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Review

Photosensitivity and epilepsy: Current concepts and perspectives—A narrative review

A. Martins da Silva[a,b,c,*], Bárbara Leal[b,c]

[a] Serviço de Neurofisiologia, Hospital Santo António/Centro Hospitalar do Porto, Porto, Portugal
[b] Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal
[c] UMIB/ICBAS, Universidade do Porto, Porto, Portugal

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ABSTRACT

The authors review the influence of photic stimuli on the generation of epileptic seizures, addressing the first descriptions of the phenomenon and its subsequent exploration. Initially defined in the 1950's, links between intermittent photic stimulation (IPS) and seizures were well understood by the 1970. Since then the increasing exposure to photic stimuli associated with modern life (for instance through TVs, patterns, computer games and electronic instruments with flickering displays) has led to an increased interest in this issue. Diverse stimulation procedures have been described and difference in the effects of stimulation frequencies and types, colour and lighting have been recognised. Approximately 5% of patients with epilepsy have photosensitive epilepsy (PSE). PSE is commoner in younger individuals, more frequent in women, often time-limited, generally easy to treat and closely related to generalised epilepsies, especially Juvenile Myoclonic Epilepsy (JME).

Structural and functional studies of PSE indicate abnormalities beyond the frontal lobes and evidence for the role of the visual cortex in human PSE. A reduction in connectivity between prefrontal and frontopolar regions and increased connectivity between occipital cortex and the supplementary motor area may be the basis for triggering motor seizures in JME. Due to the changes observed in such areas, it is hypothesised that photoparoxysmal responses (PPR) could be a final expression of pathogenic phenomena in the striato-thalamocortical system, and possibly a core feature of JME as system epilepsy. The familial transmission of epileptiform responses to IPS is well-recognised, but no clear relation between PSE and specific genes has emerged. Although the influence of ethnic factors on PSE has been widely studied, clear conclusions are still lacking. Pharmacological therapeutic approaches are beyond the scope of this review although preventive measures allowing patients to avoid PS seizure initiation and/or generalisation are discussed. Given the gender/age group most commonly affected by PSE, the risks and benefits of drug treatment need to be carefully weighed up.

1. Introduction

The effect of photic stimulation on the Electroencephalogram (EEG) was first described by Adrian and Matthews, in 1934, when studying the Berger Rhythm [1], and was subsequently assumed to be related to epilepsy. This view is reflected in statements such as: "the Electroencephalogram (EEG) had demonstrated that precipitation of seizures by light is not a purely emotional phenomenon"; or "closing the eyes brings out the heightened Berger rhythm in the occipital leads"; or even "this also may precipitate a petit mal (3/sec SW)" and "brain waves could be driven to a different rate by rhythmic photic stimulation" [2]. The possibility that intermittent photic stimulation precipitates seizures was recognised by Cobb in 1947 who recalled Monrad Krohn's suggestion that "attacks could be induced by voluntary hypernictitation (blinking) for 10 or 20 minutes" and who reported three cases in whom minor attacks had followed exposure to flickering lights [3]. More than 80 years have passed since these classical studies were published. In the interval, many studies have explored the relation between photosensitivity and epilepsy. A pivotal contribution to the characterization of epileptic discharges induced by Intermittent Photic (or Light) Stimulation (IPS or ILS) and their relation to epilepsy was made by Bickford et al., in 1952 [4]. From that point forward photo-convulsive (PCR) and photo-myoclonic (PMR) responses to IPS have been viewed as distinct entities. Rather than PMR in which

* Corresponding author.
E-mail address: ams@icbas.up.pt (A. Martins da Silva).

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the myoclonic response is stimulus-locked, PCR is characterised by repetitive bilateral discharges continuing after stimulus cessation [4] that can easily evolve to overt epileptic seizures [4,5]. During the 1950s and 1960s, two developments initiated a new era of research in this field. One was the pioneer work of Jeavons and collaborators [6] that allowed a better understanding of the brain structures and responses – physiologic or epileptiform – involved in photic sensitivity. The other was the increasing and worldwide spread use of devices emitting intermittent light being capable of elicit epileptiform activity in the brain and induce epileptic seizures (including TVs, fluorescently lit advertisements, and later specific patterns in print media or computer games).

This review, covers the natural history and interplay between epilepsies and photosensitivity. We discuss epidemiological aspects, human and animal models, functional or structural brain changes, the genetics of epilepsies associated with photosensitivity, gender or ethnic influences, stimulus characteristics and procedures to study photosensitivity. Although therapeutic approaches are not a particular focus of this review, we will comment on the role and effectiveness of protective measures.

2. Natural history of epilepsies with photosensitivity

Photosensitivity typically manifests around the time of puberty and may disappear during the third decade of life. This relation between age and photosensitivity has been consistently replicated since it was initially observed in the studies of Jeavons' group. These authors thought of Photosensitive Epilepsy (PSE) as a temporary, time-limited condition which would disappear in the third decade of life in 2/3 of valproate- treated patients and in over 50% of the remaining untreated patients [7]. However, recent studies have demonstrated that this can be more complicated since the prognosis of photosensitivity differs among patients with a family history of PSE compared with those without family history [8]. In patients with a family history PSE is not a temporary, age-dependent condition. Additionally, absences triggered by photosensitivity have been shown not to remit [9].

2.1. IPS and generalized epilepsies

Wolf and Goosses characterised PSE as an age-related disorder, more frequent in females, and closely related to Juvenile Myoclonic Epilepsy (JME) [10]. This idea was supported by the finding of generalised polyspike wave discharges and the common precipitation of myoclonic seizures by IPS. These authors reported that versive seizures with visual hallucinations were the only focal seizure type related to photosensitivity. They also considered that "no correlation with photosensitivity could be demonstrated in juvenile absence epilepsy and this has to be contrasted with JME which had the highest rate of photosensitivity of all epileptic syndromes". Curiously, both syndromes manifest at approximately the same age. The hypothesis underlying such difference is that "photosensitivity is a pathoplastic factor and that the presence or absence of photosensitivity could be decisive for the seizure type that develops". The authors aditionally noted that "the female preponderance in both childhood absences and photosensitivity could be due to the same unknown factor". The association between photosensitivity (PS) and JME was also described by Appleton et al., in a significantly more noteworthy extent of patients: 61% of JME children exhibited PS with routine IPS. This proportion increased to 90% of children if IPS was extended to a maximum of 5 minutes. Based on these observations, they concluded that the EEG ought to incorporate IPS for up to five minutes when a JME diagnosis is considered [11].

