The Importance of Photosensitivity for Epilepsy

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Editor

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To my dear Mother who all along encouraged me to learn, work and pursue my scientific ambitions, despite being married with children as she was.
Without her support till her very end in 2020, this book on photosensitivity would not likely have emerged.

Foreword

I have read with great interest this excellent multiauthored comprehensive book edited by Dorothee Kasteleijn-Nolst Trenite which addresses all aspects of photosensitivity. The book is very well planned and structured and eminently readable. It consists of 34 chapters which are grouped into five themed parts. Each chapter gives the background and history of the relevant subject as well as the most recent developments and advances in the field and a discussion of possible future research. The titles of the themes and of the chapters frequently end with a question mark, suggesting that, despite the voluminous literature on this subject, there still remains a lot to be discovered. For example, although photosensitivity appears to be a genetic trait and was thought to be autosomal dominant with variable penetrance, no single gene has been identified to date, suggesting possible multifactorial or complex inheritance. Furthermore, there is some evidence that photosensitivity may be inherited independently from the many genetic epilepsy syndromes with which it is frequently associated.

Although several monographs on photosensitivity have appeared in the past, no multiauthored book on photosensitivity sharing the experiences of multiple clinicians, scientists, and epileptologists from around the world exists, to my knowledge. The authors of this book originate from 20 countries (47 centers) on 5 continents. Previously, Peter Jeavons and Graham Harding from Birmingham wrote monographs on photosensitivity in 1975 and 1994; Newmark and Penry published an extensive review in 1979; and Takahashi from Sendai, Japan, wrote a monograph on pattern stimulation and low-luminance visual stimulation in 2005.

In the past quarter century, there have been many environmental changes which have affected visual sensitivity, especially in children and adolescents. These include electronic games, TV with flashing lights, LED lights, discotheques, and most likely also TVs with HD. Pattern sensitivity can also be a problem. On the other hand, there have been tremendous advances in molecular biology, especially with the advent of next generation sequencing, as well as the establishment of various modalities of functional imaging including fMRI-EEG, MEG, TMS, and the analysis of gamma frequencies in the EEG. These ongoing studies are discussed in detail and hopefully will shed further light on the etiology and pathophysiology of photosensitivity.

Although photosensitivity is usually known to be associated with generalized epilepsies, photoparoxysmal responses (PPRs) can also occur in focal epilepsies This book has three chapters dealing with this relatively poorly documented phenomenon.

The preface is a brief autobiography of the editor, Dr. Kasteleijn-Nolst Trenite, illustrated with photographs of her mentors, students, international collaborators, colleagues, family, and friends. Dr. Kasteleijn details her journey from veterinary student to medical student to a PhD in epilepsy and photosensitivity which laid the foundation of her subsequent career and eventually led to her title of "Queen of Photosensitivity." The preface illustrates her passion for her chosen work and her skills as a clinician, researcher, meeting organizer, teacher and mentor, as well as an international collaborator, a devoted daughter, wife, mother and grandmother, and a trusted friend.

Another innovative feature of the book is the introduction, where Dorothee summarized the main conclusions arising from each part and then proceeded to summarize together with US-based PharmD Dr. Reed the whole in the final chapter with ideas for future research.

My late husband Fred Andermann and I met Dorothee early in her career and were very impressed by her great energy, friendship, and intelligence. We continued to meet at various international meetings as well as epilepsy meetings around the globe.

In addition to all the science and innovative investigations, there are a number of very practical suggestions for diagnosis and treatment that are very useful for practicing physicians and caregivers, including guidelines for IPS-EEG to prevent seizures.

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Preface

You might wonder why and when my interest in photosensitivity started and how my focused investigation, my "deep-dive," into the fascinating subject of photosensitivity in epilepsy has developed over time.

Having worked evenings and weekends for veterinary surgeon and magician Dr. Winkel during my high school days, I learned to observe pets and to deal with the important bonds between a pet and an owner. At the University of Utrecht, where I switched from veterinary surgery (more dedicated at the time to farming issues) to medicine, lectures by epileptologist Marinus van Heycop ten Ham (known for his research in LaFora disease) were fascinating: he showed videos of seizures from his patients at the epilepsy center Meer & Bosch, de Cruquiushoeve (M&B) in Heemstede, The Netherlands.

It was thus no wonder that I (see Fig. 1) applied for a job as epileptologist at the children's department of this Dutch renowned epilepsy center. M&B gave, at the time (1980s), integral medical care to ~10,000 outpatients and 1000 inpatients for short- and long-stay. The internationally oriented director at that time, Harry Meinardi, president of IBE from 1977 to 1981 and ILAE from 1989 to 1993, appointed Colin D. Binnie, from London, as head of the EEG department (see Fig. 2).

Fig. 1 A 25-year-old medical student

Fig. 2 Colin Binnie in M&B

Fig. 3 New Year's Eve at home, 1983, with daughter Louise

I soon recognized his great knowledge on epilepsy, in general, and his excellence in doing research utilizing EEG. While I had many ideas about research topics, including photosensitivity, Colin convinced me to choose PhD research on the subject of photosensitivity, an interest he gained in his London years working with among others—especially Arnold Wilkins (known from his work on pattern stimulation). Colin Binnie, Jan Overweg, Jim Rowan, and Jaap Meijer thoroughly taught me the importance of EEG in epilepsy diagnostics and also about the added value of long-term video EEG and pharmacology combined.

