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Short communication

The 'Photosensitivity Model' is (*also*) a model for focal (partial) seizures

Dorothee Kasteleijn- Nolst Trenite[a,b,*], Pierre Genton[c], Christian Brandt[d], Ronald C. Reed[e]

[a] *University Medical Center Utrecht, Utrecht, The Netherlands*
[b] *Sapienza University, Rome, Italy*
[c] *Centre St. Paul, Marseille, France*
[d] *Bethel Epilepsy Centre , Bielefeld, Germany*
[e] *Husson University School of Pharmacy, Bangor, ME, United States*

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ABSTRACT

The 'Photosensitivity Model' uses a standardized stimulation protocol of repeated intermittent photic stimulation (IPS) over a three-day period, with administration of a single dose of an investigational antiepileptic drug (AED) after a baseline IPS day in photosensitive patients, followed by a third IPS day to determine duration of effect. This 'Photosensitivity Model' has shown its value in the development of new AEDs. Levetiracetam (LEV), currently a first-line AED in new-onset focal epilepsies, was not effective in classical animal models, but showed dose-dependent efficacy in the human 'Photosensitivity Model'. Nevertheless, concerns have been expressed that AEDs selectively suppressing focal seizures might not suppress generalized photoparoxysmal EEG responses (PPR), the pharmacodynamic outcome measure in the Model. Herein, the following questions have been addressed: *I. Can patients with generalized epileptiform discharges, evoked by IPS, so-called PPR, have focal epilepsy (focal seizures)? II. Are the photosensitive patients with focal epilepsy, who have participated in the photosensitivity trials, non-responsive to a new AED under investigation, as compared to those with generalized epilepsies? III. Are "focal epilepsy" AEDs effective both in the 'Photosensitivity Model' and in real life in photosensitive patients?* We performed a systematic literature review of PPR in focal seizures and focal epilepsy and we analyzed data (published and unpublished) from 20 different potential AEDs studied prospectively in the 'Photosensitivity Model'. Finally, the PPR effects of Na^+ channel-blocking AEDs (considered as the most typical AEDs for focal epilepsy) are discussed with unequivocal examples given of the focal nature of a patient's PPR. Based on the entire data evidence, we conclude that: 1. PPRs certainly exist in focal epilepsy (17% on average); 2. Clinical signs and symptoms of PPRs can be focal and 3. PPRs can definitely be used to identify or to prove efficacy of new AEDs for patients with focal epilepsy.

In epilepsy, the term "*photosensitivity*" denotes the appearance of both the epileptiform EEG discharges (EED) evoked by Intermittent Photic Stimulation (IPS) and epileptic seizures evoked by flickering light, TV, videogames etc. (Kasteleijn-Nolst Trenite et al., 2001). If the entire stimulation procedure is conducted according to the consensus guidelines (Kasteleijn-Nolst Trenité et al., 2012), about 90% of patients with a clear history of visually evoked seizures in daily life will show EED during IPS in the laboratory, so called photoparoxysmal EEG responses or PPRs (Reilly and Peters, 1973). Patients with photosensitive epilepsy are typically sensitive. to flashing bright stimuli between 2 and 60 flashes/sec (Hz) with maximum between 15 and 25 Hz (Harding and Jeavons, 1994).

PPRs can be evoked in photosensitive patients at any time and repeatedly without evoking generalized tonic clonic seizures (GTCS) (Angus-Leppan, 2007). Since PPRs are reproducible and stable over the day (Rimmer et al., 1987), they can be used in evaluation of AED effects in clinical practice (Covanis et al., 1982) and in Proof of Concept (PoC) trials (Binnie et al., 1986a). This human Phase-2a, three-day PoC 'Photosensitivity Model', compares the effect of single doses of a new AED on hourly PPR measurements on the second day, to the placebo response seen on baseline (first) and third day. In combination with pharmacokinetic data of the

* Corresponding author at: University Medical Center Utrecht, Utrecht, The Netherlands.
E-mail addresses: dkasteleijn@planet.nl, dorothee.kasteleijn@uniRoma1.it, d.kasteleijn@umcutrecht.nl (D. Kasteleijn-Nolst Trenite).

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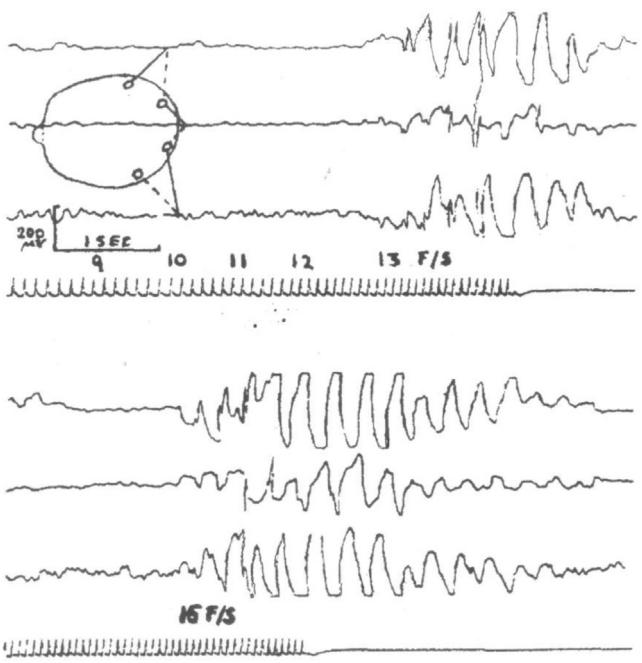

Fig. 1. Two "occipital larval (=subclinical) seizures" induced in an epileptic child by (photic) stimulation at the frequencies 13 and 16 Hz. No clinical accompaniments. (Reproduction from Walter and Grey Walter, 1949. Central effects of Rhythmic Sensory Stimulation. EEG journal 1:57-86; copyright licensed by Elsevier, 3934200969895).

investigational AED, determination of potential (complete) **-***within patient***-** reduction of PPR flash-frequency ranges has successfully been used in AED development over the past thirty years (Rowan et al., 1979; Rimmer et al., 1987; Moller et al., 1990; Overweg and de Beukelaar, 1990; Kasteleijn-Nolst Trenité et al., 1992, 1996, 2007a, 2007b, 2013a, 2007b, 2015, 2016). This 'Photosensitivity Model', following a standardized IPS protocol, has clearly shown its value in the detection of clinically useful AEDs (Yuen and Sims, 2014; Schmidt, 2007). Moreover, the utility of the Model is best exemplified by identification of the anti-epileptic properties of LEV, a SV2A ligand, which was not effective in classical animal models (Klitgaard 2001), yet showed dose-dependent efficacy in the 'Model'. LEV is currently considered a first-line AED in new-onset *focal* epilepsies and refractory idiopathic generalized epilepsies (Schmidt, 2016); it is also recommended in epileptic syndromes with marked photosensitivity (Striano et al., 2008).

Nevertheless, concerns have been expressed (see Porter, this journal) that AEDs acting selectively on focal seizures might not suppress PPR, the pharmacodynamic outcome measure in the 'Model'.

Understanding the component parts of this concern is essential:

I. Could patients with generalized epileptiform discharges, evoked by IPS, so called PPR, have focal epilepsy (focal seizures)? Why do many believe it occurs exclusively in generalized epilepsies?

Historically, IPS has been used as a means of studying the spreading of visual rhythms (Adrian and Matthews, 1928; Cobb 1947). EED evoked by IPS were first described in a patient on large doses of anticonvulsants (Walter et al., 1946). Cobb showed IPS-evoked petit mal with jerking and others registered the first IPS evoked seizures with onset in the occipital lobe (Walter and Grey Walter, 1949; see Fig. 1).

Since then, IPS has been considered as a method to lower the epileptogenic threshold in order to detect increased susceptibility for epileptic seizures; in the 1950's IPS was even combined with the administration of the epileptogenic agent metrazol to elicit PPRs for diagnostic purposes (Schwab and Abbott, 1950). Emphasis has especially been placed on the relationship of photosensitivity/PPR and idiopathic generalized epilepsies (IGE): high prevalence rates of PPR (40–90% of patients) were found in Juvenile Myoclonic Epilepsy (JME) (Wolf and Goosses, 1986; Appleton et al., 2000). Not so surprisingly, this has led to the common, yet erroneous belief that the presence of a PPR means the patient *must* have the diagnosis of IGE.

Due to the renewed interest in focus localization in epilepsy, PPRs were discovered in patients with occipital and temporal lobe epilepsy, even with ictal focal seizure symptomatology during the PPR (Aso et al., 1987; Seddigh et al., 1999; Guerrini et al., 1995; Hennessy and Binnie, 2000). A series of seven patients with both focal (epigastric, gustatory, déjà-vu and one with visual aura) and generalized epilepsy has been described (Nicolson et al., 2004): three had hippocampal atrophy, all showed generalized spike-waves and two showed spikes over the temporal region. Interestingly, six of these seven patients showed generalized PPR. One of those, a female with a PPR, left temporal focus and focal seizures evolving into GTCS underwent epilepsy surgery (L-amygdalo-hippocampectomy with mesial temporal sclerosis confirmed), became and remained seizure free, also after discontinuation of gabapentin. and clobazam. After 2 years, still on CBZ monotherapy, she developed morning myoclonus with GTCS. Others have similarly shown overlapping grey areas between 'typical' focal and 'typical' generalized epilepsy, such as in absence seizures using dense-array scalp EEG (Holmes et al., 2004). In these cases, the onset was typically highly localized over dorsolateral or orbital frontal areas before generalization occurred, suggesting that the cortex is the driving force of the epileptic network. MEG studies confirmed this concept (Tenney et al., 2014). Similarly in IPS-evoked seizures, the epileptic network driver is most likely the visual cortex, although it has been suggested that a temporal focus can be the driver in photosensitive temporal lobe epilepsy (Benbadis et al., 1996).

To prove that PPR is indeed found in focal epilepsy and can even elicit focal seizures, we identified published articles in PubMed that contained the search term 'photosensitivity' or 'PPR' in the title, abstract or body of the manuscript, and from this, those studies that contained information about distribution of seizure/epilepsy type were selected for analysis. We excluded studies with an '*a priori*' selection of epilepsy type, such as PPR in JME.

Accordingly, we found:

a) #15 EEG studies from 10 different countries that identified PPR-positive patients with and without clinical photosensitivity (see Table 1); of a total of 955 patients (55% female), 159 (17%) patients had focal epilepsy.
b) #3 studies, where all patients had seizures provoked by visual stimuli in daily life, *i.e.* the 'classical' photosensitive patient (see Table 2). Focal epilepsy was found in 2–49% of patients. The Pokémon cartoon was especially related to focal epilepsy (49%, Takada et al., 1999).

We assembled also published case reports of "typical" focal epilepsy patients with a 'temporal lobe' epilepsy and a 'generalized PPR' (see Table 3). Herein, we found five patients (age 12–44 yr) that showed not only interictal spontaneous localized EED over the temporal lobe, but also clear ictal symptomatology during the generalized PPR, typically arising from the same temporal lobe. IPS can thus be considered as a provocative method to lower the threshold for occurrence of seizures.

Two details become apparent from the review of the data in Tables 1–3: 1. Generalized PPR is indeed regularly found in focal epilepsy; 2. IPS can also elicit focal, temporal lobe seizures.

II. Are photosensitive patients with focal epilepsy, who participated in the various photosensitivity trials, non-responsive