Photosensitivity is very common in younger patients with progressive myoclonus epilepsies (up to 90%) and is frequently associated with other phenotypic features such as psychomotor delay or pathologic brain MRI findings [12]. For example, in Dravet Syndrome, Photoparoxysmal Response (PPR) is seen in about 40% of patients, and is clearly identifiable from the first two years of life without female predominance. In these patients, PPR is unequivocally associated with disease severity [13].

One epileptic syndrome related to photosensitivity that has not yet been adequately classified is Jeavons Syndrome (JS). JS is characterised by eyelid myoclonus (EM), eye closure-induced seizures/EEG paroxysms, and photosensitivity. JS is a distinctive myoclonic epileptic syndrome with myoclonus constrained to the eyelids which may be followed by an absence [14,15]. Distinct EEG patterns have been observed in this syndrome: (1) focal interictal epileptiform discharges (EDs) from posterior regions; and (2) predominantly focal posterior ictal EDs preceding generalised EDs. Further studies of seizures induced by eye closure, photic stimulation, and hyperventilation and the EEG changes associated with these seizures could help us gain a better understanding of the role of the occipital cortex in initiating the generalised epilepsy network involving brainstem, thalamo-cortical and transcortical pathways in JS [16]. Vaudano et al. studied a cohort of 15 patients with EM Absences (EMA/JS) at eye closure, using EEG-correlated functional magnetic resonance imaging (fMRI) and voxel-based morphometry (VBM) [17]. Patients were studied in two conditions: eyes open and eyes closed. Spontaneous blinking, and eye closure-triggered spike and wave (SW) discharges were noted. The findings were compared with those in a group of 14 IGE patients without eye closure sensitivity and with a group of 16 healthy controls. In the EMA/JS group, the authors found "higher blood oxygen level dependent (BOLD) signal related to eye closure over the visual cortex, the posterior thalamus, and the network implicated in motor control of eye closure, saccades, and eye pursuit movements; and increments in the grey matter concentration at the visual cortex, thalamic pulvinar, whereas decrements were observed at the bilateral frontal eye field areas". These results demonstrated changes in anatomo-functional properties of the visual system in EMA [17].

2.2. IPS, initial symptoms and focal seizures

Moderating the idea that PSE is closely related to generalised epilepsies, many authors have described the IPS-induced elicitation of symptoms in patients with partial (focal) seizures. Hennessy and Binnie recognised such symptoms in a cohort of patients investigated with IPS and/or reporting seizures triggered by environmental visual stimuli such as television (TV) screens or computer monitors [18]. About two-thirds of patients described initially maintained awareness in their visually precipitated seizures, which sometimes evolved into events associated with confusion or into a secondarily generalised seizure. Initial symptoms were usually visual and positive – coloured circles or spots – but blindness and subjective symptoms as "eyes going funny" were additionally described. Other symptoms, such as nonspecific cephalic sensations, dejà-vu, auditory hallucinations, nausea, and vomiting were also observed. None of the patients clearly, reported spontaneous partial seizures resembling the ictal phenomenology of the visually induced attacks. The authors concluded that "physiological studies indicate that the trigger mechanism for human photosensitivity involves binocularly innervated cells located in the visual cortex (the seat of the primary epileptogenic process)", and that the "photically triggered discharges and seizures may be regarded as partial with secondary generalisation" [18]. Gungor-Tuncer et al. drawn similar conclusions [19]. This group studied aura phenomena among a large cohort of IGE patients with JME, eyelid myoclonus with absences (EMA) and juvenile absence. They found 6.3% of patients reporting

visual auras: flashing lights, macropsia, illusional movements, and blindness. They recognised that "eyelid myoclonus with absences was significantly more common in the IGE-group with visual aura, and photosensitivity was found significantly more common in IGE patients with visual aura (90% vs. 46% of the total IGE patients)". They concluded that "visual auras do not exclude a diagnosis of IGE" [19]. Gungor-Tuncer et al. described elementary visual ictal hallucinations in IGEs as stereotypic, brightly coloured, and as circles or balls exhibiting rotatory movements. They concluded that the differentiation between IGE and idiopathic occipital lobe epilepsies causing visual symptoms requires the combination of clinical features with EEG analysis [19]. These observations were also supported by the study of Taylor et al. [20]. These authors studied a group of patients with IGE and Idiopathic Photosensitive Occipital Epilepsy (IPOE) – a focal epilepsy with colourful elementary visual auras. They stated that "visual aura and conscious head version are under-recognized features of JME, particularly among photosensitive patients" [20]. Unfortunately, the pathophysiology or the genetic basis of common clinical phenomena associated with IGE as well as idiopathic occipital lobe epilepsy – including photosensitivity and headache – are still poorly understood [21]. Finally, a PPR can also occur, albeit rarely, in patients with pure temporal lobe epilepsy and be associated with other features of focal temporal lobe seizures [22].