My clinical and research endeavors were very important to me early on. Then, as in modern times, I recognize that many women in medicine urgently try to find balance between their challenging career and hectic but precious home-life (see Fig. 3): here, I hope to show, by example, that it can be done! I am very proud to say that I had two wonderful children (Louise and Laurens) to care for while pursuing my varied clinical and research interests. For sure, the strong support of my husband, Bart, was and is still crucial all along!

In 1986, I received the Young Physician's award—Gowers Prize at the Golden Jubilee Conference and Northern European Epilepsy Meeting in York (UK) for my self-initiated and performed study on symptoms and signs during intermittent photic stimulation and their relation to seizures in daily life (JNNP, 1987, 50:1546–49).

Certainly, receiving such an esteemed award gave me the confidence that I indeed could do clinical research and start answering questions/hypotheses

Fig. 4 The setting of photic stimulation

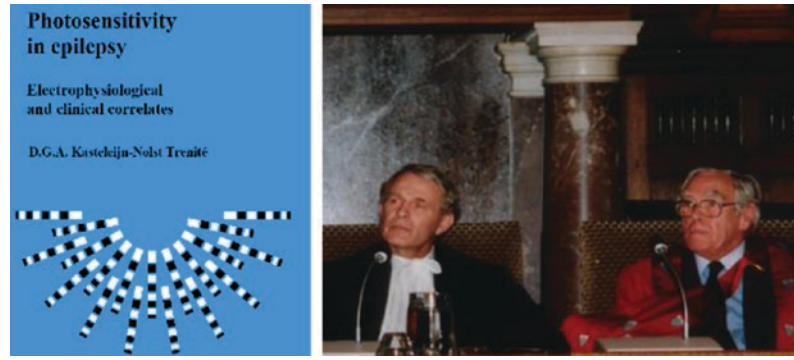

Fig. 5 Kobus Willemse (seated left) and Peter Jeavons (seated right) moderate my thesis defense, Utrecht, The Netherlands

I gathered from clinical experience in treating a variety of patients of all ages and any handicaps. Excellent EEG technician Erwin Dekker (see Fig. 4) played an important role in studying photosensitivity.

In 1989, I defended my thesis in Utrecht in the presence of child neurologists Jacobus Willemse (my promotor from Utrecht University) and Peter Jeavons from Birmingham—the founding father of photosensitivity in the UK (see Fig. 5). The thesis is published in *Acta Neurologica Scandinavica* (1989; 125:3–149).

From then on, research certainly started to play a very important role in my professional life.

I started the foundation of a research department at M&B to focus on the following:

1. Strengthening our collaboration with various national and international universities; among others especially child neurologist Hans Stroink from Erasmus Medical Center, Rotterdam was very interested in detailed studies of his photosensitive patients
2. To establish the working group "Paroxysmal Disorders" of The Netherlands Research Foundation, The Hague, to stimulate collaboration between basic and clinical scientists in epilepsy
3. To organize summer schools for education in epilepsy

At this time, I became intensely involved in the further development of the human "Photosensitivity Model of Epilepsy" as Proof-of-Concept (PoC), Phase IIa research, to accelerate AED development, in close collaboration with colleagues from France, Germany, and USA. My earlier work in the 'Photosensitivity Model of Epilepsy' required that I score large volumes of paper EEG tracings over time (hourly photic stimulation in three eye conditions over a 3-day period). I give tribute to my friend and colleague, Edouard Hirsh, France, as a great proponent for this PoC epilepsy research (see Fig. 6).

Realizing that nearly every EEG department had their own photic stimulation procedures, European guidelines for *standardized* photic stimulation needed to be developed for diagnostic purposes and especially for collaborative research. I therefore organized together with Colin Binnie, Graham Harding, and Arnold Wilkins a workshop in Heemstede on standardization of photic stimulation (see Fig. 7).

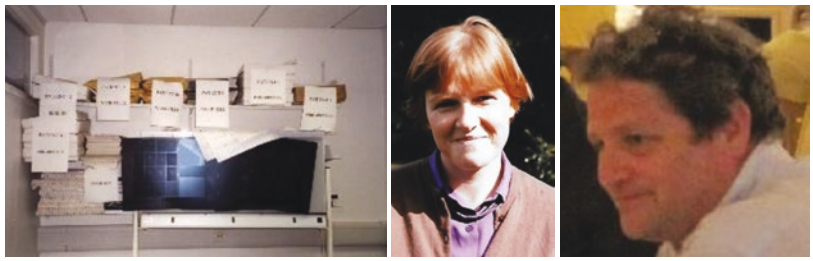

Fig. 6 EEGs to read for a Phase II 'Photosensitivity Model of Epilepsy' study; Edouard Hirsch

Fig. 7 Workshop in 1998 at M&B, outcome published with all participants: Kasteleijn-Nolst Trenite DGA, Binnie CD, Harding GFA, Wilkins A, CovanisT, Eeg-Olofsson O, Goosens L, Henriksen O, Krämer G, Leyten F, Lopes Da Silva FH, Martins Da Silva A, Naquet R, Pedersen B, Ricci S, Rubboli G, Spekreijse H, Waltz S. