


CRITICAL REVIEW**Visually sensitive seizures: An updated review by the Epilepsy Foundation**

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Abstract

Light flashes, patterns, or color changes can provoke seizures in up to 1 in 4000 persons. Prevalence may be higher because of selection bias. The Epilepsy Foundation reviewed light-induced seizures in 2005. Since then, images on social media, virtual reality, three-dimensional (3D) movies, and the Internet have proliferated. Hundreds of studies have explored the mechanisms and presentations of photosensitive seizures, justifying an updated review. This literature summary derives from a nonsystematic literature review via PubMed using the terms “photosensitive” and “epilepsy.” The photoparoxysmal response (PPR) is an electroencephalography (EEG) phenomenon, and photosensitive seizures (PS) are seizures provoked by visual stimulation. Photosensitivity is more common in the young and in specific forms of generalized epilepsy. PS can coexist with spontaneous seizures. PS are heritable and linked to recently identified genes. Brain imaging usually is normal, but special studies imaging white matter tracts demonstrate abnormal connectivity. Occipital cortex and connected regions are hyperexcitable in subjects with light-provoked seizures. Mechanisms remain unclear. Video games, social media clips, occasional movies, and natural stimuli can provoke PS.

Virtual reality and 3D images so far appear benign unless they contain specific provocative content, for example, flashes. Images with flashes brighter than 20 candelas/m² at 3-60 (particularly 15-20) Hz occupying at least 10 to 25% of the visual field are a risk, as are red color flashes or oscillating stripes. Equipment to assay for these characteristics is probably underutilized. Prevention of seizures includes avoiding provocative stimuli, covering one eye, wearing dark glasses, sitting at least two meters from screens, reducing contrast, and taking certain antiseizure drugs. Measurement of PPR suppression in a photosensitivity model can screen putative antiseizure drugs. Some countries regulate media to reduce risk. Visually-induced seizures remain significant public health hazards so they warrant ongoing scientific and regulatory efforts and public education.

KEYWORDS

EEG, epilepsy, photosensitivity, seizures

1 | INTRODUCTION

Reflex seizures¹ refer to seizures that are reliably provoked by certain sensory inputs, such as light, pattern, or color flashes²; or activities such as eating,³ playing games,⁴ thinking,⁵ or other cognitive processes. In 1881, Gowers described seizures that were provoked by bright lights.⁶ Adrian and Matthews⁷ constructed a photic stimulator and registered occipital waves different from alpha and dependent on flash frequency in 1934. Thereafter, a group of European and American scientists, most prominently Walter, Gastaut, Bickford, Melin, Cobb, and Lennox, explored the modulation of electroencephalography (EEG) rhythms by photic stimulation and the link to epileptic seizures.⁸

Terminology in this field has been confusing, referring to certain EEG abnormalities as a “photoconvulsive response,” even in the absence of a convulsion. The currently favored term for abnormal EEG responses to light is the photoparoxysmal response (PPR). Epilepsy associated with light sensitivity occasionally is called “photoconvulsive” epilepsy, although seizures may not be in the form of convulsions, so “photosensitive” is a better modifier term for visually-provoked seizures or epilepsy. Photosensitivity is a broad term in medical literature, sometimes designating sensitive skin or eye conditions. In this review, the meaning is restricted to a neurological response to light, color or patterns. Several recent reviews are available.^{9–22} The prior reviews are not systematic reviews and neither is this one. A paucity of controlled studies in this field would make such a review difficult.

Key Points

- A photoparoxysmal response (PPR) occurs on electroencephalography (EEG) of 0.6% to 30% of people with epilepsy, depending upon syndrome.
- Provoking factors depend on flash frequency, intensity, duration, retinal coverage, and certain colors and patterns.
- Several photosensitive syndromes have a genetic component. Mechanisms are beginning to be understood.
- The best treatment is prevention, but several medications are effective.
- The popularity of the internet, three-dimensional (3D) media, and virtual reality add to so-far uncharacterized risks. Further education and public protection are warranted.

2 | GENERAL CLINICAL ISSUES

2.1 | Seizure types and syndromes associated with photosensitivity

Photosensitivity occurs in several epilepsy syndromes as a common but not defining feature. It is most prevalent in genetic generalized epilepsies, such as juvenile myoclonic epilepsy (30%-90%), childhood (18%) and juvenile (8%) absence epilepsies, generalized tonic-clonic seizures on awakening (13%), and benign myoclonic epilepsy of infancy

(10%).^{23–26} In Japan, photosensitivity is seen in 17% of patients with juvenile myoclonic epilepsy.²⁴ Photosensitivity also is seen in other conditions, including Dravet syndrome, Lennox-Gastaut syndrome, Lafora's disease, Unverricht-Lundborg disease, myoclonic epilepsy with ragged-red fibers, and type 2 neuronal ceroid lipofuscinosis.^{23,25,27,28} Myoclonic, absence, and generalized tonic-clonic seizures occur with some regularity among photosensitive individuals.²³ Photosensitivity is less common in focal epilepsies. In a study of patients with focal epilepsy of unknown cause, the reflex seizure rate was 6.5%.²⁹

The 2017 International League Against Epilepsy seizure classification^{30,31} defined “generalized absence with eyelid myoclonia” as a seizure type. Eyelid myoclonia are myoclonic jerks of the eyelids associated with upward deviation of the eyes.³² Eyelid myoclonia, absence seizures, and photosensitivity constitute Jeavons' syndrome^{33, 34} in which seizures are induced by eye closure and photosensitivity is nearly universal.³⁵ Orbitofrontal myoclonus refers to flash-driven contractions of the eye-movement muscles and peri-orbital muscles. Associated EEG changes can be difficult to identify and it is unclear whether orbitofrontal myoclonus is a seizure or a normal physiological response. In contrast, eyelid myoclonus is epileptic, has associated epileptiform EEG findings, and may be linked to absence seizures. These syndromes are discussed in more detail in the following text.

Kasteleijn-Nolst Trenité and colleagues³⁶ proposed a classification for clinical syndromes associated with visual sensitivity (Table 1).

Visual stimuli can generate subjective symptoms that are not necessarily associated with seizures—for example,

hallucinations of lines or colors, dizziness, eye pain, or gastrointestinal distress. The prevalence of provocative factors for reflex seizures varies among different populations. In most populations, visual triggers are the most common provoking factor for reflex seizures.

2.2 | Sunflower syndrome

“Sunflower syndrome,” a term coined by Ames and Saffer³⁷ and recently summarized by Belcastro and colleagues,³⁸ describes a condition characterized by stereotypic seizures. Patients turn their bodies and look toward a light source, usually sunlight and then extend their elbow and lift one hand and wave abducted fingers in front of their eyes. Most patients consistently wave the same hand, which may or may not be their dominant one.³⁹ There is blinking or eye fluttering with or without further evolution to absence and generalized tonic-clonic seizures.^{37,39,40} Sunflower syndrome predominantly affects young females with mean age at onset between 2 and 8 years.^{39,40} EEG shows normal background activity, with generalized spike-waves or polyspike-waves in association with handwaving, and a photoparoxysmal response to intermittent photic stimulation with the greatest response at 10–20 cycles per second.^{37,39–41} Approximately one-half to two-thirds of patients have other seizure types without handwaving, including absence, myoclonic, and tonic-clonic seizures.^{39,40} Family history of absence or juvenile myoclonic epilepsy occurs in one-third of patients, but sunflower syndrome itself is rarely familial.^{37,39,40} An early description of these features was provided by Gastaut in 1951,⁴² but because of the apparent sun-seeking behavior (heliotropism) of these patients, which was in marked contrast to the usual avoidance of light stimuli by patients with photosensitive epilepsy, he considered these seizures to be self-induced by handwaving. This interpretation persisted in other reports but was challenged by Livingston and Torres,⁴³ and later by others^{37,39} based on the observation that EEG changes occurred almost simultaneously with handwaving. This was further confirmed in a recent video-EEG monitoring study, where 89% of the handwaving episodes occurred <1 s after the onset of epileptiform EEG activity, suggesting that the handwaving was part of the seizure itself rather than a provoking factor,⁴¹ with the behaviors during the seizure possibly perpetuating the seizure. The reason that the patients appear to be drawn to light remains unknown. However, several patients confide feelings of pleasure, and dopamine-blocking agents (pimozide) suppress this behavior without reducing the PPR.⁴⁴

The natural history of sunflower syndrome is not well characterized, but the literature suggests that the frequency

TABLE 1 Photosensitive symptoms.

Classification of clinical symptoms (adapted from¹)

1. Mild subjective symptoms
2. Orbitofrontal photomyoclonus
3. Eyelid myoclonus
 - a. Eyelid myoclonus with absences
 - b. Self-inducing behavior
4. Focal, asymmetrical, myoclonus
5. Generalized myoclonus
 - a. Without loss of consciousness, often isolated
 - b. With impairment of consciousness
6. Tonic, versive phenomena
7. Absence seizures
8. Generalized tonic—clonic seizures
9. Partial (focal) seizures
 - a. With simple visual symptoms
 - b. With complex visual symptoms
 - c. With limbic symptoms

of handwaving episodes and light-seeking behavior decreases as the patients grow older. In general, the epilepsy is refractory to anti-seizure medicines,³⁸ but valproate and fenfluramine may be helpful.^{40,45–47} A variety of nonpharmacological approaches have also been found to be useful, including stimulus avoidance; wearing hats, sunglasses, or special tinted glasses; staying indoors; focused attention; and using one or both hands for other activities.^{39,40,48} Some photosensitive patients have the same behavior and seek patterns in their environment⁴⁹ to evoke absence and tonic-clonic seizures; similarly treatment is very difficult.

2.3 | Jeavons syndrome

Jeavons syndrome (or JS), first described in 1977,⁵⁰ comprises upward jerking of the eyelids called eyelid myoclonia, EEG paroxysms induced by eye closure, and photosensitivity.^{34,51} Absence seizures may be associated. Eyelid closure also involves loss of fixation, but the eyelid closure is more important than is fixation loss.⁵² JS is considered to be rare, probably because it is underdiagnosed; one study of 5796 patients with epilepsy identified JS in 0.55%.⁵³ JS presents in childhood but can persist into adulthood,⁵⁴ with one series identifying 61 adults with JS. The syndrome is encountered predominantly in females^{33,55} and one-third to one-half have a family history of epilepsy.^{51,53} The family association has encouraged a search for genes⁵⁶ with preliminary identification of four possible candidates: SYNGAP1, KIA0202/NEXMIF, RORB, and CHD2. Cognitive impairment is common in JS but not inevitable⁵⁷ and the majority of patients do not have impairment.⁵¹

Because absence seizures are associated only in 25%⁵¹ to 50%⁵³ of cases, JS might better be considered a subset of myoclonic seizures, with myoclonus restricted to the eyelids, rather than a primary absence epilepsy.³³ The syndrome also may be accompanied by tonic-clonic seizures in about 25%.^{51,58} It is worth noting that eyelid myoclonia is not unique to JS, but also appears in other syndromes, such as juvenile myoclonic epilepsy.⁵⁹

Generalized spike-waves are the most common EEG finding, but additional focal EEG findings are not rare.^{53,55} Does JS include generalized or focal seizures? Discharges often appear to be generalized, but JS can show subtle occipital discharges preceding eyelid myoclonia,⁵⁵ suggesting that the syndrome may comprise a focal occipital epilepsy with rapid propagation. In patients with JS, eye closure increased functional magnetic resonance imaging (fMRI) blood oxygen–level dependent (BOLD) signal over visual cortex, posterior thalamus, and eye movement control areas, consistent with a focal abnormality of the visual system.