2.3. Epidemiological aspects

In a case-control study of Kasteleijn-Nolst Trenité, PPR-positive patients were prospectively identified between 1980–1983 regardless of age or reason for referral [22]. Only generalised PPRs outlasting the stimulus duration were considered (Bickford criteria). Of all patients referred to the epilepsy clinic, 5.6% were found to be PPR positive. Of those aged 10-20 years PPR was positive in 7.3%. Sixty-three per cent of the PPR-positive patients had a history of visually and/or self-induced seizures compared to 2.3% of those found to be PPR-negative [23]. Doose and Waltz studied photosensitivity in a different way: 1) The photic stimulation included a wider definition of the EEG pattern of photosensitivity with responses of lower expression (Type 1, 2 and 3 of Waltz); 2) Their sampling included not only patients with generalised PPRs but also patients with PPRs Type 1, 2 and 3 of Waltz [24] and 3) The study cohort comprised 662 healthy children aged 1–16 years [25]. With such approach the authors found a PPR average incidence rate of 7.6% in healthy children being girls more commonly affected. Considering the occurrence of PPRs in epileptics and in healthy children as well as the incidence of epilepsy up to the age of 20 years the authors calculated that "only 3% of the children with PPRs of the given wider definition will manifest epilepsy up to the age of 20 years" [25].

Harding et al., refer to PSE as occurring in approximately 1 in 4,000 of the population [26,27]. They stated that the incidence is 1.1 per 100,000 per annum, five times higher in the 7–19 year age group. Onset is typically around the time of puberty. They reported that less than 25% of the patients lose their photosensitivity in their twenties. PSE is twice as common in females as in males. "Photosensitivity is most commonly elicited by a stimulus frequency between 15 and 20 flashes/sec, namely if IPS is binocular, in the centre of the visual field. It is more likely to be demonstrated if a pattern is present in the stimulus. Forty-nine % of patients are sensitive to 50 flashes/s, explaining the reaction to TV images" [26,27].

In a national prospective study covering about 90% of all EEGs performed throughout Great Britain in a period of 3 months (May 24th-August 23rd, 1993) Quirk et al., studied the incidence of PSE in "any new patient who presented for EEG following one or more recognised seizures" and that have PPRs [28]. The incidence of epilepsy cases with generalised discharges (PPR Type 4 of Waltz et al. [24]) was 2% of the global group, reaching 10% of patients between 7-19 years old [28].

During an extended follow-up of PSE patients, Radhakrishnan et al. found that generalised epileptiform discharges were elicited with standard patterns in two-thirds of patients, and restricted to the posterior head region in one-third [29]. In this cohort, TV images were the most commonly reported precipitant factor (41%). In 39.7% of the patients a clear history of one or more seizures precipitated by viewing environmental patterns such as "window screens, garments, tablecloths or ceiling tiles" was recorded. Other patients admitted that they preferred to avoid looking at patterned objects because this made them feel uncomfortable. The authors concluded that pattern sensitive epilepsy is a distinguishable subtype of PSE in which the excitable regions within the visual cortex concerned with different attributes of observed objects or patterns determine susceptibility to a specific trigger and result in an electro clinical response [29]. The long-term outcome of patients with pattern-sensitive epilepsy was analysed by Brinciotti et al. [30]. Generalised seizures were the most common type of spontaneous seizures (60%) whereas reflex seizures were more frequently partial (74%) [30]. At the end of follow-up, 80% of the patients had been seizure-free for more than two years [30]. The long-term outcome of patients with pattern-sensitive epilepsy indicates a good prognosis with a favourable course for both spontaneous and reflex seizures.

Finally, eye closure sensitivity (ECS), a condition that is frequently associated (45%) or overlaps with photosensitivity, is independent of photosensitivity and may be seen in different epilepsy syndromes including idiopathic occipital epilepsy. There is a clear female preponderance (73%) [31]. A good approach to understand the relevance of elicited epileptiform events was proposed by Harding and Fylan [32]. They investigated the relationship between PPRs and occipital spikes (OSs) finding that PPRs but not OSs show linear contrast dependency, elicited by stationary stimuli and by non-colour-opponent isoluminant stimuli. PPRs and OSs are generated independently by the parvocellular and magnocellular visual systems, supporting the hypothesis that only PPRs are clinically relevant [32].

In summary,

Photosensitive Epilepsy (PE) is mostly an age-related, time-limited condition, more frequent in females and closely related to JME. However, there is also a close association between PSE and focal (partial) seizures, namely those involving the visual cortex. Auras are more commonly described by patients with idiopathic partial epilepsies involving the visual cortex origin but are also a recognised feature of JME in photosensitive patients.

3. Animal models

Studies in the primate Baboon Papio Papio (B P-P) and Fayoumi Photosensitive Chickens (FPC), improved our knowledge of the anatomical and functional structures and the genetic basis of photosensitivity and epilepsy. The most consistent findings are derived from Baboon studies. The change in the sunlight brightness caused by leaf trees oscillations is recognised to induce myoclonic jerks in the B P-P, leading to its fall from trees (AMdS, Personal Observations).

Changes in brain function have been reported after stimulation of the visual cortex by IPS and when seizures were induced by kindling [33] or by using IPS at low frequencies [34]. Other studies reported an association between myoclonic responses elicited immediately after cessation of the stimuli, and occurrence of generalised seizures. These results indicate that IPS facilitates seizure development at all stages of kindling of the visual cortex. Menini and Naquet analysed the myoclonic types induced by IPS in

the Baboon P-P [35]. They described three types with different aetiologies: A, B and C. Type A has an epileptic nature and it is due to a dysfunction of the GABAergic system. The dysfunction is bilateral and synchronous, originates in the fronto-rolandic cortex and is always preceded by spike and waves. Initially, it involves the eyelids and face and can secondarily generalise to tonic-clonic seizures. Type B originates in the lower brainstem (ponto-bulbar reticular formation) and may be caused by a cerebellar lesion. It never generalises and is not associated with paroxysms or epileptic seizures. Type B is non-epileptic. Type C has a variable symptomatology associated with spike-waves during slow-wave-sleep. It has its origin in the lower brainstem and can involve the cortex and be accompanied by spike-waves. Different types of myoclonus can co-exist in the same photosensitive animal.

