipital spikes may not be

epileptiform in the Jeavons and Harding classification (which we favor), they may be useful markers for genetic studies. Category 3 photoconvulsive responses were abnormal, and could be further divided into six types:

1. Spike-wave bursts, usually around 3/sec
2. Spike-waves at 4-7 (theta) frequencies
3. Polyspikes or polyspike-wave
4. Spikes coinciding with the flash, but extending widely
5. Spike-waves at 3/s lasting at least 5 seconds, and associated with a clinical absence
6. Bilateral, diffuse high-amplitude slow waves

Any of these patterns was sufficient for Jeavons and Harding to classify the patient as having a photoconvulsive response. Pattern number 1, with 3/sec spike-waves, was most common, being seen in 88% of the photoconvulsive studies. Jayakar and Chiappa (24) investigated characteristics of EEG photoparoxysmal responses. Among 3,557 patients who had EEGs at their institution, 35 patients (1%) had such responses. Most of these patients had a history of epilepsy. They found no photoparoxysmal responses in 48 normal subjects, which is likely a function of the small number of normals surveyed, since previous literature reports of such responses in numbers ranging from 1 to 7% of patients (see discussion of Air Force studies in the epidemiology section below).

Reilly and Peters (25) found photoparoxysmal responses to be more likely associated with a clinical history of seizures if the spikes persisted for at least 100 milliseconds after termination of the flash. Jayakar and Chiappa (24) asserted that photoparoxysmal responses were rare and any such responses were likely to be associated with epilepsy. Prolonged photoparoxysmal responses that outlast the stimulus are more likely to be associated with epilepsy, but the relationship is complex and depends upon whether other epileptiform abnormalities are observed (26). Clinical correlates of EEG photosensitivity include a variety of subjective and objective phenomena, such as impaired consciousness, jerking on one or both sides of the body, eye opening and closing, and discomfort in the eyes (27). In carefully screened, asymptomatic populations, a photoparoxysmal response occurs in less than 1% of a sample of 100 adult subjects (28) and therefore is statistically unlikely to exceed 5%. Changes in visual fixation, rather than flashing lights, can account for some rare instances of so-called "fixation-off epilepsy" (29).

IV. Epidemiology of Photosensitivity

The prevalence of "photosensitivity" has been said to range from less than one in 10,000 to "5-9%" (30, 31). This wide variance stems mainly from two factors: lack of clarity in what condition is being reported, and bias in referral populations. The prevalence of photosensitivity is far higher than is the prevalence of PPIS. Discussions about populations "at-risk" of a PPIS are even more problematic, because most individuals at risk will never have had an EEG, many EEGs do not adequately test for photosensitivity (32), and the value of photosensitivity in predicting an actual seizure is not known. Additionally, some individuals may have a PPIS without demonstrating photosensitivity on the EEG, because of inadequate stimuli during the EEG, medications or chance variation.

For the most part, asymptomatic individuals do not have EEGs. Therefore, any study based upon patients referred to EEG laboratories will be biased towards individuals more likely

to have an abnormal EEG or consist of individuals for whom EEGs are a part of a routine medical assessment, such as pilots. Among patients with certain types of epilepsy, for example juvenile myoclonic epilepsy, the prevalence of photosensitivity can be 15-20% (33), or even higher (34). Approximately 0.7-1.0% of the world's population has diagnosed epilepsy (35), defined as seizure, in conjunction with a disorder of the brain, characterized by an enduring predisposition to generate epileptic seizures (36). An unknown number of individuals with no prior evidence of epilepsy have the potential for seizures precipitated by flashing lights. As noted above, large population studies on EEG photosensitivity are lacking. An exception is found in Air Force studies, in which a paroxysmal EEG abnormality is taken as a disqualification for flying aircraft. Among 13,658 men aged 17-25 years applying for Royal Air Force training, 48 (0.35%) demonstrated photoparoxysmal EEG responses (37). A Danish Air Force study (38) found a somewhat higher number of EEG abnormalities in 2.4% of 5,893 asymptomatic applicants. The abnormality consisted of interictal spikes in six patients (0.1%) and a photoparoxysmal responses in 2.2% (38). Individuals with a photoparoxysmal response were denied flight training. Even though air force studies performed bulk EEG screening, the population studied was likely to be healthier than was the population at large, in that ill individuals, or those with a history of epilepsy, do not tend to apply for military flight training. Such studies also exhibit bias towards males, who have a lower incidence of photosensitivity (39). Since the prevalence of photosensitivity is higher in the younger population and in people with epilepsy than in people without epilepsy, the Air Force estimates of photosensitivity are most likely underestimates.

One review of 20,000 EEGs discovered eight patients who had seizures induced by light in a natural setting, 17 with seizures that could be induced in a laboratory setting, and 225 with photoparoxysmal EEG activity only (40). This would suggest that about 1.25% of individuals might have an abnormal EEG response to certain types of light stimulation, among those referred for EEGs. Another study (41) showed that 6.5% of 408 patients with a single seizure had EEG changes in response to light flash. A history of a prior seizure was associated with a higher risk for light sensitivity (41). Steinkruger (42) estimated that PPIS occur in one of every 10,000 people in the general population, a number at least 4-fold less than the estimate of those having an abnormal EEG response to IPS.

Children are more prone than are adults to photoparoxysmal EEG changes and PPIS. Doose and Waltz (43) found photoparoxysmal responses in 7.6% of 662 normal children, but used "looser criteria" for an abnormal response to IPS than those used now. Eeg-Olofsson and Petersen (44, 45) found that 8% of 673 normal children aged 1-15 years, and 1% of 181 individuals 16-21 years old had an abnormal response to intermittent photic stimulation.

The December 16, 1997 Pokemon incident in Japan provides an inadvertent "experiment-in-nature" to judge the prevalence of photic-induced seizures in a population of children. In a Pocket Monstor cartoon, a rocket-launch sequence, with flashing red, then blue screens, changing at 12.5/sec for about four seconds, was shown on Tokyo TV, resulting in hospital visits by 685 children (46-48). Subsequent studies suggested that at least 560 of these children had seizures, although some had migraines, visual distortions, nausea and motion sickness or other non-seizure symptomatology. Approximately three-quarters of the children had no prior history of epilepsy (49), and more than half the children who had experienced a previous convulsion had a history of a seizure induced by television (50). Given that about 7 million children were watching the children's program, this suggests that roughly 1 in 10,000 children had a seizure in response to this photic stimulation. This figure is probably an under-estimate of the total

population of pediatric patients able to have seizures in response to visual stimulation, since some might have been sensitive to other frequencies of stimulation or to patterns of light. On the other hand, photosensitivity is less common in adults, so the estimate of 1 in 10,000 would overestimate the global population figure. The incidence estimated from the Pokemon incident thus is remarkably similar to that obtained by Quirk et al. (51) in a study based upon EEG lab surveys in the UK (see below).

Genetics plays a role in tendency to develop PPIS. Waltz (23) in Germany performed family studies of 41 patients with PPIS. In this study, 50% of siblings with one photosensitive parent were themselves photosensitive, suggesting a dominant mode of inheritance of the tendency. A 1989 study (52) found that a family history of PPIS was present in 14% of 2,053 patients presenting to a seizure clinic with any type of seizure. Takahashi (53) performed EEGs on 21 siblings of 17 patients with photoparoxysmal responses. Generalized paroxysmal EEG discharges occurred in 24% of the siblings. The prevalence and incidence of photosensitivity varies with age, being higher in the young. Onset of PPIS usually arises at age 12-15 years (9, 52).

In Great Britain, the annual incidence of new-onset seizures due to unequivocal photosensitivity was 1.1/100,000 in the overall population, but 5.7/100,000 in the age range 7-19 (54). PPIS occur in 1/4000 of individuals between 5 and 24 years. Photosensitivity and photic-induced seizures usually manifest around puberty, and 90% of patients with PPIS have an initial seizure before 20 years of age (18). However, it is an oversimplification to state that individuals grow out of photosensitivity. Harding and associates (55) and Jeavons et al. (39) demonstrated that approximately two-thirds of 100 people with photosensitivity continued to show photosensitivity on the EEG, and in some instances continued to have photic-induced seizures, for a mean of 14 years after the initial diagnosis. In contrast, photosensitivity disappeared over long-term follow-up in 25 of 42 photosensitive patients (56). Scott and Elian (57) explicitly studied photoparoxysmal responses in 52 patients over 30 years of age, demonstrating that photosensitive responses can be identified in adults.

Female to male ratio for photosensitivity ranges from 1.5 – 2.0 (18, 39, 58). However, males predominate among video game - induced seizures, because many more boys than girls play such games. Racial or ethnic background may make a difference in incidence of photosensitivity. In Africa, photosensitive EEG responses were seen in in 2.5% of the Caucasian, 1.3% of the mixed race, and in 0.9% of the African population subgroups (59). Among adult Arab seizure patients, 24/327 (7.3%) showed EEG spikes to light flash (60).

A PPIS does not require a prior diagnosis of epilepsy – in fact, for many individuals who have such a seizure, it is their first seizure. The prevalence of photic or pattern-induced abnormal EEG discharges is higher for those known to have epilepsy. Among people presenting with new-onset epilepsy, approximately 2% have PPIS (51). People with primary generalized epilepsies are more likely than those with partial epilepsies to be sensitive to light; although any type of seizure can be associated with light sensitivity. In a group of 61 children with juvenile myoclonic epilepsy (JME; age range 7-16), 90% were photosensitive, defined as a generalized spike or spike-wave occurring at least twice during photic stimulation (34).

Photoconvulsive seizures are most common with generalized processes, including acute alcohol withdrawal syndromes (61) and idiopathic generalized epilepsy (62). However, partial seizures also can be provoked by flashing lights or patterns. Among 80 patients demonstrating some form of PPIS (52), precipitants comprised TV in 48%, sunlight or electric lights in 7%. Apparently generalized tonic-clonic seizures were seen in 44% and secondarily generalized

seizures in 35% (52). The prevalence of focal seizures among those with photic-induced seizures ranges from 2.8% (3) to 29% (10), and as high in some studies as 60% (63). Most of these focal seizures were spontaneous, not photic-induced. Focal paroxysmal responses in the EEG have been correlated with focal seizures, and generalized photoparoxysmal responses with generalized seizures (64). Most individuals with reported video game - induced seizures have photoparoxysmal responses in EEG testing, but some do not (65).