Patients with JS and seizures can be treated with anti-seizure medications. Valproic acid, ethosuximide, lamotrigine, and levetiracetam have been listed as drugs of choice.⁵⁸ Valproate is undesirable in women of childbearing age, in which case levetiracetam may be a useful substitute.^{60,61} Lacosamide monotherapy benefited a case not helped by other medicines.⁶² Case studies documented worsening with oxcarbazepine⁶³ and cannabidiol.⁶⁴ The ketogenic diet has been helpful in a few patients with JS.⁵³ Anti-seizure medications often ameliorate the seizures associated with JS, but usually do not provide full control. One series³² of 51 patients documented full seizure control in 21.6%.

In summary, Jeavons syndrome is a probably undiagnosed condition occurring mainly in young females presenting with eyelid myoclonia, eye closure precipitation, and photosensitivity. Absence seizures and other seizure types may or may not be associated. Complete control can be elusive.

2.4 | Photomyoclonus

Electrical recordings in response to light flashes can comprise both brain potentials and muscle artifacts from peri-orbital, frontal, or temporal muscle contractions. Walter first reported paroxysmal EEG changes in response to light flashes in 1948.⁶⁵ A year later, Gastaut & Rémond⁶⁶ identified a component of the frontal EEG response to flash as being from muscle. Bickford⁶⁷ referred to the EEG response to flash as the “photoconvulsive” response and the artifact from face twitching as the “photomyoclonic response.” Meier-Ewart⁶⁸ characterized the photomyoclonic response in a series of 11 subjects with epilepsy and 2 without. The response was a diphasic potential lasting 15–20 ms, sometimes with after-potentials, maximal over frontal and temporal muscles. Typical amplitudes were around 1 mV. Concurrent EEG showed polyspikes or polyspike-waves with following slow waves. Photoconvulsive (EEG) and photomyoclonic (muscle) responses sometimes overlapped and at other times showed separation. A true frontal EEG response arising from brain can, however, be recorded from depth electrodes.⁶⁹

Photomyoclonus occasionally can be evoked by patterns.⁷⁰ Jaffe pointed out that normal, nonepileptic individuals can have a photomyoclonic response.⁷¹ This nonepileptiform response may be exaggerated when conjoined with other conditions that increase neuromuscular excitability, for example, hypocalcemia⁷² or alcohol withdrawal. It is not evident that a photomyoclonic response requires treatment, but it can be reduced by diazepam.⁷¹

In conclusion, light flashes may produce frontal EEG changes that are a combination of brain-derived EEG and

muscle-derived electromyographic artifact. Distinguishing epileptiform spikes in such recordings can be difficult and might only be possible in the absence of facial movements.

2.5 | Pattern-sensitive seizures

Certain patterns can evoke EEG photoparoxysmal responses or actual seizures. This was first reported in 1953⁶⁷ by describing a boy who had seizures and EEG spike-wave discharges when gazing at striped patterns on curtains or his father's tie. Numerous additional reports followed. Patients who are exclusively pattern-sensitive tend to be more likely to have focal epilepsy.⁷³ A systematic study of pattern-sensitive epilepsy was performed on 73 patients at the Mayo clinic.¹⁶ Patterns were viewed as still images and then shaken vertically and horizontally for 10 seconds. At presentation, 60% had generalized tonic-clonic seizures, 49% absence seizures, 38% myoclonic seizures, and 11% focal seizures. Some had more than one seizure type. Among those followed for more than 5 years, 46% had outgrown their seizures. Brinciotti and Matricardi⁷³ prospectively studied the long-term (5 years or greater) outcome in 35 patients with pattern-sensitive epilepsy. Five (14%) had only reflex seizures, whereas others had both reflex and spontaneous seizures. The most common type of spontaneous seizures was generalized (60%), but reflex seizures were more frequently focal (74%). At the end of the follow-up period 80% were seizure-free, indicating a good prognosis for spontaneous as well as reflex seizures.

3 | DIFFERENTIAL DIAGNOSIS OF PHOTSENSITIVITY

Photosensitive seizures can be difficult to distinguish from other types of reflex seizures that are provoked by other sensory, affective, or cognitive stimuli.^{74–82} EEG ictal recording with polygraphic and extensive long-term, neurophysiological investigations^{83–85} may be required to secure a correct diagnosis. The photoparoxysmal EEG reaction to intermittent photic stimulation represents an EEG focal or generalized response that can be an isolated EEG feature or a clinical phenomenon ranging from very simple ocular discomfort, photophobia, headache, or more serious changes in the state of consciousness.^{86,87}

3.1 | Syndromes imitating photosensitivity

Hyperekplexia is an exaggerated startle in response to external stimuli associated with a generalized increase in tone seen in neonates or infancy with both a sporadic and genetic

predisposition. This is an uncommon neurological, nonepileptic entity that can be misdiagnosed as seizures, with or without light stimulus or photosensitivity.^{78,88} Rare manifestations and special EEG features of progressive myoclonic epilepsy (PME) may be confused with occipital epilepsy or photosensitive epilepsy. Thus, if the continuous occipital spikes and photosensitivity are presented in a patient with refractory seizures and developmental regression, PME should be considered.⁸⁹ Some patients can have a clinical course with persistent and protracted vomiting along with occasional loss of consciousness and subtle motor manifestations (including some features of Panayiotopolous⁹⁰ syndrome), and in this case the differential diagnosis can include also photosensitive epilepsy.⁹¹ Seshia¹⁷ points out that seizures also can be triggered by negative stimuli, such as intermittent darkness. Driving past trees blocking the sunlight provides a potent example of interrupted-light stimulation. Flashing police car lights only rarely provoke seizures, perhaps because the image rarely occupies a large part of the visual field.⁹²

Three cases of operculo-insular reflex seizures were documented, triggered by somatosensory stimuli in two and loud noises in the third. Limited operculo-insular resection resulted in an excellent outcome.⁷⁷ Seizures can be triggered by hot water or bathing, requiring differentiation from photosensitive epilepsy.⁷⁴ Paroxysmal kinesigenic dyskinesia can be a differential diagnostic challenge.⁹³ Functional seizures (also called nonepileptic seizures) may present as apparent light-provoked seizures. Photic stimulation during video-EEG recording can be useful for recognition of this condition.^{94,95}

3.2 | Photosensitivity and headache

Headache has a complex relationship to light-provoked seizures, and awareness of a link between photosensitive seizures and migraine headaches has been growing.⁹⁶ Both relate to intermittent changes in brain excitability, considered as dysexcitability (either hypo- or hyperexcitable or mixed) conditions, which can facilitate each other.⁹⁷ Visual aura and other autonomic symptoms often precede both occipital epilepsies and migraine headaches. In both, the symptoms and signs of the visual aura can be elicited by bright and flashing lights and can be either positive (flicker scotoma, hallucinations) or negative (temporary loss of vision). Ictal epileptic headache (IEH; see the original diagnostic criteria in⁹⁸) represents an overlap of seizures and headache, and some of these patients are photosensitive.^{86,97} Diagnosis can be difficult because migraine can produce seizure-like symptoms, seizures commonly induce headaches, and both conditions can coexist.

Wendorff and Juchniewicz⁹⁹ studied the frequency and type of PPR in idiopathic headaches in children and adolescents, 7–18 years of age: 77 children with migraine with aura, 112 children with migraine without aura, and 74 children with tension-type headache. The frequency of PPR did not differ significantly in the three types of idiopathic headaches, although PPR was found most frequently (17.6%) in children younger than 12 years of age affected by migraine with aura. In this group of children, the PPR consisted of generalized spike or polyspike and waves in 11.8% and it localized to the temporo-parieto-occipital region in only 5.9%. Frequent coexistence of PPR and visual provocation of a migraine attack in children supports the theory about a general cortical dysexcitability with presence at different times in the same subject of both hypoexcitability and hyperexcitability, during different phases and at different ages, and along the psychomotor developmental stages.^{86,87} The accumulated burden of migraine seems to alter the physiology of the visual cortex and an increase in alpha rhythm variability up to 72 hours before the next migraine attack.¹⁰⁰ Sensory cortex may be hypoexcitable between migraine attacks¹⁰¹, confirming a dysexcitability state.¹⁰² Other studies, however, have argued for a cortical hyperexcitability state.¹⁰³ Fogang and colleagues¹⁰⁴ documented good sensitivity (82.24%), but moderate specificity (69.36%), of the visually-identified photic driving H response (enhanced photic driving during high-frequency flicker stimulation) in migraineurs.

Video-EEG recordings during headaches, particularly if unresponsive to antimigraine therapy, in specific populations with known epilepsy in family members, can be diagnostically decisive.^{87,98,105}

4 | EPIDEMIOLOGY AND PROGNOSIS

The presence of a PPR has been reported 0.3%-8% of the normal population and 0.6%-30% in patients with epilepsy.¹⁰⁶ Many types of seizures can be provoked by visual stimuli, including most commonly tonic-clonic seizures in about 80%⁹ and the remainder with lower prevalence, including absence seizures,¹⁰⁷ tonic seizures, focal seizures from the temporal lobe,¹⁰⁸ myoclonic absence seizures in patients with Dravet syndrome,¹⁰⁹ myoclonic seizures,¹¹⁰ and idiopathic photosensitive occipital lobe epilepsy (IPOE).¹¹¹⁻¹¹⁴ Photic-induced myoclonic seizures may be underrepresented in epidemiological studies, since some people seek medical attention only after having a tonic-clonic seizure. IPOE^{111,112} is on a continuum between focal and generalized seizures and may present with photosensitive absence, myoclonic or tonic-clonic seizures. Clinical symptoms of IPOE include colorful visual auras,

tonic eye-head movements, and sometimes myoclonic jerks.¹¹⁵

4.1 | Photosensitivity in individuals without epilepsy

All epidemiological studies of photosensitivity in people without recognized epilepsy are challenging due to selection bias.¹⁹ Focal and absence seizures are likely underreported, since many may not be noticed, particularly in the general population. Military Air Forces are among the few agencies that routinely screen large numbers of applicants with EEG, and studies from several countries¹¹⁶⁻¹²⁰ have identified epileptiform abnormalities in 0.35%-2.4%. However, these samples of predominantly healthy young adults may not be representative of the general adult population. Children appear to have a higher prevalence of PPR, and a study of 743 healthy, developmentally normal children without epilepsy ages 1-15 years identified a PPR in 8.3%, with a higher preponderance in girls compared to boys, and in children older than 10 compared to younger children.¹²¹

4.2 | Photosensitivity in individuals with epilepsy

Studies from England in the 1990s suggest that the prevalence of photosensitive epilepsy among the general population is approximately 1 in 4000.^{10,121,122} Studies focusing specifically on people with epilepsy report that 0.6%-30% have a PPR. Patient characteristics (age, gender, type of epilepsy) as well as the EEG methods used to diagnose photosensitivity contribute to this variability. New-onset seizure patients in Great Britain showed photic-induced generalized spike-waves in about 2% of all new-onset seizure cases or 1.1 per 100,000 in the general population and 5.7% in children ages 7-19.¹²³ Consideration of other types of PPR beyond spike-waves would elevate these percentages.