The group of Szabó et al. studied changes in cerebral blood flow (CBF) induced by IPS in baboons. They used PET images co-registered with MRI to analyse the occipital and motor cortices. According to the authors "the PS animals showed strongest IPS activation in the right anterior cingulate and medial orbital gyri, amygdala, globus pallidum, and left inferior and superior temporal gyri suggesting the involvement of specific cortico-subcortical networks in photosensitivity". They also revealed that "a striking finding was the absence of occipital and variable motor cortex activation in the PS animals" [36]. Moreover, the "decreased activation on specific sulci reflects anatomical markers for potential generators or cortical nodes of the networks underlying spontaneous seizures and photosensitivity in the baboon" [37]. When CBF responses co-registered with MRI during ILS were studied, there was evidence of increased interhemispheric connectivity and bidirectional feedback loops in the PS baboons representing electrophysiological synchronisation associated with the generation of epileptic discharges [38]. In another study, the same group found significant increases in gray matter concentration (GMC) in the frontopolar, orbitofrontal and temporal antero-lateral cortices of animals with seizures or IED induced by IPS. In the photosensitive group of B-PP they also found a major decrease in the right primary visual cortices and in the reticular, anterior and medial dorsal nuclei of the thalamus. The authors considered that such results may indicate a combination of developmental and acquired structural changes in the epileptic baboon [39].

In summary:

Differences in cortical volumes were found in animals with PSE. Grey matter concentration decreases in thalamic and occipital cortices, and increases in the anterior frontal and temporal lobes have been observed, suggesting that abnormalities extend beyond the limits of the frontal lobes, advocating a role of the visual cortex in PSE.

4. Changes in function and brain structures in human PSE

The functional brain changes underlying PPR have been studied using EEG and MEG, fMRI and TMS, regional cerebral blood flow measures (RBF) and PET. Structural and metabolic changes have been identified using MRI techniques including MR spectroscopy (MRS).

Mukundan et al. studied the spatiotemporal distribution of photic driving (PDR), photoparoxysmal (PPR), and photoconvulsive (PCR) responses by EEG with implanted depth electrodes during presurgical assessment of a patient with generalised photosensitivity and right frontal lobe cortical dysplasia [40]. These authors classified cortical responses to ILS as Photic Driving (PDRs), Photoparoxysmal (PPRs), and Photoconvulsive (PCRs) responses. "PDRs were restricted to the occipital lobe at ILS frequencies below 9 Hz, spreading to the parietal and central regions at ILS >9 Hz. PPRs were characterised by activation of multifocal discharges in the parieto-occipital, posterior cingulate, and medial prefrontal cortices. The prominent parietal activation during PPRs reflects the cortical synchronisation found in MEG and fMRI studies. Photoconvulsive responses (PCRs) were characterised by either a bilateral upper extremity myoclonus lasting throughout the stimulus associated with activation of the motor cortices (Type 1) or a brief generalised myoclonic seizure related to a frontally-predominant generalised ictal discharge extensively involving the premotor cortices (Type 2). Regional posterior-to-anterior propagation was noted in the Type 1 PCR, from the parietal lobe cortices to the motor and premotor cortices. The Type 2 PCR did not demonstrate a similar cortico-cortical propagation; rather, the emergence of a generalised spike-and-wave discharge suggests activation of a cortical–subcortical network, albeit with a lead from the posterior cingulate region and after medial parietal spiking. Generalised IEDs were also generated in the setting of PPRs". These authors concluded that both types of PCRs could occur during the same stimulus but could involve different cortical areas, suggesting activation of distinct cortico-cortical or cortical–subcortical networks. Regardless of the pathway, PCRs only occurred when PDRs involved the medial parietal cortices. Furthermore, spiking during ILS was first noted in occipital and parietal regions before the sensorimotor cortices and frontal lobes, contradicting the pervasive view that photo epileptic responses are generated fronto centrally [40].

In idiopathic PSE patients Parra et al. described "an enhancement of phase synchrony in the MEG gamma-band (30–120 Hz), harmonically related to the frequency of stimulation preceding the development of the PPRs, and also on the genesis of uncomfortable visual illusions, and different from those not followed by PPR in controls" [41]. This finding could be related to the pathological deviation of normal synchronisation of gamma oscillations (as is normal in the generation of processes of perception) mediating the epileptic transition in PSE [41]. Later, in a review of the mechanisms of photosensitivity and visually induced seizures, the same group focussed especially on the "presence of two different mechanisms underlying PSE: one dependent on luminance changes and the other dependent on wavelength. Both mechanisms can coincide in the same individual, although one may be dominant" [42]. The "enhancement in gamma frequency preceding the development of a paroxysmal response as well as underlying uncomfortable visual illusions" suggest "that a loss of control over high-frequency oscillatory processes may be involved in the genesis of both types of phenomenon" [42].

Differences in cortex volumes have been assessed by MRI – magnetic resonance, voxel-based morphometry (VBM). When compared with JME-NPS, a reduced left hippocampus and left inferior frontal gyrus volume was observed among patients with JME-PS [43]. "Structural abnormalities are beyond the limits of the frontal lobes and evidence for the role of the visual cortex in human PS, reinforcing the existence of functional-anatomic ictiogenic networks in JME, in line with the concept of 'system epilepsies'" [43].

In JME, the dynamic evaluation of BOLD (blood oxygen level dependent) signal changes related to PPR revealed an early positive response in the putamen and primary sensorimotor cortex (SM1), followed by BOLD signal decrements in the putamen, caudate nuclei, thalami, and SM1. In JME patients interaction between the motor circuit and other neuronal networks may be altered, with prominent involvement of basal ganglia circuitry. PPR could be "a final expression of pathogenic phenomena occurring in the striato-thalamo cortical system, possibly a core feature of JME as a system epilepsy" [44]. Studies of structural changes assessed by diffusion MRI also showed PPR associated with subcortical micro structural changes in precentral, parietal, and occipital regions. The coexistence of PPR and IGE seems related to white matter abnormalities in the thalamus and precuneus [45,46]. These findings highlight