Photosensitivity is stable over intervals of days in a given individual, if allowances are made for circadian (time of day) variation (66). This stability allows EEG measures of photosensitivity to be useful for screening of antiepileptic drugs as a model for testing AEDs (66). In such screening, the acute suppression of photosensitivity serves as evidence of antiepileptic action but not of long-term efficacy for treatment of photosensitive epilepsy.

Concurrent conditions may predispose certain individuals to photoconvulsive attacks while viewing a screen. Such factors include alcohol withdrawal (67) and sleep deprivation (68). Among patients with epilepsy, about 2-5% can have seizures precipitated by watching television (9, 69), but not every study has found a high prevalence of television sensitivity in patients with photosensitivity (70).

What is the incidence of seizures precipitated by video games? No definitive answer to this question is yet available. A three-month *Department of Trade and Industry* study involving 118 patients (51, 54) surveyed about "90%" of all EEG departments in Great Britain over a three-month time during 1993-1994, for all patients presenting seizures with photosensitivity, and all people whose presenting seizure occurred while playing in electronic screen game, whether or not they were photosensitive on the EEG. Seizures were categorized by direct review according to the criteria of Waltz (see above). Type IV responses (generalized spike-waves) were most closely associated with a tendency toward seizures.

Patients were divided into group A: seizure definitely considered to have been triggered by playing the screen game, including a requirement for type IV photosensitivity. Group B were probable cases; Group C were people with seizures unlikely to be related to the screen game. Among the group A definite cases, 43/46 had the presenting seizure while playing the electronic game and 3/46 within 10 minutes of finishing a session. Among the 25 group B cases who were classified as probable (mostly because they had type 1-3 EEG photosensitivity), 22/25 had a seizure while playing and 3/25 within 10 minutes of finishing. Most of the seizures occurred within 30 minutes of starting play. An estimated annual incidence of an initial seizure triggered by a video game was 1.2 per 100,000, and 5.7 per 100,000 among children 7-19 years old. This can be compared to an overall incidence of new cases of seizures of all types of 55 per 100,000 in this age group. Precipitating factors were evenly divided between broadcast TV and electronic screen games, although more hours were spent watching TV. Sleep deprivation was an associated factor. Possible inaccuracies in the estimates discussed by the authors derived from the likelihood that not every individual with PPIS was captured (particularly if a seizure was mild), and not every EEG identified photosensitivity. This study remains one of the very few population studies of seizures induced by light stimulation.

Seizures induced by patterns occur with an incidence of about 30% of flash-sensitive patients in the case of stationary patterns, and about 70% for vibrating patterns (14). Individual patients may have sensitivity to flash, to certain patterns or to both. Patterns particularly likely to produce either an abnormal EEG response or a seizure in susceptible individuals include lines or gratings, especially in an oscillating motion (71-74); however, a wide variety of patterns can provoke seizures in particular patients.

V. Mechanisms of Photosensitivity

Why does a light flash induce a seizure? Only partial answers are available. Cellular mechanisms are difficult to study in patients because of ethical and practical constraints. Animal models of photic-induced seizures are available, for example, photic-sensitive chickens (75) or light-sensitive baboons (76). If a seizure-producing drug is applied in low concentration to visual cortex of a rabbit, then a continuous progression can be seen from normal visual evoked potentials to light flash and epileptiform spikes evoked by light flash, as the epilepsy develops (77). However, the extent to which findings in these models predict or explain human epilepsy is unknown. It would be very useful to have a validated animal model as a screening tool for visual stimuli.

Seizures involve synchronization of large networks of brain cells, so that the cells fire in unison during a seizure. EEG during a seizure reflects summed synchronous activity of millions of brain cells. During normal awake brain activity, cells fire in independent patterns, and EEG remains low voltage. Photic abnormalities in cortex probably arise from mechanisms that process visual information, and these may be quite normal. Photosensitivity can occur in patients whose vision is normal, not only as regards acuity, but as regards the ability to see low-contrast gratings that would, at higher contrasts, elicit seizures (14). Wilkins (14, 78) has pointed out that the visual stimuli that provoke seizures are "strong" stimuli in that they (1) have low thresholds (2) interfere with (or mask) the perception of other target stimuli; (3) are able to trigger relatively high amplitude visual evoked potentials (4) result in relatively high cerebral blood oxygenation. Meldrum and Wilkins (79) on the basis of pharmacological evidence postulated a diffuse insufficiency of GABAergic inhibition as one possible mechanism for photosensitivity. Pyramidal cells share inhibitory processes and when strong stimuli result in a high level of excitation in pyramidal neurons these shared inhibitory processes are compromised, resulting in a spread of excitation. A sudden sensory stimulus can engage sensory regions of brain and cause brain cells in that region to act in unison.

Binnie et al. (71) showed that gratings that drift continuously toward the center of gaze are not provocative for epileptiform discharges, although those that move with the same velocity but repeatedly change their direction of movement or phase (black-white; white-black) can be highly provocative. Stationary gratings pose a risk somewhere between these two extremes. Wilkins and colleagues (80) argued that the contours from drifting gratings move into and out of the overlapping receptive fields of cortical neurons, providing a sustained level of firing but without any temporal synchrony. Gratings that repeatedly change direction of movement cause a synchronous change in the population of neurons firing by virtue of the direction selectivity of the receptive fields. Similarly gratings that change their phase also synchronise the firing of large numbers of cells. It is presumably when excessive numbers of cells are acting in concert ("hypersynchrony"), that inhibitory mechanisms can be insufficient to meet demand, and the synchronised firing spreads. Limited regions of synchrony can produce EEG changes (photoconvulsive or photoparoxysmal response) with no behavioral seizures.

The visual cortex is located in the occipital lobe of the brain. The most posterior part of the visual cortex is sensitive to light, more anteriorly to edges, and even more anteriorly to moving or changing edges and other complex geometric patterns (81, 82). Individual brain cells respond to edges in particular orientations, with some cells being excited by a given pattern and others inhibited. Thus, a visual stimulus selectively activates certain regions of brain containing cells "tuned" to respond to the characteristics of that stimulus. In a series of psychophysical

studies of the EEG response to pattern in photosensitive patients, Wilkins and colleagues (14) have shown how the response varies with the line length within the pattern, the angular subtense of the pattern, its spatial frequency, duty cycle, luminance and contrast. The response is greater when the image is fused in binocular vision, indicating binocular interaction, one of several lines of evidence indicating a trigger in the visual cortex. From a series of inferences they conclude that seizures begin when normal physiological excitation in the occipital cortex exceeds a critical amount. Stimulation in the central visual field is as effective as that in the periphery when cortical magnification is taken into account. Although large areas of the visual cortex appear to be equipotential for evoking seizures, the seizure threshold in one cerebral hemiphere can differ markedly from that in the other, even in patients with primary generalised epilepsy.

The normal response to a light flash or reversal of black-white edges is a synchronous firing of neurons in the visual cortex. This can be measured with computer EEG enhancement techniques in normal individuals, and is called the "visual evoked potential" or the "visual evoked response." Patients with PPIS tend to have enhanced visual evoked potentials to light flash or checkerboard (16, 83). Porciatti and colleagues (83) show that the increase in the size of the evoked potential with increasing contrast is abnormal in photosensitive patients at high contrasts, which is consistent with the above hypothesis that the seizures are triggered when normal physiological excitation exceeds a critical level as a result of a failure of shared inhibitory processes. Dopaminergic mechanisms may be particularly important in photosensitivity (84).

Common wisdom has held that photoconvulsive attacks begin by affecting the occipital lobe, the region of brain processing of visual information. However, discharges in the photosensitive baboon, Papio papio, often begin frontally in the region of motor cortex (85, 76), for reasons that appear to involve periocular afferents. Occasional patients also appear to have EEG frontal origin of seizures in response to visual stimuli, for equally obscure reasons, although in others a progression from posterior regions to frontal can be seen. A study by Matsuoka (86) of the children in Japan with PPIS and five patients with reflex writing seizures was done to investigate the region of EEG onset of seizures. The photic induction was performed by red flickering light at 20 candles/meter squared (cd/m^2). Seizures tended to begin in the occipital region and spread anteriorly. Takasaka and colleagues (87) utilized computer measurements of coherence between different EEG channels to determine where PPIS began. In patients with predominantly occipital discharges, the occipital EEG leads paced discharges elsewhere. However, for patients with generalized photosensitive EEG patterns, frontal leads appeared to lead the discharges.

Studies utilizing magnetoencephalography (MEG) (88) documented enhancement of phase synchrony in the gamma-band (30-120 Hz), harmonically related to the frequency of photic stimulation, and preceeding the PPRs. Their findings were consistent with the idea that normal synchronised activity of large numbers of cells brought about by repetitive visual stimulation (evidenced by the harmonic gamma activity) results in a failure of inhibitory processes and culminates in the pathological synchronisation of the epileptic discharge. Magnetoencephalography was utilized by Inoue and associates (89) to investigate localization of electronic screen game-induced spikes. Patients who were photosensitive had MEG-documented posterior predominance of source dipoles in patients who had spikes during electronic screen games (89), but additional dipoles were localized to the supplementary motor area, peri-Sylvian region and medial temporal lobe.

Functional MRI and magnetic resonance spectroscopy (90) showed elevated lactate levels in occipital cortex in the resting state and increased visual cortex activation with photic stimulation. Other altered areas included motor cortex and posterior cingulate gyrus in the medial frontal region between the hemispheres. PET studies with oxygen-15 (91) showed that statistically significant increases in regional cerebral blood flow occurred in occipital cortex, Brodmann's areas 17, 18, 19, hypothalamus, caudate, hippocampus and scattered other regions.

When visual stimuli are restricted to one portion of the visual field (left-right, superior-inferior), the evoked EEG response tends to be maximal in the part of the occipital lobe responsible for processing that part of the visual field (92). The likelihood of generating a photosensitive response in a susceptible individual appears proportional to the amount of visual cortex activated in either hemisphere by a suitable stimulus (14, 78). Although occipital lobe is the key structure in generation of PPIS, occasional patients with complex partial seizures that can be triggered by light flash can be cured by a standard temporal lobectomy (93). In properly localized cases, complex partial seizures triggered by light may respond to temporal lobectomy even when photic spikes continue in the occipital lobe (94). This suggests surgical interruption of a seizure propagation pathway, or that a "critical mass" of synchronised neural activity is necessary for a seizure.