The presence of photosensitivity in patients with epilepsy varies by age, especially in cases of juvenile myoclonic epilepsy, juvenile or childhood absence, and catastrophic epilepsy syndromes.^{15,124} In a study of consecutive EEG studies of children without acquired brain injury, only 1% (53/5055) of children younger than 5 years of age had a PPR, compared with 3.5% in 5- to 10-year-olds and 4.6% in 10- to 15-year-olds; 21% of the youngest age group had Dravet syndrome.^{125,126} A second study of 10,671 EEG studies of 7188 patients also found that patients 11-20 years of age were most likely to have a PPR.¹²⁷ Among 5950 EEG studies in adult epilepsy patients (age >15) only 1.2% demonstrated a photosensitive response.¹²⁷

Female gender is a second risk factor for photosensitivity, with females being approximately twice as likely as males to have photosensitive epilepsy.^{22,125} Several studies have suggested that adolescent girls at puberty initiation are at especially high risk.^{22,127}

Patients with generalized epilepsies are more likely than those with focal epilepsies to have a PPR, but patients with focal epilepsy should still be evaluated for photosensitivity. Among the general population of all ages, Wolf and Goosses²³ examined 1000 patients with epilepsy and concluded that 15% of generalized epilepsies and 3% of focal epilepsies demonstrated photosensitivity. A recent study of 1893 patients with epilepsy over the age of 2 years found that 9% of patients with generalized epilepsy and 0.9% of those with focal epilepsy had a PPR.¹⁰⁶

A population study specifically focused on children found that 46% with generalized epilepsy¹²⁸ showed PPR, contrasted with 20% who had focal epilepsies. A second recent study of all children with photosensitivity at a tertiary care hospital found that 51% had generalized, 24% had focal, 10% had combined, and 14% had unknown epilepsy diagnoses. Of interest, those children with untreated focal epilepsy were most likely to have self-sustaining PPRs.¹²⁹

Other clinical and demographic factors likely influence the risk of photosensitivity. The incidence varies with geography, such that living in a country with 50 Hz line voltage (eg, Europe, Japan) rather than 60 Hz (the US) is a risk factor—at least for discovering underlying photosensitivity by provocation of a seizure. It used to be said¹⁰ that Europeans commonly had their first seizure in front of a TV, although this is unlikely to still be the case now that digital screens have replaced cathode ray tubes that refreshed at 50 Hz. Studies of ethnic origin and photosensitivity have not been conclusive, but several studies suggest a lower prevalence in Black Sub-Saharan Africans compared with their White counterparts.¹¹³

Prevalence PPR studies documented the highest values in adolescents.¹²⁵ A very recent study evaluating PPR prevalence based on a scored database of 10,671 EEG studies confirmed this prevalence.¹²⁷ A study by Jeavons and Harding¹³⁰ showed that 10 of 18 of those without medication were no longer photosensitive at a mean age of 24.5 ± 4.9 years. The Harding study of 1997¹³¹ entitled “The persistence of photosensitivity” argued that at least two-thirds continued to be photosensitive. However, this study is difficult to interpret because it included numerous family members and considered occipital spikes as still being photosensitive.

Long-term outcome of pattern-sensitive epilepsy was evaluated in 35 patients.⁷³ Half had focal and half had generalized-onset seizures. After a mean 13.9 years of follow-up, 80% were seizure-free, perhaps indicating a good prognosis for this condition or perhaps reflecting

the improvement in television technology. Thirty children (1.8% of 1705 clinic patients) younger than age 12, with a history of television-induced seizures, were followed for at least 2 years.¹³² EEG showed spontaneous generalized epileptiform spikes in 77%, and 90% had such spikes with photic stimulation. The general prognosis of visually-sensitive seizures is fair, but not excellent and is also dependent on the associated epilepsy type and syndrome. Harding estimated a 14%-37% probability of remission in light- and pattern-sensitive individuals.¹³¹

5 | GENETICS

Our knowledge regarding the genetics of photosensitivity stems from studying the heritability of the photoparoxysmal response (or PPR) itself, as well as epilepsies with prominent photosensitivity. Several reviews have considered the genetics of photosensitivity.^{15,22,26,133}

5.1 | Genetics of the photosensitivity response

Screens of family members of people with photosensitive epilepsy indicate that the PPR is highly heritable. Monozygotic twins demonstrate nearly 100% concordance with regard to photosensitivity, and siblings of affected individuals have a 5-fold elevated risk of having photosensitivity compared to the general population.^{134,135} Studies suggest that the PPR can be inherited in an autosomal dominant fashion, with reduced and age-dependent penetrance.¹³³ There is also evidence that the PPR segregates separately from epilepsy. Children of women with photosensitivity have a 25% chance of demonstrating a PPR, but only half go on to develop epilepsy.¹³¹ In families with photosensitive epilepsy, the incidence of the PPR is similar in siblings with and without epilepsy.¹³⁶ Furthermore, Piccioli et al.⁸⁶ studied family members of 4 patients with photosensitive epilepsy and found that 9 of 12 relatives without epilepsy showed EEG photosensitivity, with two demonstrating an ictal EEG pattern after light flashes.

5.2 | Genetics of epilepsies with prominent photosensitivity

Photosensitive epilepsies have been classified in various ways. Taylor and colleagues¹³⁷ divide idiopathic epilepsy and photosensitivity into genetic generalized epilepsy, idiopathic photosensitive occipital epilepsy, or a mixture of the two. Other authors^{15,22} categorize photosensitive epilepsies as either (1) “pure” photosensitivity epilepsies

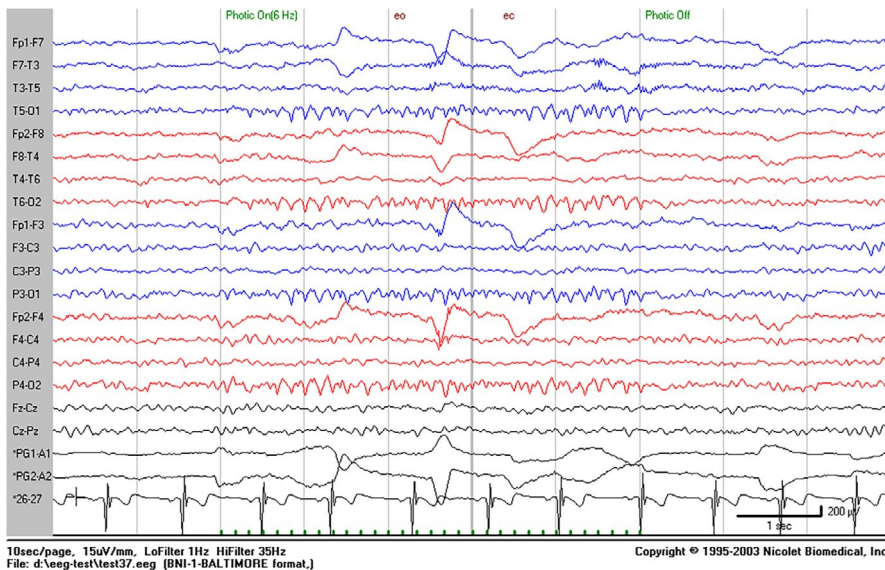


FIGURE 1 Waltz type 1 response, with occipital spikes that do not spread anteriorly or outlast the stimulus. This response is now considered to be normal

in which seizures are primarily provoked by visual stimulation (ie, eyelid myoclonia with absences; idiopathic photosensitive occipital lobe epilepsy); and (2) epilepsy syndromes associated with photosensitivity (ie, the genetic generalized epilepsies; progressive myoclonic epilepsies; and several epileptic encephalopathies) in which patients have a mixture of provoked and unprovoked seizures.

Large linkage studies of genetic generalized epilepsies have identified potential photosensitivity loci on chromosomes 6, 7, 13, and 16.¹³³ This association, particularly in patients with juvenile myoclonic epilepsy,¹ may be mediated by genes at region 6p21.2 and 13q31.3: the former locus is linked to photosensitivity and the latter to epilepsy.¹³⁸ Another study suggested that regions 7q32 and 16p13 may be linked to the PPR in families with idiopathic myoclonic epilepsies.^{139,140}

Specific susceptibility genes for photosensitive seizures remain poorly characterized, but a few candidates have been identified. The neuronally expressed developmentally downregulated the *NEDD4-2* gene, which regulates voltage-gated sodium channels, was identified in one cohort of 124 families with genetic generalized epilepsy,¹⁴¹ but the finding was not replicated.¹⁴² Approximately 50% of patients with mutations in the alpha-1 subunit of γ -aminobutyric acid (GABA)_A receptors¹⁴³ (*GABRA1*) have a PPR; otherwise they display wide phenotypic variability ranging from juvenile myoclonic epilepsy to epileptic encephalopathy. A study of more than 600 individuals with a PPR found that mutations in the chromodomain helicase DNA-binding protein-2 (*CHD2*) gene (a regulator of transcription) are specifically associated with eyelid myoclonia with absences, but not a PPR without epilepsy.¹⁴⁴ *CHD2* variants are also associated with self-induced photosensitive seizures.^{145,146} Other recently identified genes

associated with eyelid myoclonia and absences include *SYNGAP1*^{147–149} (a Ras-GTPase activating protein that is part of the *N*-methyl-D-aspartate (NMDA) receptor complex and associated with excitatory neurotransmission), *KIA02022/NEXMIF*^{150,151} (X-linked Intellectual Disability Protein Related to Neurite Extension, important for neuronal migration, cellular adhesion, and circuit development), and *ROR β* ^{56,152,153} (retinoid-related orphan receptor β , important for neuronal migration and differentiation). Recently, variants in *ROR β* have also been reported in patients with a spectrum of photosensitive disorders, including eyelid myoclonia with absences and idiopathic photosensitive occipital lobe epilepsy.¹⁵⁴ Although the overlap between these syndromes has been recognized clinically, this is the first gene known to contribute to the overlap between genetic generalized and idiopathic occipital lobe epilepsies.

A number of rare and typically autosomal recessive epilepsy syndromes feature photosensitivity as a defining characteristic. For example, approximately 30%-50% of children with Dravet syndrome due to *SCN1A* mutations develop photosensitive seizures, and photosensitive seizures seem to be a marker of disease severity.¹⁵⁵ Over half of patients with neuronal ceroid lipofuscinosis type 2 disease have a pronounced PPR on EEG, often to low photic frequencies.¹⁵⁶ Many of the progressive myoclonic epilepsies are also associated with pronounced photosensitivity; new genes associated with these epilepsies continue to be identified.¹³³ PPR can be found also in patients with chromosomal abnormalities like trisomy 13, 19, or 21 (Down syndrome), X-chromosome, and other rare abnormalities, usually in combination with cognitive deficiency.¹⁵⁷ Further investigations of specific epilepsy and other syndromes may thus shed additional light on the genetics of photosensitivity.

6 | PHOTIC EEG AND IMAGING

6.1 | EEG and photosensitivity

Walter and Gastaut first reported paroxysmal EEG changes to light flashes in 1948.⁶⁵ In 1992, Waltz¹³⁶ grouped EEG responses to flash into four categories. Type 1 is spikes confined to the occipital rhythms (Figures 1 and 2. Below); type 2 is parieto-occipital spikes with a biphasic slow wave; type 3 is type 2 with frontal spread; type 4, representing the most pathological response, is generalized spike-waves.