the pivotal role of the thalamus in the pathophysiology of primary generalised seizures and suggest that thalamo-premotor connections are both an essential part of epileptic networks and important in the pathogenesis of photosensitivity [42]. In JME patients a positive correlation between diffusion tensor imaging DTI and fMRI-based measures of structural and functional connectivity was observed. This connectivity was reduced between prefrontal and fronto-polar regions and increased between the occipital cortex and the Supplementary Motor Area (SMA). Such alterations were interpreted as the anatomic basis for cognitive triggering of motor seizures in JME [47]. Metabolic differences (MRI studies) in photosensitive and non-photosensitive IGE patients demonstrate the asymmetrical neuronal dysfunction of the dominant occipital cortex and thalamus in photosensitive IGE patients. Also, Moeller et al., combining EEG and fMR, studied a photosensitive patient in whom a PPR was followed by a generalised tonic-clonic seizure [48]. The elicited PPR was associated with increases in BOLD signal in the visual cortex, thalamus and both superior colliculi and a decrease of the same signal in the frontoparietal areas [48]. The same group later reported the results of fMRI/EEG examinations in six patients with reproducible generalised PPRs (Type 4). They found activation of the parietal cortex in five patients and of the premotor cortex in all of them. "The maximum of BOLD signal increase related to PPR was found in the parietal cortex adjacent to intraparietal sulcus in 4 and in the frontal cortex in two subjects. The standard analysis revealed a deactivation of areas activated by using the early regressor and also deactivation of the caudate nucleus in two subject and changes in thalamus in one" [49].

Comparative MRI studies revealed an increased bilateral thickness in the occipital, frontal and parietal cortices in PPR-positive-subjects in comparison to healthy controls and a significant decrease in the temporal cortex. IGE patients exhibited lower bilateral cortical thickness in the temporal lobe and the right paracentral region in comparison to PPR-positive-subjects. These functional and structural changes were associated with PPR. Additionally, patients with epilepsy had changes in the temporal lobe and the SMA [50]. Finally, PET-rCBF studies have revealed an involvement of the hypothalamus in PSE and a modulator function of the caudate nucleus by inhibiting epileptic discharges during IPS in PSE patients [51].

Interesting observations about the relationship with IPS have also been made using transcranial magnetic stimulation (TMS). Prior stimulation of PS patients with IPS shortens the cortical silent period (CSP) elicited by TMS over the primary motor hand area (M1)(HAND). This response is absent in healthy individuals with a photoparoxysmal response (PPR). TMS studies exploring physiological connections between primary visual (V1) and motor (M1) areas revealed that IGE patients with PPR 'have an overactive functional response of M1 to inputs travelling from V1 which could be a fundamental factor for the anterior spread of the PPR itself and for the origin of the abnormal epileptic motor phenomenon' [52]. Resting motor threshold (rMT) and phosphene threshold (PT) were compared in IGE patients (with and without photosensitivity) and healthy controls. The marked decrease in PT and the high phosphene prevalence in IGE patients with photosensitivity indicate a regional hyperexcitability of the primary visual cortex. This evidence suggests that PT can be a biomarker for excitability in patients with IGE and photosensitivity [52]. Finally, a few studies have addressed anatomical and functional changes in optical structures in patients with PSE, but so far no consistent conclusions can be drawn from this work.

In summary:

PSE have an interhemispheric posterior cingulate onset, sparing the sensorimotor cortices. IPS-induced discharges are restricted to the occipital lobe at low ILS frequencies, spreading to the parietal and central regions at higher frequencies giving origin to other types of responses. Both types of responses can occur during the same stimulus. PCR can occur when discharges spread to the parietal cortices, structures that are critical to their generation. Functional changes related to paroxysmal responses are associated with increased cortical thickness in the occipital, frontal and parietal cortices and atrophy in the temporal lobes. The reduction in connectivity between prefrontal and frontopolar regions and the increase between the occipital cortex and the supplementary motor area may be the basis for triggering motor seizures in JME. The prominent involvement of basal ganglia circuitry associated with subcortical microstructural and metabolic changes in precentral, parietal, and occipital regions reinforce the existence of functional-anatomic ictiogenic networks in JME. PPR may be a final expression of a pathogenic phenomenon occurring in the striato-thalamocortical system. PPR may be a core feature of JME as a system epilepsy, in the way that JME patients have a specific susceptibility system prone to generate seizures also in the interictal period [53].

5. Genetic approaches

In his discussion of genetic studies in photosensitive epilepsy, Wolf noted that the key syndrome of IGEs is juvenile myoclonic epilepsy (JME), in which more than half of the patients present reflex epileptic traits (photosensitivity, eye closure sensitivity, praxis induction, and language-induced orofacial reflex myoclonic) [54]. Multimodal investigations of cerebral function indicate that "ictiogenic mechanisms in IGEs largely (ab)use pre-existing functional anatomic networks (CNS subsystems) normally serving highly complex physiological functions (e.g., deliberate complex actions and linguistic communication) which supports the concept of system epilepsy".

A review by Italiano et al. [55], argued that there was evidence for an autosomal dominant inheritance with reduced penetrance in families with photosensitivity. Molecular studies in patients with PPR identified putative susceptibility loci on Chromosomes 6, 7, 13 and 16. No specific mutations were identified in the animal model B – PP although a mutation in synaptic vesicle glycoprotein 2A was found in FPC. These authors concluded that the heterogeneity of reflex seizures and epilepsies remains poorly understood with no major causative genes identified so far [55],

Waltz et al. studied the different phenotypes of induced PPR in photosensitive patients and grouped them into four types (1 to 4): type 1 – spikes within the occipital rhythm; type 2 – parieto – occipital spikes with a biphasic slow wave; type 3 – parieto – occipital spikes with a biphasic slow wave and spread to the frontal region; type 4 – generalized spikes and waves or polyspikes and waves. Studying the genetic basis of such patterns, the authors emphasised the link between PSE and EEG abnormalities considering that "PPR patterns represent different expressions of the same genetically determined trait and that the EEG abnormalities are the best predictor of the seizure risk in probands' siblings" [24]. In another study from the same group Waltz and Stephani [56] investigated the mode of inheritance of the photoparoxysmal response (PPR) and the seizure risk in siblings of epilepsy patients in families with one photosensitive parent (Group 1) and with a photosensitive proband without photosensitive parents (Group 2) [56]. At the age of maximum penetrance, 50% of the siblings in G1 were photosensitive, compared to only 15% in G2. Siblings in G1 showed a higher seizure rate (19%). The higher seizure risk in photosensitive siblings of G1 indicates that a PPR in parents is a major determinant of PPR in the offspring (autosomal-dominant transmission with age) [56].