Evidence is substantial from animal models and clinical experience to support the concept that photic or patten stimuli can induce seizures in susceptible individuals. There is, however, no evidence that photic or pattern stimulation leads to epilepsy, the condition of spontaneously and chronically recurrent seizures.

VI. Characteristics of the Stimuli

Characteristics of flickering stimuli that influence the likelihood of provoking a seizure are listed in the monograph by Jeavons and Harding (9), and the characteristics of patterned stimuli in the monograph by Wilkins (14). These include intensity, duration, distance from the source, background illumination, diffusion of the pattern, contrast, type of pattern, color, open vs. closed eyes, one vs. two-eye viewing, and stage of sleep-wakefulness cycle.

Whether an individual is found to be sensitive to light or pattern will depend upon how the patient is tested in the EEG laboratory. Different laboratories use different protocols to perform EEGs. Some do not perform any photic stimulation as part of the routine EEG, and few employ visual patterns as part of the routine EEG. In 1996, a group met in the Netherlands to establish consensus on methodology for testing for photosensitivity (32). Characteristics of stimulators similar to that of the Grass photo-stimulator were specified. EEG was recommended to include a common reference montage of at least 16 channels distributed around the head. The subject should be positioned with eyes (or nasion) at least 0.3 m from the photic stimulator with dim surrounding illumination. Flashes should be delivered in separate trains of 10 seconds for each frequency with intervals of 7 seconds minimum. Subject's eyes should be open initially, and then closed after five seconds until the stimulation ceases. Testing frequency should include 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 20 flashes per second. A second sequence should begin at 60 Hz and decrease through 50, 40, 30, 25 and 20 flashes per second. The stimulation should be stopped if epileptiform discharges are observed. The stimulation procedure should last a maximum of six minutes. The electroencephalographer should be aware that repeating a frequency can lead either to potentiation (increase) or habituation (decrease) of the photoparoxysmal response (95).

A. **Brightness, contrast and size**

The few studies that have addressed the issue agree that seizures from light stimulation are more likely with bright light than with dim light (96, 97). A variety of different units and measurements for brightness are used. A difficulty with measurement arises because the flashes from conventional xenon discharge lamps are intensely bright, but very brief. Stroboscopes designed to induce EEG abnormalities recorded in the laboratory can deliver flashes with durations of 10 microseconds and 400,000-1.5 million candlepower at 2 feet (98). This is equivalent to 1.44 joules, or, more meaningfully, 22 lumen sec/foot-squared. At 1 (lumen second) per (foot squared) = 10.764 s cd / m^2. This is equivalent to 237 cd/m^2, which compares to 100-200 cd/m^2 for conventional TVs. High-contrast stimuli are more likely to provoke seizures than do bright lights against a light background (97), within variable individual susceptibility to brightness (99). Spreading light more diffusely over the visual field increases the risk for induced seizures, provided that luminance is kept constant (100). Chatrian and associates (72, 98) studied four patients with pattern sensitive seizures. Monocular stimuli tend to be ineffective in provoking seizures (72, 98). The effect of luminance on producing seizures is described in a sigmoid curve. At very low (scotopic) light levels there is little effect; over the mesopicl range there is a very steep effect of increasing luminosity; and then above a maximum threshold, well into the photopic levels, the curve flattens out once again. Patterns confined to the periphery of the visual field can provoke epileptiform EEG activity, provided they project to a sufficient area of the visual cortex (14).

B. **Flash rates**

Repetition rate of flash or pattern is second only to brightness in its influence over PPIS. The repetition range to provoke seizures usually lies between 15 and 25 cycles per second , but for some patients the upper limit of sensitivity can be as high as 65 cycles per second (9). Flashes at rates up to 45 cycles per second can evoke EEG discharges and myoclonus (101). A rare patient will have seizures in response to single bright flashes. One patient could produce seizures and EEG changes by mental imagery of flash (102), and another by eye blinks alone, in the absence of measurable photosensitivity (103).

FIGURE 1 NEAR HERE

Figure 1 (adapted from 18) shows the distribution of the percent of people with a photoparoxysmal EEG response to intermittent photic stimulation at different flash rates. A broad peak can be seen at about 12-30 flashes per second. The mains frequency is 60 hertz in the United States and 50 Hz in Europe; fluorescent lights flash at twice the mains frequency. In Japan, both 100 and 120 Hz are used in different regions. However, when the bulbs become old, the flashes may not be equal intensity, and the lamps may emit flicker with frequency components at values significant for PPIS. Binnie and associates (104) studied 20 patients found to be photosensitive on routine EEG investigation, by exposure to fluorescent lights. No patient was sensitive to normal fluorescent lighting, but some were minimally sensitive when the lamp was defective and emitted 50 hertz flicker. Fluorescent lights were not felt by these authors to be

a major public risk factor for photic seizures, although some photosensitive patients do complain of (normally functioning) fluorescent lighting.

C. Color

Red colored flicker, at wavelengths of 660-720 nm, is more likely to provoke seizures than is blue or white of the same overall intensity (105, 106), although some studies (107) have disputed that color makes a major difference. Sensitivity to color depends upon the type of epilepsy (108), such that with myoclonic epilepsies brightness is a key factor, but with symptomatic generalized and localization-related epilepsies, color is an important factor. Individual differences in the effects of coloured light may cause some patients to benefit from spectral filters that in other patients would exacerbate their sensitivity (109).

D. Patterns

A surprisingly high proportion of photosensitive patients are sensitive not only to flicker but also to patterns, as first documented by Stefansson and co-workers (74, 110). The proportion sensitive to both forms of stimulation depends upon their spatial and temporal characteristics. Using patterns on a television monitor, Harding and Jeavons (3) found that 30% of photosensitive patients also were pattern sensitive. Parallel lines or stripes are more seizure-provoking than are wavy lines or polka-dot patterns. Visual angles separating lines were most seizure-provoking at 4-40 minutes of an arc (60 minutes is 1 degree), i.e., the sensitivity is maximal at about 3 cycles per degree. Both horizontal and vertical patterns could induce seizures, and a given individual may be more or less sensitive to a particular orientation. (72, 74, 111).

Oscillating gratings at 15-25 per second (7.5° per second drift velocity), or 2-4 cycles per degree can be a potent stimulus for seizures in some individuals (14, 71, 112, 113). If the movement is perpendicular to the lines of the pattern and repeatedly changes direction, so as to vibrate the pattern at a frequency close to 20 Hz, the movement is extremely provocative for seizures. If the movement is continuous in one direction, then the pattern is almost without effect (71).

Wilkins, Emmett and Harding (114) have summarized characteristics of patterns likely to provoke seizures in pattern-sensitive individuals. Stationary, oscillating stripes or black-white reversals tend to evoke pattern-sensitive discharges; whereas, slow drift of lines in one direction does not. Striped patterns subtending approximately two degrees are more provocative; as stripes increase in size, their spatial frequency decreases and there are fewer stripes on the screen. The effects of the two parameters, change in size and change in spatial frequency, oppose each other. On a television screen viewed from conventional distances (at which it subtends about 10 degrees at the eye) a stationary pattern with no more than eight light-dark stripe pairs is unlikely to produce seizures at any size on the screen. An oscillating or alternating pattern is has equivalent risk when it has no more than five stripe pairs. Furthermore, seizures rarely are provoked by patterns occupying less than 25% of a screen or lasting for less than half a second.

In real life, a wide variety of stimuli can provoke photic-induced seizures. Newmark and Penry (2) list television, lightning, car headlights, automobile riding or driving, flickering arc light, patterns of sunlight, red and white checked tablecloths, sudden appearance of the sun or bright light, flickering light or sunlight (interrupted light rather than light flash), helicopter

blades, walking by a picket fence, reflections on a wall, reflections on snow or water, home movies, amusement arcades, discotheques, seizures self-induced by blinking in bright light or waving outstretched fingers across the eyes. To this list, we also add cathode-ray tubes, video display tubes, computer monitors, decorative lighting, banner advertisements, public events with stroboscopic lighting and video games.

E. Other stimulus characteristics

Patients may avoid seizures by covering one eye with the palm of a hand, provided they have sufficient warning of the seizure onset. However, closing the eyes is not necessarily effective, and may even be counterproductive because the light diffuses through the closed eyelids, and the area of retina stimulated with flicker thereby may be increased (9). The opposite phenomenon also may be observed: some children self-induce PPIS by blinking, attempting to close their eyelids against the upward deviation of their eyes (which induces eyelid tremor), head-nodding, waving their outstretched fingers in front of their eyes, or intentionally looking at striped patterns (10, 115-117). Studies have shown that from 10% (118) to approximately 33% of the photosensitive children (116) could self-induce seizures by self-inducing flicker.

VII. Seizures from Television

In 1975, Jeavons and Harding (9) reported their widely-cited study on 454 patients with epilepsy and EEG photosensitivity. Among these, 35% had seizures provoked only while watching television, 5% had seizures while watching TV or while exposed to other environmental flashing lights, but not spontaneously and 22% had seizures both spontaneously and while watching television.

In the United States and Japan, TV screens scan at 60 Hz (National Television Standards Committee, NTSC standard), but an interlaced double linear raster pattern flickers at 30 hertz, and can be resolved when the viewer is close to the screen. Televisions trace about 625 lines on the screen, roughly half of the lines drawn on one scan from top to bottom, and the remaining half on the next. The two scans of odd-numbered and even-numbered lines alternate continuously, so as to provide 30-per-second visual stimulation. In Europe (Phase alternating line, PAL standard), the numbers are 50 Hz and 25 lines per second, respectively. The frequency range of 15-25 per second is among the most common frequency range for inducing photic seizures. Since stimulation at 50 flashes per second produces photoparoxysmal responses in 49% of photosensitive patients; whereas, only 15% of patients are sensitive to 60 flashes per second, European TV is more likely to induce seizures than is American TV (117). However, factors that may alter this estimate include visual acuity of the watcher, uniformity of the TV image, refresh frequency of the screen, ambient lighting in the room and brightness of the screen, among others.