An extended classification of EEG responses to intermittent photic stimulation was proposed by a European group (Table 2).³⁶

PPR has been simplified by the “Standardized Computer-based Organized Reporting of EEG” (SCORE) group¹⁵⁸ into the following categories: (1) Unmodified; (2) Posterior stimulus-independent response, limited to the stimulus train; (3) Posterior stimulus-independent response, self-sustained; (4) Generalized photoparoxysmal response, limited to the stimulus train; (5) Generalized photoparoxysmal response, self-sustained; and (6) Activation of pre-existing epileptogenic area. Inter-rater agreement using this scale is moderately good and almost perfect for scoring epileptiform discharges.¹⁵⁹

A photoparoxysmal response (or PPR) with abnormal spikes, slowing, spike-waves, or EEG ictal events in response to photic stimulation can occur in the absence of obvious behavior change, in which case the clinical significance is uncertain. However, recognition of behavioral change depends upon the rigor of observation. One study¹⁶⁰ documented a motor task delay during the EEG photoparoxysmal response, arguing that the events were not EEG markers of a tendency, but in fact represented

seizures. This suggests that visual stimuli producing a photoparoxysmal response for more than a few seconds could have important safety implications. This was demonstrated during a routine outpatient EEG recording,¹⁶¹ when one patient with known photosensitive seizures had bradycardia to 12 beats per minute provoked by photic stimulation. Among patients with epilepsy, it is more common to encounter those in whom certain photic stimuli sometimes trigger seizures, but not all seizures in these individuals need be photic-induced.¹⁵ Most, but not all of those with a PPR in an EEG lab have epilepsy,⁹ yet they may or may not have had a light-induced seizure. Conversely, it is common to find a PPR with EEG recording in those who have light-induced seizures, provided that a suitable range of light flash frequencies is tested,¹⁶² A study of 35 individuals who had a seizure while playing video games¹⁶³ demonstrated a PPR in 52%. Studies done in EEG labs have an obvious selection bias, and it is likely that many people who would have a PPR had they been tested are never aware of this tendency. Rare, pure forms of photosensitive epilepsy syndromes only manifest seizures when provoked by certain light stimuli.

The Mayo Rochester Epidemiology Project¹⁶⁴ identified 449 residents with newly diagnosed epilepsy; photic stimulation yielded a diagnosis in 3.3%. Photic stimulation across a range of frequencies has long been advocated as a part of routine EEG recording.¹⁶² Use of a suitably bright (at least 1 Joule per flash) and a diffused light stimulator may be needed to identify photosensitivity.¹⁶⁵ Recording can be done with eyes closed, as the light penetrates the eyelids and diffuses across the retina. Testing a range of flash frequencies is important to identify individual susceptibilities. Signal analysis suggests that the optimal frequency to produce a driving response is 16 ± 10 Hz for normal subjects, but 8 Hz for patients with epilepsy,¹⁶ although, a driving response does not indicate an abnormal photoparoxysmal response.

Analysis of propagation patterns for photic discharges¹⁶⁷ showed multiple patterns of spread. The most common pattern was symmetric bilateral occipito-temporo-frontal spread. Power spectral density and coherence methods can estimate coherence among EEG channels during photic stimulation.¹⁶⁸ During 14 Hz photic stimulation of patients with generalized photosensitive epilepsy, inter-channel coherence in the 0-30 Hz frequency spectrum did not change, but the coherence increased in the gamma¹⁶⁹ frequency band in occipital electrodes with frequencies above 30 Hz. Because gamma activity in part reflects the activities of inhibitory interneurons,¹⁷⁰ changes in gamma coherence may have relevance to mechanisms of seizure generation.¹⁷⁰ The stimuli that are most provocative in photosensitive epilepsy match the stimuli that strongly drive gamma oscillations.¹⁷¹ Parra¹⁶⁹ studied synchrony

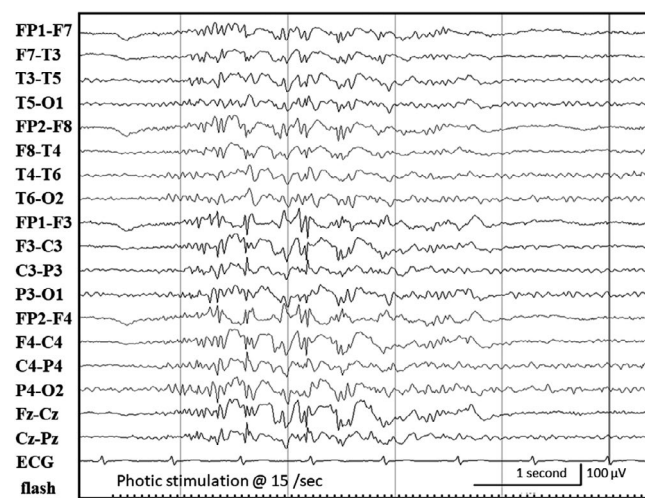


FIGURE 2 Waltz type 4 response, with generalized spike-waves in response to intermittent photic stimulation

TABLE 2 EEG responses to intermittent photic stimulation**An extended classification of EEG responses to intermittent photic stimulation**

1. Photic following
 - a. At flash rate
 - b. At harmonics
2. Orbitofrontal photomyoclonus
3. Posterior-stimulus-dependent response
4. Posterior-stimulus-independent response
 - a. Limited to the stimulus train
 - b. Self-sustaining
5. Generalized photoparoxysmal response
 - a. Limited to the stimulus train
 - b. Self-sustaining
6. Activation of preexisting epileptogenic area

Note: Grade 3, 4, and 5 are generally described as photoparoxysmal responses.

in the 30-120 Hz gamma frequency domain occurring just before a PPR in 10 patients with idiopathic photosensitive epilepsy and 8 controls. Phase synchrony was enhanced in patients with photosensitivity, suggesting that this synchrony might contribute to photosensitive seizures in these patients. This subject recently has been reviewed in detail by Avanzini.¹⁷² Future studies of gamma frequencies will provide additional insights into mechanisms of origin and propagation of the PPR.

Localization of the PPR is relatively imprecise with standard scalp-recorded EEG. The distribution of the photoparoxysmal response was mapped by intracranial electrodes in a patient being studied for possible epilepsy surgery.¹⁷³ Photic stimulation produced focal medial occipital discharges, parietal discharges, and sometimes apparently generalized spikes. Photic-provoked myoclonic seizures were associated with generalized spike-wave discharges, particularly involving the parietal cortex. A constraint on this study is the limited sampling of brain regions (especially frontal) by the implanted electrodes.

In general, it is assumed that photic stimulation provokes epileptiform and seizure activity. However, sensory stimulation can inhibit or interrupt some seizures and light flashes are a form of such stimulation. One study¹⁷⁴ recorded a mean reduction of interictal spiking from 1.17 per minute at baseline to 0.8 per minute during light flashes across the range of 5-50 Hz. This raises the unexpected possibility that some types of light stimuli might be beneficial against seizures. A reconciliation of this possibility with the more frequent elicitation of spikes by light flashes currently is lacking.

Photic seizures occurred during 1.4% of 1000 retrospectively and randomly selected EEG studies, and during

31% of EEG studies in patients with generalized or photosensitive epilepsies, although no generalized tonic-clonic seizures (GTCSs) were evoked.¹⁷⁵ In a later prospective nationwide study in the UK¹⁷⁶ 0.7% had photic seizures in the lab of whom two (0.04%) had a GTCS. EEG technologists usually are trained to stop stimulating if they recognize a build-up to a possible seizure, since production of a tonic-clonic or even a less-intense clinical seizure is not encouraged. An exception is during video-EEG monitoring, where the goal is to provoke and record a seizure.

6.2 | Brain imaging and photosensitivity

In most cases of photosensitive epilepsy, structural brain MRI is normal. However, special imaging techniques that assess structural and functional connectivity or blood flow and energy metabolism associated with photosensitivity may provide additional insights into the mechanisms of photosensitivity. Although assessment of the response to photic stimulation is rarely employed in neuroimaging studies (in part due to the danger of inducing seizures), several neuroimaging studies of patients with photosensitive epilepsies have been conducted.

Of the structural studies, one MRI study in PPR-positive idiopathic generalized epilepsy (IGE) patients and PPR-positive subjects found bilateral increase of cortical thickness in the occipital, frontal, and parietal cortices compared to healthy controls, whereas the same comparison revealed a decrease in the temporal lobes of those with a PPR but not epilepsy.¹⁷⁷ Another study using voxel-based morphometry (VBM) investigated 60 patients with JME (19 with photosensitivity) and 30 sex-matched healthy controls.¹⁷⁸ This study showed reduced bilateral gray matter volume in visual cortices using VBM in the JME-photosensitive group compared to healthy controls but not when compared to the nonphotosensitive JME patients. However, they also observed reduced left hippocampus and left inferior frontal gyrus volume in the JME-photosensitive group compared to JME nonphotosensitive patients.

MRI studies of fractional anisotropy (FA) and mean diffusivity (MD) point to white matter structural abnormalities in the precentral and lateral occipital regions of subjects with PPR.¹⁷⁹ In the same study, patients with IGE and PPR showed additional increases in FA in the thalamus and precentral/parietal white matter. PPR was associated with changes in axial and radial diffusivity in the occipital regions. Another study in 18 JME patients (8 with PPR) compared diffusion parameters to 27 healthy controls to identify widespread microstructural abnormalities in JME including increased FA in the ascending reticular activating system and ventromedial thalamus,

whereas reduced fractional anisotropy of the lateral geniculate nucleus was observed in the entire JME group compared to healthy controls.¹⁸⁰ Yet another study conducted tract-based spatial statistics (TBSS) analysis in 8 patients with photosensitive epilepsy (PSE) and 16 age-/sex-matched healthy individuals; PSE participants had significantly lower FA values in the corpus callosum.¹⁸¹ Another study compared 31 patients with JME (12 PPR positive) and 27 healthy controls matched for age/sex also using TBSS.¹⁸² These authors showed reduced FA in longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, anterior and posterior thalamic radiation, corona radiata, corpus callosum, cingulate gyrus, and external capsule. However, subgroup analysis revealed no significant differences of white matter alterations between PPR positive and negative patients and with clinical and epilepsy-related factors. The overall conclusion is that white matter connectivity in various brain networks is abnormal in subjects with PPR or PSE, although the studies do not demonstrate cause versus effect.

Functional MRI (or fMRI) is a technique to judge the amount of oxygen extracted from the blood flowing into brain tissue; it is a measure of both blood flow and metabolism. Combined EEG-fMRI can portray the blood-flow/oxygenation changes associated with photic responses or generalized spike-wave discharges (GSWDs). People with JME exposed to intermittent photic stimulation in the scanner demonstrated a positive BOLD response in visual areas and reduced positive BOLD response in the fronto-parietal areas and putamen but a stronger negative BOLD response in the primary sensorimotor cortex and in cortical regions belonging to the default mode network (DMN).¹⁸³ Furthermore, in JME, the dynamic evaluation of BOLD signal changes related to PPR revealed an early positive response in the putamen and the primary sensorimotor cortex, followed by BOLD signal decrements in the putamen, caudate nuclei, thalami, and sensorimotor cortex. Another EEG-fMRI study investigated evoked GSWDs in six patients with PPR (four with IGE and two with tension-type headache) to show that intermittent photic stimulation led to a significant activation of the visual cortex. PPR activation was found in the parietal cortex adjacent to the intraparietal sulcus in five and in the premotor cortex in all six subjects with early deactivation in early activated areas in all subjects to suggest that PPR is a cortical phenomenon with an involvement of the parietal and frontal cortices (and not thalamic involvement as in generalized spike-wave discharges). Another study by the same group used EEG-based coherent source imaging and EEG-fMRI to show that both methods identified the occipital, parietal, and the frontal cortex in a network associated with PPR.¹⁸⁴ However, only when PPR preceded a generalized tonic-clonic seizure, the thalamus

was involved in the generation of PPR as shown by both imaging techniques, indicating that the thalamus acts as a pacemaker while PPR could be explained by a cortical propagation from the occipital cortex via the parietal cortex to the frontal cortex.