Tauer et al. performed a genome-wide linkage scan to map susceptibility loci for PPR and to explore their genetic relationship

with IGE [57]. The study included families with at least two siblings displaying PPR: families with predominantly pure PPR and photosensitive seizures (PPR-families) and families in which PPR was strongly associated with IGE (PPR/IGE-families). Two PPR-related susceptibility loci were described, depending on the familial background of IGE. The locus on 6p21.2 seems to predispose to PPR itself, whereas the locus on 13q31.3 also confers susceptibility to IGE [57].

Due to the strong neurobiological association of JME and PPR, Lorenz et al. suggested that PPR and JME share epileptogenic pathways, for which BRD2 might be an underlying susceptibility gene [58]. Pinto et al. mapped two susceptibility loci for epilepsy-related photosensitivity to regions 7q32(PPR1) and 16p13 (PPR2) in PPR families with a prominent background of myoclonic seizures (MS-related PPR) [59]. To follow-up these results and evaluate interaction effects between these regions, they conducted two-locus (2L) linkage analyses. The results suggest that the genes underlying the PPR1 and PPR2 susceptibility loci may have similar functions or act in the same biochemical pathway [59]. Dibbens et al. screened NEDD4-2 for mutations in a large cohort of families with IGEs and PPR. They identified three NEDD4-2 missense mutations in highly conserved residues: S233L, E271A and H515P [60]. This data raised the possibility that PSE may arise from a defective interaction of NEDD4-2 with an, as yet, unidentified accessory or target protein [60].

Interesting findings emerged from the study of de Kovel's et al. [61]. These authors performed a mega-analysis of 100 families with photosensitive epilepsy [61]. Using non-parametric linkage analysis, the authors identified three suggestive peaks for photosensitivity – one previously confirmed (16p13.3) and two described for the first time (5q35.3 and 8q21.13) [61]. They found no evidence of linkage at four previously detected loci (6p21, 7q32, 13q13 and 13q31). They conclude that family studies support the described role of PPR as a risk factor for IGE and that different family datasets are not linked to a shared locus. Distinct loci seem to be linked to subsets of PPR-positive families that may differ in terms of clinical phenotypes or geographic origin [61].

For Taylor et al. the genetics of the idiopathic photosensitive epilepsies exhibit a phenotypic spectrum from generalised epilepsies (GGE) to idiopathic photosensitive occipital epilepsy (IPOE), with overlap between the focal features of IPOE and all the GGE syndromes [62]. The authors claim that shared genetic determinants are likely to contribute to the complex inheritance pattern of photosensitivity, IPOE, and GGEs.

Finally, Galizia et al. compared the data from individuals with epilepsy; either with photosensitive seizures or abnormal PPR, or both, and individuals with PPR but without seizures [63].The CHD2 mutation was the first identified cause of the archetypal generalised photosensitive epilepsy syndrome, eyelid myoclonus with absences. Unique CHD2 variants were also associated with photosensitivity in common epilepsies.

In summary:

Photosensitive siblings have a higher seizure risk, indicating that PPR in parents is a major determinant of PPR in the offspring (autosomal-dominant transmission); however, the heterogeneity of the genetic background of photic epilepsies remains poorly understood, as no major causative gene has been identified in humans so far. Nevertheless, mega-analysis shows distinct loci in subsets of PPR families differing in terms of phenotype and geographic origin.

6. Gender and ethnic influence

Several studies have found a predominance of photosensitivity in females and, in some cases, a female/male ratio of up to 3:1 [8]. In an extensive study, Radhakrishnan et al. found that 59% of patients with different visual pattern sensitive epilepsies were females [29]. Taylor et al. emphasise that the striking female predominance must be taken into account in the exploration of the genetic basis of photosensitivity [20].

Population studies have endeavoured to answer the question whether there are differences in the incidence and prevalence of photosensitivity in populations of different ethnicity. Aziz et al. studied photosensitivity in a large cohort of Asian individuals with epilepsy[64]. Among these individuals, 3.9% were found to have some form of PSE, and a family history of PSE was observed in 14.1% of cases. In another Asian population, Shiraishi et al. showed that 1.7% of individuals in different age groups and with different types of epilepsies and epileptic syndromes had PPR [65]. Lower frequencies were also found by Sallem et al. in a further Asian population [66]: about 6 per thousand individuals had PSE, and a similar number had PPR. In black Africans, Danesi and Oni found 2.76% with PSE and 1.6% with PPR [67]. De Graaf et al. studied the influence of ethnic and geographic factors on the classic PPR in 128 patients from South Africa with "chronic epilepsy" from three different ethnic groups: whites, mixed race and black individuals in a proportion reflecting the unequal distribution of these ethnic groups in the region [68]. They found "higher classic PPR in whites than in blacks or mixed race (2.7 *vs.* 0.1 and 0.9%)" [68]. Differences were particularly noted when the age ranges were restricted to 6-15 and 15-25 years. In the group of 6-15 years, 4.4% of white males, 7.3% of white females, 0.6% of mixed race males and 3.3% of mixed race females were found to be classic PPR posivite. No data was available for the black population. In the group of 16-25 years, 1.9% of white males, 4.7% of white females, 0.8% mixed race males, 2.0% of mixed race females and 1.7% of black females (no data available for black males) were found to be classic PPR positive [68]. In a large cohort of 16,500 patients, from Zimbabwe, referred for EEG examination, Adamolekun et al. described a significantly higher incidence of PPRs in whites (1.5%) and Asians (1.18%) than in black individuals (0.09%) [69]. Obeid et al. studied the occurrence of PS in Arab epileptic patients [70]. They found 7.3% of patients to be photosensitive, an incidence comparable to that observed in whites and higher than that previously reported among black Africans. The authors concluded that the occurrence of PS among patients with epilepsy might strongly depend on the presence of an epileptic syndrome known to have an association with PS. Finally, in an EEG survey, Bental studied 70 normal South African black albinos to determine whether the lack of pigment in the retinae and eyelids would have any effect on the PPR during IPS. Only 2.85% showed PPR on IPS, not confirming the "pigmentary protection theory" and suggesting that other intrinsic inhibitory factors are responsible for the level of the PPR threshold [71].