Early studies (110) documented the association of pattern-sensitive seizures with horizontal or vertical scan lines on standard (British) televisions. TV characteristics most likely to provoke seizures were frequency of the TV screen (50 hertz was more provocative than was 100 Hz, the distance from the screen (0.5 m was more provocative than 1 m) and the specific pattern of the images (119-121). Video display units should be less likely than TVs to provoke seizures, because VDUs tend to be smaller, less bright, usually refresh at 70 Hz, as opposed to 50

or 60 Hz, and they do not have the interlaced double raster scan that provides a flicker at half of the scan frequency (113). However, video display computer screens still can produce photic seizures in the sensitive subject (113). A photoparoxysmal response is to be expected among most patients who have a seizure while watching TV. Among 13 patients having a seizure to the Pocket Monster cartoon, 12 had a photoparoxysmal EEG response (122).

VIII. Studies of Video Games

In 1981 Rushton (123) wrote a letter to the Lancet about "Space invader epilepsy." A near-simultaneous report was filed by Jeavons and colleagues of seizures provoked by a hand-held video game (124). This was followed by a report in England of seizures during the video game "Dark Warrior" (125). Several other cases were reported from Europe. The first case in the United States of seizures associated with video games was reported by Dahlquist and associates (126). A death of a 14 year-old boy in the UK in 1992 precipitated media coverage (127) and plans for a conference on the issue, held in London in 1993 (128). In 1994, Ferrie (68) reviewed 15 patients who experienced seizures while playing video games, and discussed these in context of 20 previously published cases in the English literature, and coined the inaccurate term "video game epilepsy." In Ferrie's review, 27 of 35 cases experienced their first seizure while playing video game, emphasizing the difficulty of predicting risk factors in the general population. About two-thirds of these patients had idiopathic generalized epilepsy with tonic-clonic seizures, and somewhat typical myoclonic jerks during video games. Of the group with idiopathic generalized epilepsy, 70% were photosensitive to intermittent photic stimulation during recording of the EEG. The term "video game epilepsy" is inaccurate in two ways: first, the games provoke seizures, but are not known to cause epilepsy; second, these seizures are not specific in most cases to video games.

Video-game-induced seizures subsequently have been reported in a total of 553 subjects (51, 54, 59, 119, 129-133) although some subjects might have been represented in more than one study. The largest study in this area was that of Kasteleijn-Nolst Trenité and colleagues (131), who united five study sites in four European countries to collect information on patients with video game related seizures. A total of 387 patients were studied: 75% female, and 55% less than 18 years old. In the EEG laboratory, photic stimulation, pattern stimulation, viewing of television and playing of certain video games were performed. Photic stimulation produced epileptiform discharges in 85%, 50-hertz television in 45%, and pattern presentation in 28%. In the study of Graf et al. (59), seizures tended to occur in association with high-intensity, repetitive flashes or rapid movements across the screen, rapid scene changes, linear patterns rolling or flickering across the screen. Internal psychological characteristics, such as mental calculations (134) or sustained attention (135) or changes in pattern but not light flashes (130) can induce seizures in rare cases.

It can be difficult to decide whether a seizure was provoked by a video game. Seizures occur spontaneously and in coincidence with a variety of proceeding stimuli. A community-based study in the United Kingdom by Quirk et al. (51) was performed on 118 patients reported to have had a seizure within 10 minutes of playing an electronic screen game. Patients were captured through reports from a consortium of 118 EEG Departments, representing about 90% of the EEGs done on seizure patients in Great Britain. They classified the 118 patients with presumed seizures in association with electronic screen games into three groups: A (definite),

with the seizure triggered by playing the game; B (probable), with the seizure probably triggered by the game; C (unlikely), with probable chance association. Their group divided 46 in A, 25 in B, 47 in C. Therefore, about 40% definitely had a game-provoked seizure, about 20% may have had a game-provoked seizure, and about 40% had seizures only coincidentally related to the game.

William et al. (136) recommended three criteria to associate a seizure with a video game: 1. Repeated occurrence of seizures while playing video games; 2. History of prior photosensitivity with epileptiform activity triggered by other visual stimuli; 3. EEG demonstration of photoparoxysmal response including two during video-game playing. According to the National Survey of Photosensitivity and Seizures Induced by Electronic Screen Games of the Institute of Neurology, London (51), most of the seizures occurred within the first 30 minutes of playing, but some were delayed, and some occurred within a matter of seconds. However, the seizure may be a first seizure, with no prior association with photic stimuli and occasionally no EEG findings. Should such a first seizure occurring while playing a video game be excluded? There is no clear answer, but most authors have considered a seizure occurring during a video game to be precipitated by the video game. Seizures occurring more than a few minutes after cessation of a video game are of questionable relationship, but still may reflect some, as yet poorly understood persistent brain hyperexcitability.

An occasional patient with a video game-provoked seizure may have no response in the EEG to intermittent photic stimulation, although this is an exception (73).

Different video games have variations in brightness from scene-to-scene. Ricci and Vigevano (136) identified four categories of video game factors responsible for triggering seizures: 1. patient-dependent (the internal sensitivity of the patient to flicker, pattern, etc.); 2. Screen-dependent factors (size, flicker frequency, number of scan lines, refresh rate, brightness, contrast); 3. Image-dependent factors (brightness, contrast, lines, colors, flashing, moving patterns); 4. Software-dependent (opportunities for the player to move a joystick, change the program or interact – cognitive load also could go here, though not mentioned). Review of 12 video game programs in 30 subjects suggested that a "steady maximal brightness" above 100 lux was a key factor and could (in the presence of other stimuli characteristics) induce seizures in susceptible patients (137). We note, parenthetically, that lux is a measure of illuminance, rather than luminance, so this might more usefully have been expressed in cd/m^2 of luminance. Steady maximal brightness less than 50 was generally safe. By comparison, steady maximal brightness varied from 6 and 305 lux among the games.

Can individuals with epilepsy, but with no known photoparoxysmal sensitivity safely play video games? This question was investigated by Millett and colleagues (138) in the study of 212 patients with epilepsy, all lacking photoparoxysmal or pattern sensitivity abnormalities during EEG testing. Patients were randomly assigned to a video game playing session or to other leisure activities. They then crossed over groups, while undergoing video-EEG monitoring. End point was a clinical seizure. Twenty-five patients experienced a seizure while participating, 13 during video game play and 12 during other leisure activities. No support was seen for prohibiting video games in the 95% or greater group of patients with epilepsy who do not give evidence of photosensitivity.

Similar findings to those of Millett et al. (138) were presented in abstract form by one of the current authors (Ledin K and Fisher RS, unpublished). The investigators studied 46 patients playing video games, compared to the same time of day 24 hours later, when not playing a video game. A total of 20 of the 46 patients had seizures: six while playing video games and fourteen

during the control period. None of the subjects had an abnormal photoparoxysmal response, and only two had primary generalized seizures. No evidence was found to justify prohibition of video game playing in patients with partial seizures and no evidence of EEG photosensitivity.

The relative safety of playing video games for the majority of seizure patients is not uniformly recognized by people with epilepsy. A survey by Millett et al. (139) in the United Kingdom found that one of thirteen patients in a seizure clinic believed that every individual with epilepsy was at risk of a seizure from video games, and risk estimation by the patient population was 2-3 times the realistic risk.

IX. Recommendations in the Literature

Multiple authors and several convened groups have formulated recommendations for people with PPIS, for manufacturers of devices that might provoke photic- or pattern-induced seizures, and for governmental regulatory bodies. No one agency speaks authoritatively on this subject, although the International Standards Organization is in the process of issue a summary of its workshop. Relatively little discussion of photosensitivity has taken place in the United States.

Ferrie et al. (68) recommend that patients who have experienced a video game-induced seizure may be allowed to continue playing in some circumstances. Play should be stopped in presence of absences, jerking or unusual visual phenomena. Photosensitive patients should avoid black and white checkered floor tiles or patterns, stripes, light through window vents, rotating ceiling fans, flashing lights, sitting less than three meters from a television. Funatsuka and colleagues (113) recommended that pattern-sensitive individuals avoid the following: 1. Geometric patterns, especially stripes occupying much of the display; 2. Fine patterns with spatial frequencies exceeding 2 cycles per degree; 3. Frequencies around 20 hertz with pattern-reversal stimulation; 4. Patterns with large differences in brightness; 5. Rapid pattern movements. The National Association of Commercial Broadcasters in Japan and Nippon Hoso Kyokai made recommendations for producers of animated programs. They suggested that flickering, especially red flickering at more than 3/sec, should be avoided. Reversing of contrasting images and rapid conversion of images, should be no faster than 3/sec. Stripes, whorls, and concentric circles should not occupy a large part of the screen.

In their major monograph, Harding and Jeavons (3) made six recommendations for precautions to be taken by people who are sensitive to flickering lights. These were as follows: 1. View television from eight feet or more; 2. View in a well-lit room with a small lamp on top of the TV set; 3. Do not approach the TV set to adjust or switch channels; 4. Cover one eye if it is necessary to go near the TV; 5. Avoid discotheques or places with flashing lights; 6. Wear polarized glasses on sunny days to reduce flickering reflections from water, etc.

X. Screening devices

Risks pertaining to photosensitivity can be reduced in several ways. One approach is to prevent the promulgation of seizure-provocative video material and the second is to prevent individual patients from being exposed to such material.

Preventing provocaltive image sequences

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The widespread use of video material that can cause seizures arises because the material is eye-catching, and can be attractive to individuals whose health is not affected, and indeed to a few who are seizure prone. Guidelines preventing the broadcast of hazardous video sequences have been in place in the UK and Japan since 1994 and 1998, respectively. The implementation of the guidelines previously required human review frame-by-frame, but the UK guidelines have been implemented in an automatic screening device that is now widely used among UK broadcasters, developed by Cambridge Research Systems (140). The equipment analyzes a video sequence for flashes in relevant frequency ranges, flashing red and certain visual patterns. Potentially provocative material is thereby identified and removed prior to transmission.

Broadcast screening clearly is desirable, but it does not prevent exposure to provocative sequences of images on video games. The games can be played interactively in countless pathways, so that the visual features may be different each time the game is played. However, sequences from games still can be assessed for risk, while recognizing that all possible play sequences cannot be examined.

Prevention of exposure

Computer-controlled video filters can be developed to attenuate the effect of flicker. These are called "adaptive temporal filters." Such a filter (141) was used to modify the notorious Pocket Monster 12/sec 4-second segment of red flashing eyes. The original cartoon evoked a photoparoxysmal response in 11 susceptible patients. After processing by the adaptive temporal filter, the TV image no longer produced EEG changes in any of the patients. A recent study (142) claimed computer-mediated reduction of the red-blue dynamic range could reduce seizure risk, with a relatively small impact on appearance of the image.