A recent study investigated the hemodynamic correlates of the spontaneous alpha rhythm in 16 participants with IGE and photosensitivity, 13 participants with IGE and no photosensitivity, and 15 patients with focal epilepsy using EEG-fMRI.¹⁸⁵ Patients with IGE with photosensitivity demonstrated significantly greater mean alpha power with respect to healthy controls and other epilepsy groups. In photosensitive IGE, alpha-related BOLD signal changes demonstrated lower decreases relative to all other groups in the occipital, sensory-motor, anterior cingulate, and supplementary motor cortices. The same brain regions also demonstrated abnormal connectivity with the thalamus that was present only in epilepsy patients with photosensitivity. These findings indicate that the cortical-subcortical network generating the alpha oscillation at rest is different in people with epilepsy and visual sensitivity.

Positron emission tomography (PET) evaluation of baboons with or without photosensitivity showed the greatest activation in several structures including bilateral occipital lobes in the control animals but absence of such activation in the photosensitive animals.¹⁸⁶ An older human study of photosensitivity using [¹¹O]-H₂O in photosensitive healthy and epilepsy participants documented increases in the occipital cortex in both groups,¹⁸⁷ with differences seen in other brain regions between the healthy controls and epilepsy patients; epilepsy but not healthy controls also exhibited increased hypothalamic radioisotope uptake.

7 | MECHANISMS OF PHOTOSENSITIVITY

The mechanisms of photosensitivity and pattern sensitivity are largely unknown, although the available evidence indicates that the occipital cortex and the networks to which it belongs have physiological abnormalities. These changes are expected, since hypersensitivity to flashing lights can provoke a variety of neurological symptoms, including headaches, dizziness, nausea, disorientation, and of course, seizures.

Characteristics of the visual stimuli capable of evoking seizures in patients with photosensitivity may provide some insight into the underlying mechanisms. The visual system has evolved to process images from nature efficiently using sparse coding.¹⁸⁸⁻¹⁹² The flicker and patterns that provoke seizures are rarely encountered in nature. For these stimuli, the energy components of images are

not distributed as is typical for natural scenes but concentrated instead at temporal and spatial frequencies to which the visual system is generally most sensitive.¹⁹³ In healthy individuals, such unnatural stimuli generate both visual discomfort and a large hemodynamic response.¹⁹⁴ Haigh and others showed that images with a large chromaticity difference (rare in nature) also evoked discomfort and a large hemodynamic response, and they interpreted the differences between the epileptogenic properties of colored flicker¹⁹⁵ in these terms.^{196,197} A large neural response, possibly due to failure of gain control,¹⁹⁸ is necessary for a PPR, but it is not sufficient. Drifting gratings that induce both discomfort and a large hemodynamic response¹⁹⁹ do not provoke seizures, presumably because they fail to synchronize the activity they evoke.²⁰⁰ A large neural response and synchronization of neural activity are both necessary for a PPR.

Several observations indicate that the occipital cortex or visual system in patients with photosensitive epilepsy is hyperexcitable. Visual evoked potentials (VEPs) have a higher amplitude in photosensitive patients with generalized or occipital lobe epilepsies when compared to healthy controls or patients without photosensitive epilepsy.^{198,201-203} The increase in VEP amplitude depends on factors such as the contrast of the stimuli used and eye closure. In addition, VEPs in patients with photosensitive epilepsy respond differently to repetitive transcranial magnetic stimulation (rTMS) than VEPs in controls. rTMS can serve as a tool to assay cortical excitability with 0.5-1 Hz pulses tending to have an inhibitory effect.²⁰⁴ Bocci and colleagues²⁰⁵ showed that VEPs in patients with photosensitive epilepsy recovered faster after rTMS, which may correspond to the tendency to have photosensitive seizures. Patients with photosensitive epilepsy were more likely than nonphotosensitive people with epilepsy to perceive phosphenes with low-intensity TMS.²⁰⁶ Finally, examination of occipital gamma frequency activity/high frequency oscillations evoked by light flashes or high-contrast gratings provides further evidence for increased excitability in the occipital cortex or visual system of photosensitive patients. Visual stimuli evoke higher-amplitude occipital gamma frequency activity/high-frequency oscillations as assessed by magnetoencephalography or EEG in photosensitive patients compared to controls.²⁰⁷⁻²⁰⁹ Occipital gamma activity may serve as a nonprovocative biomarker.¹⁷¹

Abnormal excitability in patients with photosensitive epilepsy extends beyond the occipital cortex and visual system. Subdural electrode recordings from a patient with epilepsy showed that photoparoxysmal (PPR) and photoconvulsive responses involved the occipital lobe, parietal lobe, posterior cingulate, and medial frontal convexity.¹⁷³ However, even photic driving alone involved the parietal

lobe in addition to the occipital lobe. Intermittent photic stimulation (IPS) normally does not modulate the cortical silent period in the motor cortex of healthy patients with a PPR and in patients with genetic generalized epilepsies.^{210,211} Normally, IPS decreases the cortical silent period in the motor cortex. This property is lost in patients with a PPR and in patients with genetic generalized epilepsies regardless of whether they have a PPR. An interesting case report of a photosensitive seizure while recording EEG and fMRI²¹² showed that PPR to light flashes resulted in increased MRI BOLD signals in visual cortex, superior colliculi, and thalamus, but decreased BOLD signals in the frontoparietal areas. Vaudano et al. performed an EEG-fMRI study at rest in patients with genetic generalized epilepsies with and without photosensitivity.¹⁸⁵ They found that patients with photosensitivity had greater posterior alpha power with altered functional connectivity with the pulvinar and reduced alpha-related inhibition in the supplementary motor area, the sensorimotor cortex, and the premotor cortex. These findings begin to delineate the networks involved in generation of photosensitive seizures.

Often the assumption is that photosensitive seizures are generalized in onset. However, the results summarized above underscore the importance of the occipital lobe and the visual system to photosensitive seizures. Indeed, patients often experience sensations or visual images before losing awareness, reflecting focal seizure origin. Kasteleijn-Nolst Trenité et al. concluded from a literature review that 17% of focal epilepsies show PPRs and that PPRs can be focal.²¹³ Substantial evidence exists for photosensitive seizures originating focally near the visual cortex.¹⁷ The PPR is stochastic, and the probability of epileptiform activity is closely dependent on the parameters of pattern stimulation, including the contrast, the spatial frequency, and the size and shape of the pattern and its position in the visual field.²¹⁴ From a study of these parameters and their relation to the known properties of cortical neurons it can be inferred that the two cerebral hemispheres act individually and independently in the induction of epileptiform EEG activity. The activity occurs when normal synchronized physiological excitation within the visual cortex of one or both hemispheres exceeds a critical area of cortical tissue that differs from one individual to another.

Vertebrate and invertebrate models of photosensitive seizures such as the *Papio papio* baboon, the Fayoumi chicken, the Rhodesian Ridgeback dog, and the ceramide phosphoethanolamine synthase (*cpes*)-null mutant *Drosophila* share features of photosensitivity found in patients.^{133,215-217} For example, EEG recordings from baboons typically show 4-6 Hz generalized spike and wave discharges with 23% having photosensitivity.²¹⁸ EEG studies have captured myoclonic seizures, which are the

predominant seizure type in these baboons, but they also have absence and generalized tonic-clonic seizures.²¹⁹ These baboons respond to sunlight flashing off rippling leaves with myoclonic jerks, causing them to fall from trees.¹³ Although the genetic basis has not been identified in the baboon, genetic studies in the other models have helped to identify the potential molecular basis for photosensitivity. However, the mechanisms by which these molecular defects confer photosensitivity remain unclear.

Takahashi²²⁰ identified two different mechanisms of the PPR. One, called wavelength-dependent mechanisms, elicited PPRs when the subject viewed red light with wavelength greater than 700 nm. This mechanism was likely implicated in the Pokémon incident with the red-blue flash sequences of the rocket-launch segment.²²¹ The second, called quantity of light-dependent mechanisms, generates a PPR in response to bright light flashes independent of color. Color filters or general light filters, based upon each of these mechanisms failed to inhibit PPR in about half of test cases. However, compound filters addressing both mechanisms inhibited PPR in 90%.

Light sensitivity usually is defined and tested as an immediate EEG response, yet a clinical response might be delayed by minutes and therefore not predicted by a falsely reassuring EEG. In addition, the range of possible light triggers in the real world is far larger than the stimuli tested in an EEG lab.

Seizures occur when excitation exceeds inhibition and synchrony overcomes desynchronization in relevant brain networks. The above information provides clues but does not lead to an explanation of how certain light stimuli provoke seizures. The answer will likely lie in analyzing how cellular and molecular changes resulting from genetic and environmental insults alter the networks involved in processing visual information. Some indications may be found in recent computational models of the visual cortex, however, in which strong (epileptogenic) visual stimulation has been shown to result in “winner takes all” behavior when inhibitory connections are impaired.²²²

8 | LIGHT-INDUCED SEIZURES FROM MODERN STIMULI

8.1 | Video-game-induced seizures

The ability of some video games to provoke seizures has been recognized since 1981, with “Astro Fighter” provoking a seizure in a boy playing in an arcade.²²³ A “Captain Powers” television program in the United States provoked seizures in the 1980s.²²⁴ In 1992, a 14-year-old boy in the UK died while playing a video game.²²⁵ In 1993, a Golden Wonder, Pot Noodle commercial on TV provoked multiple

seizures, including a fatality.²²⁴ Several other examples of TV-provoked seizures came to public attention. In Great Britain, the annual incidence of first seizures precipitated by video games has been estimated at 1.5 per 100,000 among those ages 7- to 19-years-old.²²⁶

Video games might provoke seizures by several mechanisms. The first is by bright flickering lights, the second by patterns, the third by certain color changes, and the fourth by content, provoking individual cognitive triggering factors. These may act in combination. Piccioli and Vigeveno²²⁷ exposed nine children who had prior TV- or video game-induced seizures to the Nintendo video games *Super Mario World*, *Super Mario Kart*, *Street Fighter II*, *Super Bomberman II*, *The Magical Quest*, *Super Mario All Stars*, *Super Aleste*, *Donkey Kong Country*, *Kick Off*, *Nigel Mansell's World Championship*, *Super Strike Gunner*, and *Biometal*. All had PPR to IPS. Loss of consciousness was seen in eight of the children and myoclonus in all nine. Longer seizures with loss of consciousness occurred with Bomberman II, a game with high brightness. Subtle signs, such as eye deviation or partial closure, might have been missed.

Kasteleijn-Nolst Trenite¹² studied 163 subjects with a history of light-induced seizures. Epileptiform EEG discharges were seen in response to IPS in 85% and to patterns in 44%. Games played on a TV screen were more likely to provoke a seizure than was playing on the Nintendo device, perhaps because of increased screen size, brightness, and subtle flickering of the TV image. The scan rate of the TV mattered: 59% showed epileptiform discharges with 50 Hz TV raster frequency vs 29% with 100 Hz TV.

Information on limiting flash and patterns to accommodate users with visually sensitive seizures is included in an influential set of accessibility guidelines (<http://gameaccessibilityguidelines.com/contact/>) issued in 2012 for video game developers. The guidelines, which received an FCC award for advancements in accessibility, contain suggestions for accommodating people with a wide spectrum of medical and cognitive conditions, including those susceptible to light-provoked seizures.

8.2 | Movies

Movies shown in cinemas usually do not provoke photic seizures, because of low light intensity relative to the brightness of a TV or computer screen. However, image sequences in some films have triggered seizures in theaters equipped with newer, brighter screens. In recent years, movie studios and epilepsy advocacy organizations have occasionally issued seizure warnings for popular movies, although this is typically done after seizures have already occurred in some patrons. In one instance, after reports of

seizures in *Incredibles 2* audience members, Disney-Pixar announced a warning and re-edited the film to alter the problem sequences. In the UK, the British Board of Film Classification, which reviews all movies prior to release in cinemas, requests that filmmakers and distributors warn viewers about sequences that could provoke seizures.