In summary:

PSE is a condition found in all ethnic groups. Diverse population studies suggest a higher incidence in females, in "Whites" and "Arab" patients with epilepsy, less in other ethnic groups and lowest in "Black" Africans. However, the results of different studies are not directly comparable. Neither the methodologies for testing PPR – including the novelty of pattern studies – nor the different cohorts of epileptic patients – with a variable prevalence of patients with IGE *vs.* PE or the mix of "chronic" *vs.* new (untreated) patients are comparable.

7. Characteristics of stimuli and methods to elicit photosensitivity

7.1. Frequency and types

Diverse types and frequencies of stimuli have been studied exhaustively to enhance photosensitivity. IPS most often elicits a positive response by a "stimuli frequency range between 15 and 20

flashes/s, namely if IPS is binocular, in the centre of the visual field. But 49% of patients are sensitive to 50 flashes/s, explaining the role of television systems" [27]. A higher rate of positive responses to IPS is achieved if the stimulus includes a pattern.

Wilkins et al. [72] summarised the different types of stimuli eliciting IPS discharges as: (a) Visual stimulation that resembles the stimulation normally responsible for seizures (TV or video-games). This experience was more frequently found when monitors incorporated cathode ray tubes (CRTs) in which the display is created in a flickering pattern. Such stimulation is more epileptogenic when programmes are presented with flashing or patterned material; (b) Elementary visual stimuli that enable inferences concerning the physiological trigger mechanisms. The trigger is cortical and requires synchronised mass action of neurons; (c) Stimuli that avoid paroxysmal EEG activity and permit an investigation of the sub epileptic response to visual stimuli, using the evoked potential.

7.2. Colour

According to Binnie et al., photosensitivity is not related to red light per se but results from the fact that, with commercially available filters this light can stimulate only red sensitive cones. Additionally, due to "the overlap of the absorption spectra of the visual pigments it is difficult to stimulate only green or blue sensitive cones" [73]. The authors emphasise that the stimulation of a single cone population can be achieved by the 'silent substitution method' which has been used for evoked response studies. Stimulation of either red or green cones by the silent substitution method may produce epileptiform discharges in patients that present greater sensitivity for green than for red cone stimulation [73].

Watanabe et al. studied the effect of excessive cortical excitation due to visual stimulation [74]. Even in healthy subjects, prolonged stimulation with low-luminance chromatic flicker evokes neuromagnetic activity in the primary visual cortex. It develops slowly and depends on the colour combination of flicker, the critical factor of cortical excitation, which can be amplified over time. Transient activity occurs in the parieto-occipital sulcus as early as 100–400 ms after flicker onset. It is negatively correlated with the subsequent occipital activity and reflects a defensive mechanism that suppresses cortical hyperactivity due to chromatic flicker [74].

Takahashi et al. evaluated the role of long-wave length red light emission using a TV programme that induced photosensitive seizures [75]. Measuring the luminance energy of the programme, the authors concluded that high amounts of long-wavelength red light emitted from CRTs might have played a significant role in the induction of photosensitive seizures reported in the "Pokemon" incident [74].

7.3. Lighting

Van Egmond et al. assessed the management of IPS under conditions of normal and reduced ambient lighting [76], concluding that, for routine clinical EEG examination, there is no advantage in the current practice of darkening the room during IPS. However, for exhaustive testing of photosensitivity, it is necessary to perform IPS both in light and darkness.

Leijten et al. tested the photosensitivity range stimulating with and without a diffuser in front of the subject's eyes. Maximal sensitivity was achieved in the condition 'eyes open with diffuser' [77]. Diffusion of light can explain the influence of the eyelids on photosensitivity, attenuated by loss of intensity. The use of a diffuser may simplify the testing for photosensitivity in the EEG laboratory.

Takahashi et al. studied the pathophysiology of PPRs in photosensitive patients with hereditary dentate rubral-pallido luysian atrophy (DRPLA) [78] concluding that PPRs were elicited by flashlights and depended on the wavelength spectrum and the quantity of light.

7.4. Standardization of procedures

As previously stated, photosensitivity is associated with the use of specific TV/video/PC programmes and games that are rather common today. This evidence suggests that there is a need for collaborative studies using comparable procedures to achieve generalizable results. First, a consensus was reached on the standardisation of methods to elicit IPS (distance from patient to photic stimulator; characteristics of photo stimulator; ambient lightening; flash frequency used and intervals; duration of stimulation; and mode of presentation). Additionally, distinct types of epileptiform responses have been characterised: confined to the occipital area (OSW), starting in occipital and spreading to frontal regions (OGSW), or generalised from the start (GSW). Other responses (OR) include generalised spikes. The standard procedure was assumed to be safe, quick, simple and reliable, allowing collaborative research and the comparison of data within and between patients [79]. A European study was performed in four countries and five centres. Patients were selected on the basis of a history of seizures evoked by TV/video/PC game, sunlight or discotheque, black and white pattern or they were already known to be sensitive to IPS. Females accounted for 75% of the sample, and 55% were less than 18 years of age. IPS, pattern and television stimulation were performed in a standardised way. On a 50- and 100-Hz television, patients were investigated with two types of programmes: one more provocative (Super Mario World – SMW) and a standard, relatively non-provocative TV programme. Regardless of the distance, SMW proved to be more provocative than the standard programme. IPS elicited epileptiform discharges in 85% of patients; 55% were 50-Hz television sensitive, and 26% were 100-Hz television sensitive. Pattern sensitivity was found in 28% of patients. Television, video- or computer-game seizure's patients were significantly more sensitive to pattern and to the 50-Hz television. Video game-viewing and-playing on the 50 and 100 Hz TV was considerably more provocative (namely in 50 Hz TV) than viewing the standard programme [80]. Fourteen per cent of the patients were not photosensitive. Although no difference in age or use of medication was observed, there were twice as many men as women in this non-photosensitive group. The authors concluded that most children and adolescents with a history of video game seizures are photosensitive and should be investigated with a standardised photic stimulation procedure [81]. The photic stimulation procedure was based in a consensus algorithm developed in another collaborative European study [82]. The use of this algorithm may identify patients with epilepsy and photosensitivity and assist in their monitoring. The algorithms were defined for different scenarios: (1) requirements for defining photosensitivity in patients and family members of known photosensitive patients and (2) requirements for tailored studies in patients with a clear history of visually induced seizures or complaints and in those already known to be photosensitive [82].