Several investigators have recommended glasses or lens filters to take advantage of the observation that bright light, perhaps especially bright red light (which can be attenuated by blue glasses), is more likely to provoke PPIS (98, 109, 112, 143). Polarized and cross-polarized glasses can reduce susceptibility to problems from some visual stimuli (144, 145). A recent study (146), however, advocated a more sophisticated optical filter (special eyeglasses), combining even attenuation over most of the visible spectrum, with an additional attenuation of long wavelength light. These filters reduced photoparoxysmal responses from video screens in 90-95% of cases.

XI. Medications

Most physicians prefer to avoid use of antiepileptic medications in photosensitive patients, if possible. The first line of therapy is avoidance of video games, or modification of exposure along the lines described above. Prevention with special screens, protective glasses, warnings can be helpful (147). If conservative therapy fails, or if PPIS coexist with spontaneous seizures, then several seizure medications have been advocated. Harding and Jeavons (3) reviewed medications that had previously been tried, namely trimethadione, phenacemide, amobarbital, phenobarbital, nitrazepam, diazepam, sodium valproate, phenytoin, ethosuximide. Rimmer and colleagues (148) showed that a single dose of sodium valproate or the GABA metabolism inhibitor, vigabatrin, could inhibit EEG photosensitive responses. Some authors believed that sodium valproate was most efficacious (39). Harding et al. (149), in a comparative study of photosensitive patients either treated with sodium valproate or not treated, demonstrated that the drug was 78% effective in significantly reducing the photosensitive range and abolished photosensitivity in 50% of treated patients. Moller and colleagues (150) studied beta-carbolines, a drug active on the GABA inhibitory neurotransmitter system in six patients, but sample size was too small for a conclusion. Sodium valproate was recommended for children with idiopathic generalized epilepsy (68), but those with seizures only during video games perhaps do not require anti-seizure medications. Benzodiazepines, particularly clonazepam (151) also have been found to be effective. A young boy with Lennox-Gastaut syndrome and pattern sensitive seizures was responsive to bromocriptine 5 mg tid. (152). This is based upon the theory that photosensitivity relates to transient decrease of dopamine in the cerebral cortex. Occasionally, seizure medicines can aggravate photosensitive eplepsy, as was reported in a case of a child given phenytoin (153). A small study supports the use of levetiracetam (154).

XII. Guidelines

Recommendations to reduce risk of PPIS can be directed at manufacturers, consumers or regulatory agencies. A group of international experts in photoconvulsive and pattern-sensitive seizures met in London in September of 1993 under the auspices of the British Epilepsy Research Foundation to form a consensus statement based upon currently available information (155). They concluded that "there is no reasonable doubt that epileptic seizures may be precipitated by playing interactive computerized 'video-games,' a term used to include not only those games using an interlaced video monitor but also small hand-held liquid crystal displays and arcade games ...". Contributing factors to a seizure included a photosensitive response to the physical characteristics of a display screen, a photosensitive response to the visual contents of the game independent of hardware, seizure precipitation by specific cognitive activities or movements; seizure precipitation by nonspecific emotional factors; lowering of a seizure threshold by fatigue or sleep deprivation; and coincidental occurrence of a spontaneous seizure while playing a video game. The relative importance of these factors is uncertain, but photosensitivity was considered to be paramount. Recommendations to the consumer included the following: 1. While playing a video game, the screen should be less than 12 inches or the patient should sit at least four times the diagonal screen diameter; 2. Play for greater than an hour per session should be avoided and sleep should be maintained.; 3. People with a history or family history of epilepsy or photosensitivity should have an EEG examination with photic stimulation prior to playing video games; 4. People shown to be photosensitive and their caregivers should be made aware of the potential risks of seizures from video games, and provide supervision where appropriate.

In 1994, the UK Independent Television Commission drafted recommendations directed at the broadcast and TV industry. Recommendations were updated in 1999 and again in 2001. The guidance note recommends against flashing lights or regions of high luminance at three or more cycles per second, and against high contrast bars, alternating in the range of 2-3 cycles per visual degree subtended. Based upon the Pocket Monster incident, in which alternating colors seemed to be at least as important as alternating luminance, recommendations have been extended to avoidance of color changes at frequencies more than three per second. However, truly isoluminant colors were not thought to be provocative for seizures. Following the Pocket Monster incident, TV Tokyo adopted a similar set of guidelines, as did the Japanese National Association of Commercial Broadcaster and NHK. Numbers of PPIS in Japan increased from 1996-1999, and then began to decrease, which was attributed to enactment of these guidelines (156).

The International Telecommunications Union (ITU), a group affiliated with the United Nations, has issued guidelines. Further discussion of consensus opinions can be found in the companion paper to this work (1).

XIII. Conclusions

Photosensitivity is marked by an abnormal EEG response to visual stimuli, typically light flashes or light-dark striped patterns. All studies attempting to estimate the precise frequency of photosensitivity in the general population are limited by subject selection bias. The studies that do exist suggest a prevalence (number outstanding) of photosensitivity in the range of 0.3 – 3%. Photosensitivity is higher in the young and female population. Most people with photosensitivity will never have a seizure. The prevalence of photoconvulsive seizures in the general population is approximately 1 per 10,000, and 1 per 4,000 individuals between 5 and 24 years of age. Incidence (annual new onset) of PPIS is 1 per 91,000 in the overall population, but 1 per 17,500 in the age range 7-19. In the well-studied Pokemon incident in Japan, only 24% of children having a seizure during the cartoon ever had a prior seizure. This implies that three of four photosensitive individuals are unaware of their photosensitivity. People known to have epilepsy have from a 2 to 14% chance of having seizures precipitated by light or pattern. About 2% of people with epilepsy can have a seizure provoked by TV. The annual incidence of video game seizures may be about 1 per 83,000 (1.2 per 100,000 in Quirk (51)), but is higher among 7-19 year olds.

Mechanisms of photosensitivity are only dimly understood. Animal models are available, but may not closely approximate the human disorder. Normal occipital cortex comprises brain cells that respond to features of visual input: including light, edges, contrasts, orientation of edges, and motion light-dark interfaces across the retina. Since each cortex appears to have independent thresholds, the risk for a seizure induced by a visual stimulus is proportional to the area of visual cortex activated by a stimulus within a cerebral hemisphere, with unilateral hemisphere activation being almost as powerful an activation as is bilateral activation (80). Stimuli in the central visual fields (10% of the full fields) are more potent for provoking seizures than are stimuli of the same size delivered to the visual periphery, although peripheral visual stimuli are just as provocative if cortical magnification is taken into account. Genetic factors clearly play a role in photosensitivity, but neither the role nor the genes involved have been identified.

Although light stimulation can trigger a seizure in photosensitive individuals, there is no evidence that it can create epilepsy, a condition marked by spontaneously recurrent seizures. There are no data to point to neuronal injury or loss from typical photic or pattern-induced seizures, although such damage might be speculated to exist in the rare cases of photoconvulsive status epilepticus.

Intensity is one of the two most important characteristics of light stimuli able to provoke seizures. Intensities of 0.2 – 1.5 million candlepower are in range to trigger PPIS. Frequency (flash rate) is the second key variable in provocation of a photic- or pattern-induced seizure. Frequencies in the range of 15-25 Hz are most provocative, but some individuals are sensitive to single flashes or to frequencies as high as 65 Hz. Light-dark borders can induce pattern-sensitive seizures, especially with a pattern oscillating in a direction perpendicular to the line of the pattern, having 2-3 spatial cycles per degree subtended at the eye. Only rarely will flashes or patterns occupying less than 25% of a TV or videogame screen provoke seizures. Patterns with bright stripes no brighter than 50 candella per meter squared, or lasting for less than 0.5 seconds, also rarely induce seizures. Color is a controversial factor. Some believe that red colors or alternating red-blue oscillations can provoke seizures, but others think this unlikely if the brightness of the colors is matched. Rare patients self-induce PPIS by blinking, head-nodding, waving their fingers in front of their eyes, or intentionally looking at striped patterns.

Television-induced seizures result from combinations of sensitivity to flashing lights and patterns due to the TV set flicker itself, and also to flash or patterns in the content of the program. Due to differences in line current frequencies in Europe versus the US and Japan, TV flicker is more apparent in Europe, and closer to the frequencies likely to provoke seizures. However, NTSC TV (the technical protocol used in the US) does not provide protection against provocative program material. Certain videogames also present flash and patterns of a type able to induce seizures in photosensitive players or observers. Identifying which factors are relevant for increasing risk is more difficult for videogames than for broadcast or recorded TV since games can be played in so many different ways. Human factors, such as fatigue, excitement, sleep deprivation, monocular versus binocular vision, may all play a roles in PPIS, but especially in actively played games. Video games pose a minor risk for people with no known photosensitivity. Surveys suggest that the public, including patients with seizures not provoked by light, overestimate the risk for seizures provoked by video games.

Many authors have published recommendations about PPIS directed at patients, physicians, device or software manufacturers, and governmental agencies. No final set of recommendations yet exists, but European and Japanese groups have compiled extensive experience. International organizations, including the International Telecommunications Union (affiliated with the UN) and the International Standards Organization, are considering international guidelines. In the latter case the guidelines would apply not only to TV, broadcast and videogames, but to a broad range of visual stimuli. The guidelines for industry in the UK and Japan emphasize the value of limiting bright flashes at frequencies higher than three per second. Light-dark stationary, oscillating or reversing patterns should not have more than five stripes, unless they are restricted to less than 25% of the screen or are less than 50 cd/m^2 in brightness.

People with epilepsy or known photosensitivity have been advised to sit more than 2 meters from a screen, to employ good ambient lighting to reduce contrast, to avoid looking at rapidly flashing lights or alternating geometric patterns, to play video games for less than an hour at a time, to avoid sleep deprivation, and to cease play at onset of unusual visual symptoms,

jerking or blackouts. Closing one eye or looking away from the image is of more benefit than is closing both eyes.

The Photosensitivity Task Force of the Epilepsy Foundation of America believes that a seizure from visual stimulation represents a significant public health problem. No known method can eliminate all risk for a visually-induced seizure in a highly susceptible person. But accumulation of knowledge about photosensitivity is now at a level sufficient to develop educational programs and procedures in the US that substantially will reduce the risk for this type of seizure.