8.3 | Internet and social media

Daily use of electronic entertainment media rose sharply with the introduction of smartphones, fast wireless communication, and hugely popular internet and social media platforms that display moving images and connect users around the world. Facebook debuted in limited release in 2004, YouTube in 2005, Twitter in 2006, Instagram in 2010, Snapchat in 2011, and TikTok in 2016. Heavy use of these platforms and the vast amount of multimedia content shared on them have increased the likelihood that people with light-sensitive epilepsy could be exposed to potentially harmful images.

These platforms also allow ordinary people to easily create and distribute their own video and animation content, without much oversight. In some instances, individuals with malicious intent have used social media and targeted the social media of epilepsy organizations to display flashing images to induce seizures in visually sensitive individuals. The Twitter feed of the Epilepsy Foundation was attacked in 2019 with seizure-inducing posts. The UK Epilepsy Society has experienced similar attacks. In 2016, a flashing image, accompanied by a menacing message, was sent via Twitter to a *Newsweek* journalist known to have epilepsy, who then had a seizure.

Some web browsers and social media platforms have introduced protective measures, such as banning animated images (Twitter), allowing users to turn off the autoplay feature (YouTube, Twitter, Facebook, Instagram, and web browsers), and allowing users to skip over any content that the platform determines is potentially seizure inducing (TikTok). Another TikTok feature alerts content creators if they upload image sequences that could potentially provoke seizures in viewers. Many mobile phones also offer the option to disable autoplay.

Music videos, many with strobing and other visually provocative effects, migrated to the internet after the launch of YouTube, where they gained a much wider audience and became integral to the popular music industry. An irreverent 2012 article acknowledged the genre's widespread use of potentially seizure-inducing visual effects, observing, "...sometimes [music videos] just slam us in the face with superfast editing and more erratic, bright lights than is medically advisable. Everyone knows the best vids come with a surgeon general's warning." (Bein, K. "Top

Ten Seizure-Inducing Music Videos." Miami New Times. April 18, 2012.) Although more public education and user safeguards are needed, there is gradual progress on internet and social media platforms toward reducing content that provokes visually sensitive seizures.

8.4 | 3D

Movies, TV, and videogames occasionally present images in three dimensions (3D). The history of stereoscopic gaming is well summarized in a slide set available online at https://www.pcworld.com/article/220922/the_history_of_stereoscopic_3d_gaming.html#slide1 (Benj Edwards release March 3, 2011).

Little information is available on the medical dangers of 3D imaging, which perhaps is a comforting observation. 3D images can produce eye strain and blurred visions²²⁸ and motion sickness.²²⁹ A study of 433 subjects viewing movies in 3D or 2D reported a 14% incidence of side effects, with a higher incidence of headaches, eyestrain, and dizziness with 3D video.²²⁸ Tychsen and Thio²³⁰ concluded from a review that "Studies published by pediatric epilepsy experts emphasize the low risk of 3D viewing even for children with known photosensitive epilepsy." This is noteworthy because the number of hours devoted to 2D or 3D screen viewing and virtual reality (VR) headset use by children worldwide has increased markedly over the last decade.

Risks for provoking seizures vary with the technology used to present the 3D images.²³¹ An active shutter design rapidly alternates left and right eye visibility to produce a sense of visual parallax. The alternate method is passive images guided to the left or right eye by polarized glasses. This method reduces resolution of the image but provides a lighter apparatus that does not require power. Active 3D is common on light-emitting diodes (LEDs), liquid crystal displays (LCDs), plasma, and projector TVs. Passive 3D may be encountered on some LED and LCD TVs. Active imaging reduces light, while passive imaging halves the resolution. Some active shutter systems produce a perception of flicker. Typically frequencies of 48, 50, or 60 per second are beyond the usual range for provoking seizures, but they could provoke seizures in individuals who are sensitive to high-frequency flicker. Some glasses increase flicker when they are used to view 2D movies.²³²

In 2010, Samsung warned that 3D TV could cause risks to pregnant women, the elderly, children, and people with serious medical conditions, including epilepsy <https://www.telegraph.co.uk/technology/news/7596241/Samsung-warns-of-dangers-of-3D-television.html>. The data or experience upon which this warning was based were not publicly revealed.

Khairuddin²³¹ presented a car racing video game in 2D, 3D passive (polarized), and 3D active (shutter) modes to 29 healthy subjects. Signal analysis techniques were applied to the EEG. The first technique measured Hjorth complexity parameters, representing the mean power of the EEG signal, the first derivative of the EEG and the mobility or change in frequency during the recording. The second technique used the composite permutation entropy index, which breaks the EEG into segments and estimates the probabilities of containing various peaks, troughs, and slopes of the signals in those segments. A low index represents an EEG that is regular over time. The study found that complexity of the EEG signal increased with 3D vs 2D play, especially for the active shutter 3D version.

Researchers at the University of Munich and University of Salzburg exposed 100 subjects with epilepsy to 20 minutes of light stimulation and 15 minutes of 3D TV, during EEG recording. <https://www.theverge.com/2011/12/6/2614185/study-3d-tv-epileptic-seizures>. One seizure interrupted the 3D TV viewing and 20% experienced nausea, headache, and dizziness. Despite the single seizure, the researchers concluded that 3D TV viewing did not increase epileptic activity on the EEG and it was impossible with a small sample size to say that the 3D viewing caused the seizure. A study reported online (<https://www.mdedge.com/neurologyreviews/article/73230/neurodevelopmental-disorders/how-safe-3d-tv-children-epilepsy/page/0/1>) entitled “How safe is 3D TV for Children with Epilepsy?”²³³ performed a 20-minute routine EEG with intermittent photic stimulation and during 15 minutes of viewing the 3D film *Ice Age 3* with active shutter glasses. Data were gathered for 150 children and adolescents, 88 with epilepsy and 66 with miscellaneous other conditions. No patient had a seizure during viewing. One subject who typically had four seizures per day, experienced a seizure two minutes after the viewing. Three subjects showed at least a doubling of baseline interictal epileptiform EEG discharges. Ten subjects with pre-existing epilepsy showed improved EEG recordings during game playing, presumably due to the usual improvement that occurs when drowsiness is replaced by alertness. The study was not able to rule out a small increased risk in some cases, but no major risk was identified.

Internet blogs contain scattered reports of people having seizures after watching 3D movies, but a causal effect cannot be established. One study²³² concluded that “In patients with photosensitive epilepsy, the risks of a seizure being triggered by 3D movies is not greater than conventional 2D programmes,” although this conclusion was based on consideration of the typical brightness and flicker frequencies of 3D movies, rather than on direct evidence.

Viewing 3D movies produces side effects in 14%, mostly headache, eyestrain and dizziness. A few internet blogs report individual seizures after watching 3D movies, but no causal relation can be established. Some active shutter 3D lenses might be at risk for inducing seizures due to a flicker effect by the lens, independent of video content. Almost no evidence exists in the medical literature to guide safest practice for 3D material. There is no indication of a large problem to date.

8.5 | Virtual reality

Virtual reality (or VR) is used increasingly in the medical environment for rehabilitation²³⁴, pain control,²³⁵ anxiety,²³⁶ and improving quality of life.²³⁷ A survey²³⁸ of 30 hospitalized patients who viewed multiple VR experiences with Samsung Gear VR goggles described the experience as pleasant and able to reduce pain (75%) and anxiety (43%). People with epilepsy were excluded from the survey.

Very few laboratory studies have been done on the effect of VR on seizure tendency. A study in rats²³⁹ showed that brain cells in the hippocampus, a temporal lobe structure important for spatial navigation, reduced their firing rates by 68% when navigating in VR compared to navigating in the real world. The significance of this for safety of VR is unclear, but hypothetical scenarios can be imagined in which inhibitory (protective) neurons are silenced in a VR environment, increasing the excitability of brain and leading to seizures.

VR can improve rehabilitation after a stroke.²³⁴ Although stroke is a risk factor for seizures, none of 80 studied patients had seizures during rehabilitation, and in fact, no side effects were mentioned. A smaller study of 10 stroke patients²⁴⁰ placed in a VR canoe also demonstrated no seizures or side effects. VR was compared to VR plus occupational therapy,²³⁷ with 35 stroke patients who showed improvement in mood with VR. No study subjects had adverse reactions. One study²⁴¹ mentioned a seizure after VR training, but this seizure was in the conventional therapy group. A group of 141 stroke patients were randomized to conventional recreational therapy vs VR therapy with the commercially available games played on the Nintendo Wii. No difference in outcome was observed, but one VR group patient playing the Nintendo Wii had a heart attack, one in the conventional group had a brain hemorrhage, and another in the conventional group had a seizure.

Little information is available in the medical literature regarding people with epilepsy and VR. A study²⁴² of spatial navigation in 25 patients with refractory temporal lobe epilepsy used VR to test navigation skills in a virtual

warehouse of boxes to be opened. Boxes changed colors when opened, but did not flicker or move. The epilepsy patients performed worse than did normal controls, but no induced seizures or side effects were mentioned. A 3D virtual shopping market^{243,244} was used to test the ability of epilepsy patients to memorize a verbally presented shopping list. Equipment included eight surrounding touch screens. People with epilepsy found fewer objects and traveled longer distances to search.

The limited data so far available raise no special seizure concerns in terms of VR technology, although this view may change with more experience. Certain types of VR content, including bright flashes, provocative patterns, or color changes would be expected to provoke seizures, just as they do in the real world.

8.6 | LEDs

Many electronic devices, including TVs and videogame or computer screens now employ light-emitting diodes (LEDs). In the past these were not very bright and therefore unlikely to provoke problems other than eyestrain, but modern LEDs have significantly increased luminance. Modern photostimulators in EEG labs use LEDs to generate bright lights,²⁴⁵ so it is clear that flashes with LEDs can provoke photoparoxysmal responses. What is not known is whether or not LEDs have provocative properties in people with epilepsy distinct from the known responses to bright flashes. A PubMed search on January 25, 2021 using search terms "light emitting diode" and seizures produced only five results, none of which indicated provocation of seizures and two based on animal models,^{246,247} showing suppression of seizure-like activity with LEDs. Frequencies up to 11 kHz generate a visible pattern on the retina when a saccade is made across a flickering LED, and this pattern is more visible to individuals who complain of eye strain.²⁴⁸ The effect of LEDs on people with epilepsy is a subject that would benefit from additional research.

9 | TECHNIQUES TO MINIMIZE RISKS

9.1 | Provocative factors

Avoidance of provocative factors and prevention of seizures are conceptually superior to treatment with antiseizure medications (ASMs), and light-induced seizures, by definition, have provocative factors. Prevention can take place at the level of government regulation, industry, families, and individual patients.

One approach to risk minimization is avoidance of individual precipitating factors for seizures. These can be quite varied. Wassenaar and Kasteleijn-Nolst Trenite¹²⁴ sent questionnaires to 248 patients who were taking anti-seizure medications for seizure control. At least one precipitating factor was reported in 47%. Stress was listed in 33.5%, sleep deprivation in 25%, flickering lights in 17%, alcohol in 7%, sounds in 5%, fever in 4%, and menstruation in 3%. The 17% prevalence of precipitation by lights was higher than the usually reported 5-7% among people with epilepsy, possibly because EEG confirmation was not undertaken in the questionnaire study.