In summary:

Binocular IPS with stimuli frequency range between 15 and 20 flashes/s, is more likely to elicit PPR, although nearly 50% patients have IPS at 50 flashes/s, namely if a pattern is present in the stimulus. This evidence explains the photosensitivity elicited by some TV programmes, video or electronic-games. Prolonged stimulation with low-luminance chromatic flicker and high amounts of long-wavelength red light may play a significant role in the induction of some cases of photosensitivity epilepsy.

However, photosensitivity is not a property of red light *per se*. Photosensitivity is higher if stimulation is performed through a light diffuser. When patients have a history of video game induced seizures, photosensitivity should be investigated using standardised protocols to define sensitivity range and the conditions provoking the abnormal responses.

8. Protective measures

There is now a consensus of preventive/protective measures which may be used to avoid PS seizures in patients with photosensitivity: (i) patients should occlude one eye when travelling in a vehicle, when using computers or when stepping outdoors on a sunny day, or when there are various patterns before them, (ii) patients should sit at least 2-3 metres away from the TV when watching a programme, (iii) patients should avoid any object that transmits luminance variance – the rapid transition of colours and with alternating frequencies is more provocative; if this is not possible they should occlude one eye [79,80] and (iv) patients should be able to manage specific colour filtering on glass lenses.

Capovilla et al. used colour filtering in a particular type of lens in photosensitive epileptic patients [83]. Filters were effective for photosensitivity inhibition: PPR disappeared in 77% of patients and decreased in 19%. Parra et al. used a specially designed colour stimulator to understand the potential of different colours or colour combinations and white light to trigger PPRs under controlled conditions [84]. Of the primary colours, red was found to elicit more PPRs at a lower modulation-depth (MD). Of the alternating sequences, the red-blue sequence was the most provocative stimulus, and the blue-green sequence was the least. Sensitivity to alternating colours was not correlated with sensitivity to individual colours. The authors concluded that colour sensitivity follows two different mechanisms: one, dependent on colour modulation playing a role at lower frequencies ($<$30 Hz) and another, dependent on single-colour light intensity modulation correlating with white light sensitivity and activated at higher frequencies. The results suggest that the prescription of coloured lenses tailored to the patient can be an effective preventative measure against visually induced seizures.

As it was referred in the introduction of this review, pharmacological therapy is beyond our scope. However, if needed, when choosing pharmacological treatment two considerations should be addressed: first, PSE is usually time limited and easy to treat, and protective measures are often useful; secondly, PSE is more frequent in females mainly at childbearing ages so one needs to be cautious about the drug to be chosen.

In summary:

Preventive measures to avoid PS seizures include the management of stimuli sustainability and frequency. To contain or prevent seizure initiation and/or its generalisation, a more complex transition of patterns and colours could be introduced, this would reduce IPS discharges and consequent evolution to PCR or PSE. Because PSE is more frequent in childbearing-age women, the risks and benefits of drug treatment will need to be considered carefully.

9. Concluding remarks

PSE is age related, more frequent in females, time limited and is closely related to JME.

Differences in cortical volumes indicate that abnormalities extend beyond the limits of the frontal lobes and provide evidence for the involvement of the visual cortex in human PSE. Furthermore, functional changes related to PPR are associated with increased cortical thickness in the occipital, frontal and parietal cortices and a degree of atrophy in the temporal lobe.

Generalised myoclonic seizures are associated with widely spread spike-and-wave discharges with interhemispheric posterior cingulate onset sparing the sensorimotor cortices. The elicited Photic Driving Responses are restricted to the occipital lobe at ILS frequencies below 9 Hz, spreading to the parietal and central regions at higher frequencies. During the same stimulation and when PDRs involve the parietal cortices, both types of PCR can occur.

A reduction in connectivity between prefrontal and frontopolar regions and increased connectivity between occipital cortex and the supplementary motor area may be the basis for triggering motor seizures in JME. The prominent involvement of basal ganglia circuitry associated with subcortical microstructural and metabolic changes in precentral, parietal, and occipital regions reinforces the notion of functional-anatomic ictiogenic networks in JME. PPR may be a final expression of pathogenic phenomena occurring in the striato-thalamocortical system, and possibly a core feature of JME as system epilepsy.

Despite the relevance of the familial transmission of epileptiform IPS pattern no evident association between PSE and specific genes has been identified, so far.

Although there are indications of ethnic differences (with a lower incidence in Black Africans) the comparisons between series are difficult. An improvement in comparison studies, based on similar methodologies, is necessary. Photosensitive epilepsy has a female preponderance which merits further research.

Preventive measures which may avoid PS seizures include the manipulations of stimuli duration and frequency. To contain or prevent seizure initiation and/or its generalisation, a more complex transition of patterns and colours could be adopted in video games or television programmes. Given the gender/age group most commonly affected by PSE, the risks and benefits of drug treatment need to be carefully weighed up.

Conflict of interest

The authors declare no conflicts of interest.

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