References

1. Harding GF, Wilkins AJ, Erba G, Barkley GL, Fisher RS. Photic- and pattern-induced seizures: expert consensus of the Epilepsy Foundation of America Working Group. Epilepsia THIS VOLUME. . . .

2. Newmark ME, Penry, JK. Photosensitivity and Epilepsy: A Review. New York: Raven Press, 1979.

3. Harding GFA, Jeavons PM. Photosensitive epilepsy. London: MacKeith Press, 1994.

4. Gowers WR. Epilepsy and other chronic convulsive diseases. Their causes, symptoms and treatment. New York: Wood & Co., 1885.

5. Radovici MM, Misirliou VL, Gluckman M. Epilepsie reflexe provoquee par excitations optiques des rayons solaires. *Revue Neurologique* 1932;1:1305-8.

6 Livingston S. Comments on the study of light-induced epilepsy in children. *Am J Dis Childr* 1952;83:409.

7. Binnie CD, Wilkins AJ. Visually induced seizures not caused by flicker (intermittent light stimulation). *Adv Neurol* 1998;75:123-38.

8. Guerrini R, Bonanni P, Parmeggiani L, Thomas P, Mattia D, Harvey AS, Duchowny MS. Induction of partial seizures by visual stimulation. Clinical and electroencephalographic features and evoked potential studies. *Adv Neurol* 1998;75:159-78.

9. Jeavons PM, Harding GF. Photosensitive Epilepsy: A review of the literature and a study of 460 patients. Clinics in Developmental Medicine, No. 56. London: William Heineman Medical Books Ltd., 1975.

10. Kasteleijn-Nolst Trenité DGA. Photosensitivity in epilepsy. Electrophysiological and clinical correlates. *Acta Neurol Scand Suppl* 1989;125:3-149.

11. Kasteleijn-Nolst Trenité DGA. Reflex seizures induced by intermittent light stimulation. *Adv Neurol* 1998;75:99-121.

12. Parra J, Kalitzin SN, Lopes da Silva FH. Photosensitivity and visually induced seizures: review. *Curr Opin Neurol* 2005;18:155-159.

13. Verrotti A, Trotta D, Salladini C, di Corcia G, Chiarelli F. Photosensitivity and epilepsy. *J Child Neurol* 2004;19:571-578.

14. Wilkins AJ. Visual stress. Oxford: Oxford University Press, 1995.

15. Zifkin BG, Kasteleijn-Nolst Trenité D. Reflex epilepsy and reflex seizures of the visual system: a clinical review. *Epileptic Disord* 2000;2:129-36.

16. Gastaut H, Regis H, Bostem F. Attacks provoked by television, and their mechanism *Epilepsia* 1962;3:438-445.

17. Bickford RG, Daly D, Keith HM. Convulsive effects of light stimulation in children. *Am J Dis Child* 1953;8:170-83.

18. Harding GF, Harding PF. Televised material and photosensitive epilepsy. *Epilepsia* 1999;40 (Suppl 4):65-9.

19. Kasteleijn-Nolst Trenité DGA, Binnie CD, Harding GF, Wilkins A. Photic stimulation: standardization of screening methods. *Epilepsia* 1999;40 (Suppl 4):75-9.

20. Rubboli G, Parra J, Seri S, Takahashi T, Thomas P. EEG diagnostic procedures and special investigations in the assessment of photosensitivity. *Epilepsia* 2004;45 (Suppl 1):35-39.

21. Nagarajan L, Kulkarni A, Palumbo-Clark L, et al. Photoparoxysmal responses in children: their characteristics and clinical correlates. *Pediatr Neurol* 2003;29:222-6.

22. Waltz S, Christen HJ, Doose H. The different patterns of the photo paroxysmal response: a genetic study. *Electroencephalography Clinical Neurophysiology* 1992; 83:138-45.

23. Maheshwari MC, Jeavons PM. The clinical significance of occipital spikes as a sole response to intermittent photic stimulation. *Electroencephalogr Clin Neurophysiol* 1975;39:93-95.

24. Jayakar P, Chiappa KH. Clinical correlations of photoparoxysmal responses. *Electroencephalogr Clin Neurophysiol* 1990;75:251-4.

25. Reilly EL, Peters JF. Relationship of some varieties of electroencephalographic photosensitivity to clinical convulsive disorders. *Neurology* 1973;23:1050-7.

26. Puglia JF, Brenner RP, Soso MJ. Relationship between prolonged and self-limited photoparoxysmal responses and seizure incidence: study and review. *J Clin Neurophysiol* 1992;9:137-44.

27. Kasteleijn-Nolst Trenité DGA, Binnie CD, Meinardi H. Photosensitive patients: symptoms and signs during intermittent photic stimulation and their relation to seizures in daily life. *J Neurol Neurosurg Psychiatry* 1987;50:1546–9.

28. Jabbari B, Russo MB, Russo ML Electroencephalogram of asymptomatic adult subjects. *Clin Neurophysiol* 2000;111:102-5.

29. Agathonikou A, Koutroumanidis M, Panayiotopoulos CP. Fixation-off-sensitive epilepsy with absences and absence status: video-EEG documentation. *Neurology* 1997;48:231-4.

30. deBittencourt PRM. Photosensitivity: the magnitude of the problem. *Epilepsia* 2004;45 (Suppl 1):1–5.

31. Erba G. Preventing seizures from "Pocket Monsters": a way to control reflex epilepsy. *Neurology* 2001;57:1747-8.

32. Kasteleijn-Nolst Trenité DGA,Binnie CD, Harding GFA, et al. Medical technology assessment: photic stimulation: standardization of screening methods. *Neurophysiol Clin* 1999;29:318–24.

33. Shiraishi H, Fujiwara T, Inoue Y, Yagi K. Photosensitivity in relation to epileptic syndromes: a survey from an epilepsy center in Japan. *Epilepsia* 2001;42:393-7.

34. Appleton R, Beirne M, Acomb B. Photosensitivity in juvenile myoclonic epilepsy. *Seizure* 2000;9:108-11.

35. Holden EW, Thanh Nguyen H, Grossman E, et al. Estimating prevalence, incidence, and disease-related mortality for patients with epilepsy in managed care organizations. *Epilepsia* 2005;46:311-9.

36. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel, J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470-472.

37. Gregory RP, Oates T, Merry RTG. Electroencephalogram epileptiform abnormalities and candidates for aircrew training. *Electroencephalogr Clin Neurophysiol* 1993;86:75-77.

38. Trojaborg W. EEG abnormalities in 5,893 jet pilot applicants registered in a 20-year period. *Clin Electroencephalogr* 1992;23:72-8.

39. Jeavons PM, Bishop A, Harding GF. The prognosis of photosensitivity. *Epilepsia* 1986;27:569-75.

40. Wadlington WB, Rightly HD, Jr. Light-Induced Seizures. *Journal Pediatrics* 1965;66:300-312.

41. Danesi MA. Seasonal variations in the incidence of photoparoxysmal response to stimulation among photosensitive epileptic patients: evidence from repeated EEG recordings. *J Neurol Neurosurg Psychiatry* 1988;51:875–7.

42. Steinkruger M. Photosensitive Epilepsy. *Journal Neurosurgical Nursing* 1985;17:355-361.

43. Doose H, Waltz S. Photosensitivity-genetics and clinical significance. *Neuropediatrics* 1993;24:249-55.

44. Eeg-Olofsson O, Petersen I, Sellden U. The development of the electroencephalogram in normal children from the age of 1 through 15 years. Paroxysmal activity. *Neuropadiatrie* 1971;2:375-404.

45. Petersen I, Eeg-Olofsson O. The development of the electroencephalogram in normal children from the age of 1 through 15 years. Non-paroxysmal activity. *Neuropadiatrie* 1971;2:247-304.

46. Harding GF. TV can be bad for your health. *Nat Med* 1998;4:265-7.

47. Ishida S, Yamashita Y, Matsuishi T, Ohshima M, Ohshima H, Kato H, Maeda H. Photosensitive seizures provoked while viewing "pocket monsters," a made-for-television animation program in Japan. *Epilepsia* 1998;39:1340-4.

48. Takahashi T, Tsukahara Y. Pocket Monster incident and low luminance visual stimuli: special reference to deep red flicker stimulation. *Acta Paediatr Jpn* 1998;40:631-7.

49. Takada H, Aso K, Watanabe K, Okumura A, Negoro T, Ishikawa T. Epileptic seizures induced by animated cartoon, "Pocket Monster." *Epilepsia* 1999;40:997-1002.

50. Iinuma K. TV-animation induced seizures. *Acta Paediatr Jpn* 1998;40:624-5.

51. Quirk JA, Fish DR, Smith SJ, Sander JW, Shorvon SD, Allen PJ. First seizures associated with playing electronic screen games: a community-based study in Great Britain. *Ann Neurol* 1995;37:733-7.

52. Aziz H, Francis P, Ali SM, Hasan Z. Epilepsy and photosensitivity. *J Pak Med Assoc* 1989;39:212-4.

53. Takahashi T. Photoconvulsive response and disposition. *Folia Psychiatr Neurol Jpn* 1976;30:349-356.

54. Quirk JA, Fish DR, Smith SJ, Sander JW, Shorvon SD, Allen PJ. Incidence of photosensitive epilepsy: a prospective national study. *Electroencephalogr Clin Neurophysiol* 1995;95:260-7.

55. Harding GF, Edson A, Jeavons PM. Persistence of photosensitivity. *Epilepsia* 1997;38:663-9.

56. Verrotti A, Trotta D, Salladini C, di Corcia G, Latini G, Cutarella R, Chiarelli F. Photosensitivity and epilepsy: a follow-up study. *Dev Med Child Neurol* 2004;46:347-51.

57. Scott DF, Elian M. The effects on the EEG of intermittent photic stimulation in patients over 30 years of age. *Clin Electroencephalogr* 1981;12:21-3.

58. Binnie CD. Simple reflex epilepsies. In: Engel J, Jr, Pedley TA (eds.). A Comprehensive Textbook of Epilepsy. Philadelphia, Lippencott-Raven Press 1997:2507-2514.

59. De Graaf AS, Van Wyk Kotze TJ, Claassen DA. Photoparoxysmal responses in the electroencephalograms of some ethnic groups of the Cape Peninsula. *Electroencephalogr Clin Neurophysiol* 1980;50:275-81.