In addition to flashing lights and certain patterns, in rare instances, seizures can be provoked by Fourth-of-July fireworks,²⁴⁹ certain types of cognition,²⁵⁰ Mah-jong,²⁵¹ wind turbines presenting flicker of the sun,^{252,253} and massively multiplayer online role-playing games.²⁵⁴ A PPR response, but not a seizure, occurred with the rapid flashes of an iPhone designed to constrict pupils and reduce red eye during taking of a "selfie."²⁵⁵ Seizures provoked by an undulating water surface²⁵⁶ were reportedly provoked by a TV advertisement for the London Olympics in 30 susceptible watchers.¹⁰ Attending a discotheque in The Netherlands tripled the risk for a seizure.²⁵⁷ Seizures due to "sunflower epilepsy" can be self-induced by waving fingers in front of a light.^{40,258} Even though triggering stimuli may be uncomfortable, the net effect of the symptoms during a seizure may be pleasurable or able to reduce tension (see section 2.2).⁴⁹

9.2 | Stimulus characteristics

Inciting stimuli in photosensitive individuals can be light flashes, color changes, or certain moving patterns.²⁰³ In 2005, a panel convened by the Epilepsy Foundation of America^{259,260} concluded that a flash is a potential hazard if it is brighter than 20 candelas per square meter, occupies at least 10% of the visual field, flashes or changes color at a frequency between 3 and 60 Hz, and endures for at least half a second. Similar parameters apply to color changes, which are particularly problematic when to and from saturated red¹⁹⁵ with a large chromaticity difference.¹⁹⁷ Red flashes induce more photoparoxysmal responses than do other colors¹⁹⁵ and color sensitivity tends to occur at lower frequencies than does sensitivity to white light. A pattern might provoke seizures if there are at least five clearly discernible oscillating stripes (eight if drifting smoothly) brighter than 50 candelas per square meter, enduring for over one-half second. Avoidance of these characteristics is estimated to be protective for at least two-thirds of people with epilepsy.²⁶⁰

Using smaller screens (ideally <12") and maintaining a distance of at least two meters or three times the width of the screen (whichever is larger) reduces brightness and the area of the visual field involved, thereby reducing seizure risk. Screens that refresh at 100 Hz and flat screen plasma and liquid-crystal displays may be less provocative than older cathode-ray screens with slower refresh frequencies. Limiting screen exposure by taking frequent (at least hourly) breaks, limiting cumulative time to fewer than 5 hours per day, and avoiding screens entirely when sleep-deprived or fatigued may also be helpful. Software settings on social media should be changed so that videos do not play automatically.

9.3 | Regulatory issues

To regulate material planned for public broadcast, it is necessary to measure the risk for provoking seizures. The following list indicates some resources for detecting and/or eliminating flashing stimuli that might provoke seizures. The Harding FPA additionally evaluates patterns.

1. Harding Flash and Pattern Analyzer (FPA): <http://www.hardingfpa.com/>
2. Photosensitive Epilepsy Analysis Tool (PEAT): <https://trace.umd.edu/peat/>
3. Baton (Interra systems): <https://www.interrasystems.com/>
4. Pulsar Automated Quality Control (Venera technologies) <https://www.veneratech.com/pulsar-automated-file-qc/#checks>
5. Photon Player: <https://devpost.com/software/photon-player-photosensitive-epileptic-seizure-prevention>
6. Flicker Check (Hitachi Solutions Limited): <https://www.hitachi-solutions.com/pdf/flickercheck.pdf>
7. TikTok <https://newsroom.tiktok.com/en-us/makin-g-tiktok-more-accessible-to-people-with-photosensitive-epilepsy>
8. Vidchecker (Telestream, LLC) <http://www.telestream.net/pdfs/user-guides/PQA-Picture-Quality-Analyzer-User-Manual-D00010028A.pdf>

Video streaming represents 68% of peak-time data traffic.²⁶¹ Test systems can detect potentially provocative patterns in streaming video in near real time. One analyzer accepts HDMI input from streaming media.²⁶¹ Flash luminance and saturated red are quantified. The software detects flashes with luminance changing at least 10% from the maximal luminance if occurring at frequencies of at least three per second. Luminance is also analyzed for each of three component colors: red, green, and blue. To trigger a warning, the display must occupy more than 10%

of the visual field, typically about one-fourth of the screen area at typical viewing distances.²⁶¹

Some countries, including the UK, Japan, Russia, and Italy,¹⁰ have implemented regulations to limit risks of broadcast material for provoking seizures. Guidelines that are employed in Britain and Japan include limits not only on light flash and colors, but on patterns. Striped patterns are restricted if they last more than 0.5 seconds, occupy at least 25% of the screen at typical viewing distances, and have luminance above 50 candela per meter squared.²⁶⁰ The Independent Television Committee guidelines in the UK prohibit flashes at greater than 3 Hz, brightness above 20 candela per square meter or red color flashes occupying more than 25% of the screen.¹⁴ These guidelines are predicted to protect at least two-thirds of people with pattern-sensitive seizures. In the UK, devices that flash in public are limited to frequencies no higher than 4 Hz, and they should not be visible from stairways.¹⁰ Frequency, brightness, binocularity, and large area are all key factors in contributing to seizure provocation. Frequency range susceptibility is individual, but according to Martins da Silva and Leal,¹³ 15-20 Hz flashes are most likely to provoke seizures.

A study in Japan²⁶² suggested that the broadcasting guidelines were effective in reducing the number of people who had a first seizure while watching television. Many measures that individuals and families can take serve to avoid provocative flashing lights and patterns and to prevent photosensitive seizures.²⁶³

10 | TECHNOLOGY TO REDUCE RISK

Reducing screen brightness and contrast can minimize seizure risk. A physical or downloadable electronic antiglare screen filter can help to reduce brightness. Using screens only in well-lit rooms can reduce contrast. Alternatively, viewers can wear dark lenses. Lenses that diminish brightness by 80% suppressed PPR in 77%.²⁶⁴ Some blue lenses are more effective than others.²⁶⁵ Cobalt blue lenses may be especially effective,²⁶⁴⁻²⁶⁶ because they filter out red light.¹⁹⁵ Polarized lenses, which block horizontally oscillating light waves while allowing vertically oscillating light waves to pass, can provide further protection. Dark lenses can offer protection, not only from screens but also from natural flicker and flash effects (light reflected off water or filtered through trees), environmental lighting (fireworks, strobe lights, malfunctioning fluorescent lighting, camera flashes, and so on), and high contrast patterns. However, dark lenses attenuate only about 50% of light, so may not be fully protective. Dark lenses should not be used while

driving at night, and blue lenses can make red stop lights more difficult to recognize even in daylight, thus presenting significant driving hazards. Covering one eye with a hand or patch can reduce seizure provocation when dark lenses are not available. Closing both eyes is generally not protective because bright light penetrates the eyelids and is diffused across the retina.

One strategy to forestall seizures would be a device positioned between the image generator and viewing screen that would monitor and selectively reduce the saturation of red and other potentially provocative colors by real-time filtering of provocative stimuli at the level of the user. Parra and colleagues showed that red-blue transitions were especially provocative, but that induction of PPRs could be reduced greatly by lowering the modulation depth (defined as the maximal minus the minimal luminance divided by the maximal luminance) without greatly affecting the spatial properties and visual content of imagery.²⁶⁷ Photosensitive EEG responses are attenuated with the modification. Nomura, Takahashi, and co-workers²⁶⁸ developed an adaptive temporal filter to reduce frame-to-frame flicker in TV, video, or computer displays. Testing in 11 photosensitive patients showed reduction of PPR. To date, these technological solutions have not come into wide use.

A group met in 1993 to provide a consensus view on video games and seizures after visually sensitive seizures were provoked in the UK.²⁶⁹ They concluded “There is no reasonable doubt that epileptic seizures may be precipitated by playing interactive computerized ‘video-games.’” Possible contributing factors were listed as: (1) flicker from the display; (2) photosensitive response to content; (3) seizures from cognitive triggers; (4) seizures precipitated by emotions during the game; (5) induced fatigue or sleep deprivation; and (6) chance seizures from coincidence. Of these factors, innate photosensitivity was considered to be the most important. Their recommended guidelines were: (1) Use a screen ≤ 12 inches, and if larger, view from a distance more than four times the screen diameter; (2) restrict playing time to < 1 hour per session; (3) with a history or family history of epilepsy, undergo EEG with photic stimulation before playing; and (4) make photosensitive people aware of the risks and supervise them during playing.

The recommendation for EEG in people at high risk is important, because about half of individuals with EEG photosensitivity are unaware of that trait.¹⁹ Most of the children who had seizures in the Pokémon incident were previously unaware of their tendency to seizures provoked by color flashes. Martins da Silva¹³ enumerated actions that viewers could take to minimize the chance of a seizure: occlude one eye; sit more than two meters from a screen; avoid flashing images and rapid color transitions;

and consider glasses to filter out red. The Epilepsy Foundation recommends that users also take breaks in playing or viewing. A more extensive list of nonpharmacological treatments for photosensitivity was provided by Verrotti.²¹

- Avoid potentially provocative stimuli: discotheques, flickering sunlight, flashing TV programs and video games, and striped patterns
- Use of a small TV, 12-inch set
- Use of a digital TV
- Use of a lamp beside the TV
- Use of a temporal optical filter
- Use of a remote control
- Respect critical distance of more than two meters from the screen
- Monocular occlusion in case of exposure to trigger stimuli
- Avoid stress, extreme fatigue, sleep deprivation
- Avoid prolonged videogames playing (more than one hour per session)
- Avoid playing videogames if suffering from lack of sleep
- Avoid playing videogames alone
- Use of glasses: dark, polarized, colored lenses

11 | THE PHOTOSENSITIVITY MODEL

Photosensitivity is a reflex form of epilepsy and therefore an important first “treatment” option is to determine whether a potential therapy can eliminate or attenuate a photosensitive response. The clear advantage of the photosensitivity model (PM) is real-time testing in epilepsy patients, as early as possible in drug development. Animal data and single-dose safety studies in healthy volunteers are sufficient to start investigating dose-dependent efficacy.

Application of testing in photosensitive individuals should be tailored to the patient’s environment, lifestyle, and personal characteristics; for example, teenagers are most visually sensitive. Insight into a person’s risks can be gathered during IPS testing in combination with a detailed clinical history. Testing should evaluate the individual flash frequencies at which a PPR occurs (see <https://www.ilae.org/files/ilaeGuideline/PhoticStimulation-2012-1528-1167.2011.03319.pdf> and the environment most likely to evoke seizures.¹²⁵ The tester should record the signs and symptoms during the PPR and whether the subject recognizes them as being typical. Generalized myoclonic movements are most common, which is helpful in recognizing potentially provocative stimuli in daily life.²⁷⁰

EEG can help in monitoring efficacy of ASM treatment in a particular patient and can predict relapse in seizures during ASM withdrawal. However, complete suppression of the PPR is not a prerequisite for medication efficacy.

Photic-provoked paroxysmal EEG discharges can provide a test ground for putative anti-seizure drugs²⁷¹. The widely used selective SV2A ligands, levetiracetam and brivaracetam, were developed in part because of their efficacy in the phase-II PM,^{272,273} where patients with known photosensitivity serve as test subjects. The photosensitivity frequency range and dose dependence are determined before and after exposure to a test drug, with hourly stimuli over the course of three days. Change in photosensitivity range after drug intake in relation to drug plasma levels gives then a pharmacodynamic/pharmacokinetic profile of the drug under investigation. EEG can help in monitoring efficacy of ASM treatment in a particular patient and predict relapse in seizures during ASM withdrawal. However, complete suppression of the PPR is not a prerequisite for medication efficacy.

Over time, drugs with different chemical structures and mechanisms of action have been tested in the PM. These include the histamine H3R antagonist pitolisant,²⁷⁴ partial benzodiazepine agonists,²⁷⁵ the AMPA/kainate receptor antagonist BGG492,²⁷⁶ Kv7 potassium channel activation with ICA-105665,²⁷⁷ carisbamate,²⁷⁸ the sulfamide JNJ-26489112²⁷⁹ and PF-06372865, a selective GABA potentiator.²⁸⁰ Cenobamate²⁸¹ is the most recently US Food and Drug Administration (FDA) approved ASM tested in photosensitive subjects. The PM can be tailored to the relevant questions, for example, efficacy against status epilepticus or seizure clusters, as shown in the comparative time to PPR abolition after intravenous infusion of levetiracetam and brivaracetam²⁸² or inhalation of alprazolam.²⁸³

12 | TREATMENT FOR LIGHT-INDUCED SEIZURES

Avoidance of provocative stimuli, such as flashing lights, moving patterns, or rapid color changes should be the first line of treatment for light-provoked seizures. Teachers, caregivers, and other responsible adults should be informed when a child is photosensitive and should understand the need for avoidance and prevention. Photosensitive epilepsy is a medical condition that should be documented in educational plans for affected children and schools should make relevant accommodations.

Covering one eye as soon as pre-seizure sensations are perceived can be helpful. Reduction of 50% of the visual input substantially reduces the risk of evoked seizures.²⁸⁴ Closing the eyes is not effective and can even be more provocative, because diffusion of the light increases

photosensitivity,²⁸⁵ as does the act of closing itself.¹²⁵ Dark glasses can reduce seizure risk in photosensitive individuals. Because red light can be especially provocative, blue-tinted glasses can be especially effective, although this should be confirmed in the EEG laboratory.²⁶⁴ Spectacles individually tinted for maximum clarity when viewing text can often relieve the discomfort associated with light sensitivity, and occasionally reduce seizures.²⁸⁶

Avoidance of provocative stimuli is not always possible and is becoming more difficult in modern society. Prophylaxis with ASM may be warranted in those with strong photosensitivity, seizure types that go easily unnoticed such as absence, or those who have tonic-clonic seizures.²⁸⁷ Sodium valproate is particularly effective for the control of photosensitive seizures²⁸⁸ but it has numerous side effects and its use is limited in those of childbearing potential.^{288,289} Levetiracetam, lamotrigine, lacosamide, vigabatrin (limited by potential retinal toxicity), and clobazam also have been recommended. Newer ASMs such as brivaracetam and cenobamate are good candidates as well but clinical experience is yet limited. Phenytoin and carbamazepine are not considered drugs of choice for photosensitive seizures.

Medication withdrawal should be performed cautiously; in some cases, PPR and related seizures return when a medication is tapered. EEG can help in predicting whether the patient is indeed in remission or still needs pharmacological treatment during the process of gradual withdrawal. The seizure-suppressive effect of ASM can last up to weeks after complete withdrawal.²⁹⁰

13 | CONCLUSIONS AND FUTURE NEEDS

Visually sensitive epilepsy is characterized by recurrent seizures provoked by light flashes, colors, or patterns. A marker for risk of having visually sensitive seizures is the photoparoxysmal response during EEG recording, represented as epileptiform discharges that spread beyond the occipital (visual) lobe. Light-induced seizures can be provoked most commonly by bright repetitive flashes, and less often by certain color changes and patterns. Little information is available on the medical dangers of 3D or VR imaging. Allowing for interpretive limitations produced by varying methodology and selection bias, the presence of a PPR ranges from 0.3% to 8% of the normal population and from 0.6% to 30% in patients with epilepsy.¹⁰⁶ About 15% of people with generalized epilepsy and 3% of those with focal epilepsy show photosensitivity. Provoked seizures can be in the form of tonic-clonic, myoclonic, absence and focal occipital or temporal seizures, or eyelid myoclonia.

Girls are more likely than boys to be photosensitive, but boys are more likely to play provocative videogames. Videogame-provoked seizures have been recognized since 1981. In Great Britain, the annual incidence of first seizures precipitated by videogames has been estimated at 1.5 per 100,000 among those 7- to 19-year-olds.¹²³ Black Africans are less likely than Caucasians to have visually sensitive seizures.¹¹³ The prognosis of visually sensitive seizures is fair but not great, with a 14%-37% probability of remission. Photosensitivity results from both genetic and environmental factors, but genetics are especially important. Photosensitivity runs in families, although of course not all have seizures. The likelihood of photosensitivity is especially high in families with both migraines and epilepsy. Several genes are known to be risk factors for photosensitivity; no one gene explains the condition.

Testing for response to light flashes is routine during ordinary EEG recordings and ideally done with eyes open, closed and with closure. Provocative flash frequencies vary from 3 to 60 per second, but 15–20 flashes per second are maximally provocative in most subjects. Mechanisms of photosensitivity are largely unknown. Changes in the excitability of occipital cortex and connected networks are important factors both in laboratory models and patients. Photic-provoked paroxysmal EEG discharges can provide a test model for putative antiepileptic drugs, called the photosensitivity model.

To regulate material planned for public broadcast, measuring the risk for provoking seizures is needed. Several tools are available, most prominently a Photosensitive Epilepsy Analysis Tool (PEAT) by the Trace Research and Development Center at the University of Wisconsin (now relocated to the University of Maryland), and the Harding Flash and Pattern Analyzer <http://www.hardingfpa.com/> from Cambridge Research Systems, Ltd, and the Baton <https://www.intersystems.com/>. Some countries, including the UK, Japan, Russia, and Italy, have implemented regulations to limit the risks of broadcast material for provoking seizures. Guidelines that are employed in Britain and Japan include limits not only on light flash and colors, but on patterns. Striped patterns are restricted if they last more than 0.5 seconds, occupy at least 25% of the screen at typical viewing distances, and have luminance above 50 candela per meter squared. The Independent Television Committee guidelines in the UK prohibit flashes above 3 Hz, brightness above 20 cd/m², or red color flashes occupying more than 25% of the screen. These guidelines are estimated to protect at least two-thirds of people with pattern-sensitive seizures. Reducing screen brightness can minimize seizure risk. Alternatively, the viewer can

wear dark lenses. Blue lenses may be especially effective, because they filter out red light.

ASMs are another method of protection from light-induced seizures. Sodium valproate is particularly effective, but its use should be limited to those without childbearing potential. Levetiracetam, lamotrigine, lacosamide, vigabatrin, clobazam, and newer ASM such as brivaracetam and cenobamate are good candidates as well. Choice of drug treatment is dependent on the type of seizure, since efficacy varies and some ASMs can occasionally worsen symptoms, for example, exacerbation of myoclonus by lamotrigine. Withdrawal of medication requires special attention because, in many cases, PPR and related seizures can easily return when medication is reduced. EEG can help predict whether the patient is indeed in remission or still needs pharmacological treatment during the process of gradual withdrawal.

A fundamental understanding of the pathophysiology of visual-sensitive seizures is still lacking, so preventive measures will remain empirical. In 2006, Kasteleijn-Nolst Trenite¹⁹ made recommendations (rephrased for brevity) that are still largely unmet (Table 3).

In the time since the 2005 Epilepsy Foundation-sponsored review,² three significant developments have affected the possibility of photic seizures from technology-generated visual stimuli in daily life. The first is greater ability to screen potentially provocative video material—either at the point of origin or the user screen. However, the use of this screening technology is voluntary in most countries. The second is the enormous proliferation and widespread use of interactive online media, resulting in frequent and prolonged exposure to images that may trigger seizures in visually sensitive people. The third is emergence of potentially provocative material presented on the web, or via 3D and virtual media.

The Photosensitivity Task Force of the Epilepsy Foundation of America continues to believe, as in 2005, that preventable seizures from visual stimuli are significant public health problems. Avoidance of provocative images and lighting by the public is not always possible. Despite some efforts by technology providers and platforms to protect consumers from potentially hazardous visual stimuli, safety in everyday life remains a challenge for visually sensitive individuals. Educational programs and protective policies are needed in the United States to substantially reduce the likelihood of light-induced seizures.

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TABLE 3 Unmet needs regarding light-induced seizure

- I. Epidemiological studies to better define:
 - a. prevalence of visual sensitivity
 - b. laboratory findings of light sensitivity
 - c. prevalence of a PPR in asymptomatic people
 - II. Epidemiological studies:
 - a. In different epilepsy syndromes and ethnic groups
 - b. long-term follow-up
 - c. methods to distinguish photosensitive occipital epilepsy from migraine
 - d. investigate those who only have a seizure during EEG investigation
 - III. Epidemiological studies:
 - a. Prognosis of myoclonic vs. absence visually sensitive epilepsy
 - b. Are those with video game-induced seizures a distinct population?
 - c. Of prognosis in those only with visually-induced seizures
 - d. Value of focal and asymmetrical EEG findings
 - e. Importance of visual priming
 - IV. Double-blind, placebo-controlled trials of ASMs in visual-sensitive patients
 - V. Pathophysiological studies: MRI, magnetoencephalography, genetic
- Standardize information gathering to facilitate studies.

Abbreviations: ASMs, antiseizure medications; EEG, electroencephalography; MRI, magnetic resonance imaging; PPR, photoparoxysmal response.

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Epiminder, Equilibre BioPharmaceuticals, Fortress Biotech, Greenwich Biosciences, GW Pharma, Janssen Pharmaceutica, Knopp Biosciences, LivaNova, Longboard Pharmaceuticals, Lundbeck, Marinus, Mend Neuroscience, Merck, NeuCyte, Inc., Neumirna Therapeutics, Neurocrine, Neuropace, Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Passage Bio, Praxis, PureTech LTY Inc., Redpin, Sage, SK Life Sciences, Sofinnova, Stoke, Supernus, Synergia Medical, Takeda, UCB Inc., West Therapeutic Development, Xenon, Xeris, Zogenix, and Zynerba. She has also received research support from the Epilepsy Study Consortium (Funded by Andrews Foundation, Eisai, Engage, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB, Vogelstein Foundation) Epilepsy Study Consortium/Epilepsy Foundation (Funded by UCB), GW/FACES, and NINDS. She is on the editorial board of *Lancet Neurology* and *Neurology Today*, and is Chief Medical/Innovation Officer for the Epilepsy Foundation. She has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Arvelle Therapeutics, Inc., Biogen, Cerevel, Engage, Lundbeck, NeuCyte, Inc., Otsuka, Sage, UCB, Xenon, Zogenix.

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Dr. Fisher wrote the sections on Jeavons syndrome and photomyoclonus, prepared the first and last draft of the manuscript, and coordinated the submissions of the co-authors for the various sections. Dr. Kasteleijn-Nolst Trenité performed the senior author role and edited the entire manuscript and wrote the sections on diagnosis and the photosensitivity model. Dr. Parisi wrote and revised part of the section relating to the "Differential diagnosis of photosensitivity" and "Headache and photosensitivity." He also participated in the review of the final manuscript draft approved by all the authors. Dr. Tolchin contributed to the sections on epidemiology and prognosis, techniques and technologies to minimize risk and treatment for light-induced seizures. Drs. Wilkins and Thio wrote the section on mechanisms and reviewed the entire manuscript. Dr. Wilkens wrote parts of the section on pattern-sensitive epilepsy. Ms. Solodar contributed to the Internet and Social Media section as well as the Conclusion and Future Needs section. Dr. French planned the manuscript and reviewed and edited the whole document. Drs. Baumer, Tolchin, and Acharya contributed to the section on sunflower syndrome. Dr. Baumer updated and revised the epidemiology and genetics sections. Dr. Szaflarski revised the section on brain imaging. He also participated in the review of the final manuscript draft approved by all the authors.

GUIDELINE AFFIRMATION

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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