60. Obeid T, Daif AK, Waheed G, Yaqub B, Panayiotopoulos CP, Tahan AR, Shamena A. Photosensitive epilepsies and photoconvulsive responses in Arabs. *Epilepsia* 1991;32:77-81.

61. Victor M, Brausch C. The role of abstinence in the genesis of alcoholic epilepsy. *Epilepsia* 1967;8:1-20.

62. Wolf P, Goosses R. Relation of photosensitivity to epileptic syndromes. *J Neurol Neurosurg Psychiatry* 1986;49:1386-91.

63. Hennessy MJ, Binnie CD. Photogenic partial seizures. *Epilepsia* 2000;41:59-64.

64. Gilliam FG, Chiappa KH. Significance of spontaneous epileptiform abnormalities associated with a photoparoxysmal response. *Neurology* 1995;45:453-6.

65. Hormes JT, Mellinger JF, Klass DW. Testing for electroencephalographic activation with video games in patients with light sensitivity. *Am J EEG Technol* 1995;35:37-45.

66. Binnie CD, Kasteleijn-Nolst Trenité DG, De Korte R. Photosensitivity as a model for acute antiepileptic drug studies. *Electroencephalogr Clin Neurophysiol* 1986;63:35-41.

67. De Keyser J, Michotte A, Ebinger G. Television induced seizures in alcoholics. *Br Med J* 1984;289:1191-2.

68. Ferrie CD, De Marco P, Grunewald RA, Giannakodimos S, Panayiotopoulos CP. Video game induced seizures. *J Neurol Neurosurg Psychiatry* 1994;57:925-31.

69. Wilkins A, Lindsay J. Common forms of reflex epilepsy: Physiological mechanisms and techniques for treatment. In: Recent Advances in Epilepsy, No 2, Edinburgh: Churchill Livingstone, 1985:239-271.

70. Mayr N, Wimberger D, Pichler H, Mamoli B, Zeitlhofer J, Spiel G. Influence of television on photosensitive epileptics. *Eur Neurol* 1987;27:201-8.

71. Binnie CD, Findlay J, Wilkins AJ. Mechanisms of epileptogenesis in photosensitive epilepsy implied by the effects of moving patterns. *Electroencephalogr Clin Neurophysiol* 1985;61:1-6.

72. Chatrian GE, Lettich E, Miller LH, Green JR. Pattern-sensitive epilepsy. I. An electrographic study of its mechanisms. *Epilepsia* 1970;11:125-49.

73. Radhakrishnan K, St Louis EK, Johnson JA, McClelland RL, Westmoreland BF, Klass DW. Pattern-sensitive epilepsy: electroclinical characteristics, natural history, and delineation of the epileptic syndrome. *Epilepsia* 2005;46:48-58.

74. Wilkins AJ, Darby CE, Binnie CD. Neurophysiological aspects of pattern-sensitive epilepsy. *Brain* 1979;102:1-25.

75. Guy NTM, Teillet MA, Schuler B, Le Gal la Salle G, Le Douarin N, Naquet R, Batini C. Pattern of electroencephalographic activity during light induced seizures in genetic epileptic chickens and brain chimeras. *Neurosci Lett* 1992;145:55-58.

76. Naquet R, Menini C, Riche D, Silva-Barrat C, Valin A. Photic epilepsy problems raised in man and animals. *Ital J Neurol Sci* 1987;8:437-47.

77. Ostrach LH, Crabtree JW, Campbell BG, Chow KL. Effects of bicuculline-induced epileptiform activity on development of receptive field properties in striate cortex and lateral geniculate nucleus of the rabbit. *Brain Res* 1984;317:113-23.

78. Wilkins AJ, Bonanni P, Porciatti V, Guerrini R. Physiology of human photosensitivity. *Epilepsia* 2004;45 (Suppl 1):7-13.

79. Meldrum, B.S. and Wilkins, A.J. Photosensitive epilepsy: integration of pharmacological and psychophysical evidence. In: Schwatzkroin P and Wheal H (eds.), Electrophysiology of Epilepsy. London: Academic Press, 1984:51-77.

80. Wilkins AJ, Binnie C., Darby CE, Kasteleijn-Nolst Trenité DGA. Inferences regarding the visual precipitation of seizures, eye-strain and headaches. In: Avoli M, Gloor P, Kostopoulos G, Naquet R (eds.). Generalized Epilepsy: Neurobiological Approaches. Birkhauser: Boston, 1990: 314-326.

81. Hubel DH, Wiesel TN. Receptive fields of single neurones in the cat's striate cortex. *J Physiol* 1959;148:574-91.

82. Zeki S. The visual association cortex. *Curr Opin Neurobiol* 1993;3:155-9.

83. Porciatti V, Bonanni P, Fiorentini A, Guerrini R. Lack of cortical contrast gain control in human photosensitive epilepsy. *Nat Neurosci* 2000;3:259-63.

84. Quesney LF, Andermann F, Gloor P. Dopaminergic mechanism in generalized photosensitive epilepsy. *Neurology* 1981;31:1542-1544.

85. Fischer-Williams M, Ponset M, Riche D, Naquet R. light induced epilepsy in the baboon Papio papio: cortical and depth recordings. *Electroencephalogr Clin Neurophysiol* 1968;25:557-569.

86. Matsuoka H. Seizure generation mechanisms in reflex epilepsy. *Jpn J Psychiatry Neurol* 1990;44:317-20.

87. Takasaka Y, Takamatsu K, Nakagawara M. Anterior-posterior relationships of EEG in photosensitive subjects: coherence and cross-phase-spectral analysis. *Jpn J Psychiatry Neurol* 1989;43:651-63.

88. Parra J, Kalitzin SN, Iriarte J, Blanes W, Velis DN, Lopes da Silva FH. Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception? *Brain* 2003;126:1164-72.

89. Inoue Y, Fukao K, Araki T, Yamamoto S, Kubota H, Watanabe Y. Photosensitive and nonphotosensitive electronic screen game-induced seizures. *Epilepsia* 1999;40 (Suppl 4):8-16.

90. Chiappa KH, Hill RA, Huang-Hellinger F, Jenkins BG. Photosensitive epilepsy studied by functional magnetic resonance imaging and magnetic resonance spectroscopy. *Epilepsia* 1999;40 (Suppl 4):3-7.

91. da Silva EA, Muller RA, Chugani DC, Shah J, Shah A, Watson C, Chugani HT. Brain activation during intermittent photic stimulation: a [^{15}O]-water PET study on photosensitive epilepsy. *Epilepsia* 1999;40 (Suppl 4):17-22.

92. Wilkins AJ, Binnie CD, Darby CE. Visually-induced seizures. *Prog Neurobiol* 1980;15:85-117.

93. Benbadis SR, Gerson WA, Harvey JH, Luders HO. Photosensitive temporal lobe epilepsy. *Neurology* 1996;46:1540-2.

94. Isnard J, Guenot M, Fischer C, Mertens P, Sindou M, Mauguiere FA stereoelectroencephalographic (SEEG) study of light-induced mesiotemporal epileptic seizures. *Epilepsia* 1998;39:1098-103.

95. Topalkara K, Alarcon G, Binnie CD. Effects of flash frequency and repetition of intermittent photic stimulation on photoparoxysmal responses. *Seizure* 1998;7:249-55.

96. Honda Y. Photo epilepsy evoked by square-wave pulses. Report of the case studied by changing stimulus intensity and duration. *Journal Pediatric Ophthalmology* 1977;14:309-315.

97. Hiachikawa Y, Yamamoto J, Furuya E, Yamada Y, Miyazakia Y, Kanekoz E. Photosensitive epilepsy: relationships between the visual evoked responses and the epileptic formed discharges induced by intermittent photo stimulation. *Electroencephalogr Clin Neurophysiol* 1967;23:320-334.

98. Chatrian GE, Lettich E, Miller LH, Green JR, Kupfer C. Pattern-sensitive epilepsy. II. Clinical changes, tests of responsiveness and motor output, alterations of evoked potentials and therapeutic measures. *Epilepsia* 1970b;11:151-62.

99. Binnie CD, Kasteleijn-Nolst Trenité DG, de Korte R, Wilkins A. Visual display units and risk of seizures (Letter). *Lancet* 1985;1:991.

100. Leijten FS, Dekker E, Spekreijse H, Kasteleijn-Nolst Trenité DG, Van Emde Boas W. Light diffusion in photosensitive epilepsy. *Electroencephalogr Clin Neurophysiol* 1998;106:387-91.

101. Anyanwu E, Watson NA. Visually-evoked pattern and photomyoclonic responses in video game and television epilepsy: case reports. *Acta Physiol Pharmacol Ther Latinoam* 1996;46:177-84.

102. Anyanwu E. Mental imagery of photic stimulation provokes paroxysmal EEG activity in a photosensitive patient who self-induces seizures. *Ital J Neurol Sci* 1997;18:93-100.

103. Rafal RD, Laxer KD, Janowsky JS. Seizures triggered by blinking in non-photosensitive patients. *J Neurol Neurosurg Psychiatr* 1986;49:445-7.

104. Binnie CD, de Korte RA, Wisman T. Fluorescent lighting and epilepsy. *Epilepsia* 1979;20:725-7.

105. Takahashi T, Tsukahara Y. Influence of color on the photoconvulsive response. *Electroencephalogr Clin Neurophysiol* 1976;41:124-36.

106. Tobimatsu S, Zhang YM, Tomoda Y, Mitsudome A, Kato M. Chromatic sensitive epilepsy: a variant of photosensitive epilepsy. *Ann Neurol* 1999;45:790-3.

107. Binnie CD, Estevez O, Kasteleijn-Nolst Trenité DG, Peters A. Colour in photosensitive epilepsy. *Electroencephalogr Clin Neurophysiol* 1984;58:387-391.

108. Takahashi Y, Fujiwara T, Yagi K, Seino M. Wavelength dependence of photoparoxysmal responses in photosensitive patients with epilepsy. *Epilepsia* 1999;40 (Suppl 4):23-7.

109. Wilkins AJ, Baker A, Amin D, et al. Treatment of photosensitive epilepsy using coloured glasses. *Seizure* 1999;8:444-9.

110. Stefansson SB, Darby CE, Wilkins AJ, Binnie CD, Marlton AP, Smith AT, Stockley AV. Television epilepsy and pattern sensitivity. *Br Med J* 1977;2:88-90.

111. Brinciotti M, Matricardi M, Pelliccia A, Trasatti G. Pattern sensitivity and photosensitivity in epileptic children with visually induced seizures. *Epilepsia* 1994;35:842-9.

112. Anyanwu E. Evaluation of the laboratory and environmental factors that induce seizures in photosensitive epilepsy. *Acta Neurol Belg* 1999;99:126-32.

113. Funatsuka M, Fujita M, Shirakawa S, Oguni H, Osawa M. Study on photo-pattern sensitivity in patients with electronic screen game-induced seizures (ESGS): effects of spatial resolution, brightness, and pattern movement. *Epilepsia* 2001;42:1185-97.

114. Wilkins AJ, Emmett J, Harding G. Characterising the flashing and pattern images that precipitate seizures, and optimising guidelines to prevent them. Paper presented at the Photosensitivity and Seizures Workshop, Epilepsy Foundation of America Alexandria, Virginia. 2004.

115. Aso K, Watanabe K, Negoro T, Haga Y, Kito M, Maeda N, Ohki T. Photosensitive epilepsy in children. *Seizure* 1994;3:67-71.

116. Darby CE, de Korte RA, Binnie CD, Wilkins AJ. The self-induction of epileptic seizures by eye closure. *Epilepsia* 1980;21:31-41.

117. Tassinari CA, Rubboli G, Rizzi R, Gardella E, Michelucci R. Self-induction of visually-induced seizures. *Adv Neurol* 1998;75:179-92.

118. Spector S, Cull C, Goldstein LH. Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. *Epilepsy Res* 2000;38:207-16.

119. Badinand-Hubert N, Bureau M, Hirsch E, Masnou P, Nahum L, Parain D, Naquet R. Epilepsies and video games: results of a multicentric study. *Electroencephalogr Clin Neurophysiol* 1998;107:422-7.

120. Fylan F, Harding GFA. The effect of television frame rate on EEG abnormalities in photosensitive and pattern-sensitive epilepsy. *Epilepsia* 1997;38:1124–31.

121. Ricci S, Vigevano F, Manfredi M, Kasteleijn-Nolst Trenité DG. Epilepsy provoked by television and video games: safety of 100-Hz screens. *Neurology* 1998;50:790-3.

122. Enoki H, Akiyama T, Hattori J, et al. Photosensitive fits elicited by TV animation: an electroencephalographic study. *Acta Paediatr Jpn* 1998;40:626–30.

123. Rushton DN. "Space invader" epilepsy. *Lancet* 1981;1:501.

124. Jeavons PM, Barton ME, Bishop A. Seizures and hand-held space invaders. *Lancet* 1981;2:758.

125. Daneshmend TK, Campbell MJ. Dark warrior epilepsy *Br Med J* 1982;284:1751–2.

126. Dahlquist NR, Mellinger JF, Klass DW. Hazard of video games in patients with light-sensitive epilepsy. *JAMA* 1983;249:776-7.

127. Christie T. Death after an attack precipitated by playing Nintendo game. *The Sun* 1993;21:5. Q5

128. Takahashi T. Photosensitive epilepsy. Tokyo: Igaku-Shoin, 2002.

129. Bureau M, Hirsch E, and Vigevano F. Epilepsy and videogames. *Epilepsia* 2004;45 (Suppl 1):1–3.

130. Harding GF, Jeavons PM, Edson AS. Video material and epilepsy. *Epilepsia* 1994;35:1208-16.

131. Kasteleijn-Nolst Trenité DGA, da Silva AM, Ricci S, Binnie CD, Rubboli G, Tassinari CA, Segers JP. Video-game epilepsy: a European study. *Epilepsia* 1999;40 (Suppl 4):70-4.

132. Maeda Y, Kurokawa T, Sakamoto K, Kitamoto I, Ueda K, Tashima S. Electroclinical study of video-game epilepsy. *Dev Med Child Neurol* 1990;32:493-500.

133. Graf WD, Chatrian GE, Glass ST, Knauss TA. Video game-related seizures: a report on 10 patients and a review of the literature. *Pediatrics* 1994;93:551-6.

134. Takahashi Y, Shigematsu H, Kubota H, Inoue Y, Fujiwara T, Yagi K, Seino M. Nonphotosensitive video game-induced partial seizures. *Epilepsia* 1995;36:837-41.

135. Pellouchoud E, Smith ME, McEvoy L, Gevins A. Mental effort-related EEG modulation during video-game play: comparison between juvenile subjects with epilepsy and normal control subjects. *Epilepsia* 1999;40 (Suppl 4):38-43.

136. William DG, Gian-Amelio C, Stefan TG, et al. Video game-related seizures: a report on two patients and a review of the literature. *Pediatrics* 1994; 93:551-6.

137. Ricci S, Vigevano F. The effect of video-game software in video-game epilepsy. *Epilepsia* 1999;40 (Suppl 4):31-7.

138. Millett CJ, Fish DR, Thompson PJ, Johnson A. Seizures during video-game play and other common leisure pursuits in known epilepsy patients without visual sensitivity. *Epilepsia* 1999;40 (Suppl 4):59-64.

139. Millett CJ, Fish DR, Thompson PJ. A survey of epilepsy-patient perceptions of video-game material/electronic screens and other factors as seizure precipitants. *Seizure* 1997;6:457-9.

140. Harding GF, Takahashi T. Regulations; what next? *Epilepsia* 2004;45 (Suppl 1):46-7.

141. Nomura M, Takahashi T, Kamijo K, et al. A new adaptive temporal filter: application to photosensitive epilepsy patients. *Psychiatry Clin Neurosci* 2000;54:685–90.

142. Parra J, Kalitzin SN, Stroink H, Dekker E, de Wit C, Lopes da Silva FH. Removal of epileptogenic sequences from video material: the role of color. *Neurology* 2005;64:787-791.

143. Capovilla G, Beccaria F, Romeo A, Veggiotti P, Canger R, Paladin F. Effectiveness of a particular blue lens on photoparoxysmal response in photosensitive epileptic patients. *Ital J Neurol Sci* 1999;20:161-166.

144. Kepecs MR, Boro A, Haut S, Kepecs G, Moshe SL. A novel nonpharmacologic treatment for photosensitive epilepsy: a report of three patients tested with blue cross-polarized glasses. *Epilepsia* 2004;45:1158-1162.

145. Takahashi T, Tsukahara Y. Usefulness of blue sunglasses in photosensitive epilepsy. *Epilepsia* 1992;33:517-21.

146. Takahashi Y, Sato T, Goto K, et al. Optical filters inhibiting television-induced photosensitive seizures. *Neurology* 2001;57:1767-73.

147. Covanis A, Stodieck SR, Wilkins AJ. Treatment of photosensitivity. *Epilepsia* 2004;45 (Suppl 1):40-5.

148. Rimmer EM, Milligan NM, Richens A. A comparison of the acute effect of single doses of vigabatrin and sodium valproate on photosensitivity in epileptic patients. *Epilepsy Res* 1987;1:339-46.

149. Harding GFA, Herrick CE, Jeavons PM. A controlled study of the effect of sodium valproate on photosensitive epilepsy and its prognosis. *Epilepsia* 1978;19:555-565.

150. Moller A, Jensen LH, Skrumsager B, Blatt-Lyon B, Pedersen B, Dam M. Inhibition of photosensitive seizures in man by the beta-carboline, ZK 95962, a selective benzodiazepine receptor agonist. *Epilepsy Res* 1990;5:155-9.

151. Saenz-Lope E, Herranz-Tanarro FJ, Masdeu JC, Bufil J. Familial photosensitive epilepsy: effectiveness of clonazepam. *Clin Electroencephalogr* 1984;15:47-52.

152. Clemens B. Dopamine agonist treatment of self-induced pattern-sensitive epilepsy. A case report. *Epilepsy Res* 1988;2:340-3.

153. Shuper A, Vining EP. Photosensitive complex partial seizures aggravated by phenytoin. *Pediatr Neurol* 1991;7:471-2.

154. Kasteleijn-Nolst Trenité DGA, Marescaux C, Stodieck S, Edelbroek PM, Oosting J.Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam. *Epilepsy Res* 1996;25:225-30.

155. Binnie CD, Harding GFA, Richens A, Wilkins A, and the Video-Game Epilepsy Consensus Group. Video games and epileptic seizures - a consensus statement. *Seizure* 1994;3:245-246.

156. Takahashi Y, Fujiwara T. Effectiveness of broadcasting guidelines for photosensitive seizure prevention. *Neurology* 2004;62:990-3.
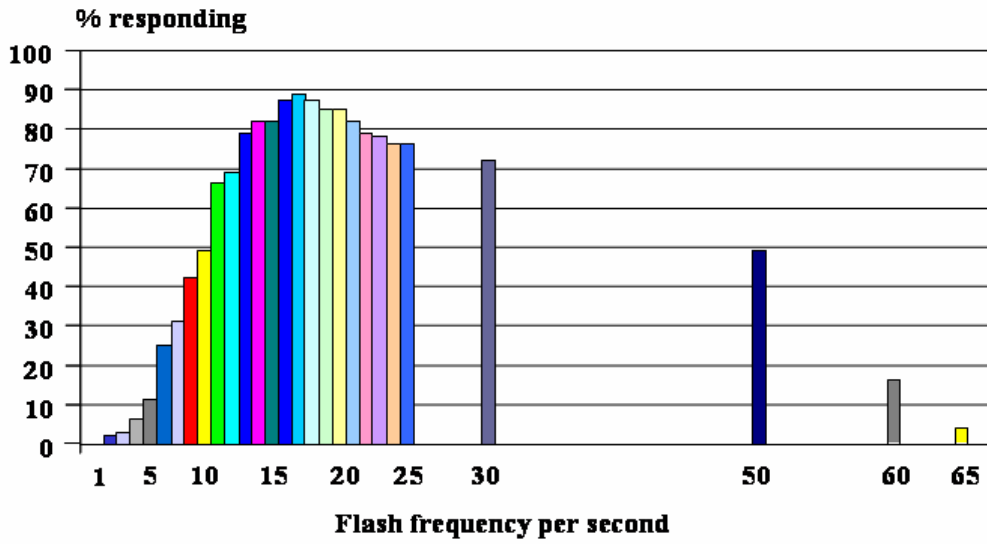
Acknowledgments

Figure 1. Histogram depicting the percentage of known photosensitive subjects who show EEG photosensitive responses at particular flash frequencies. Adapted from Harding and Harding, 1999 (18).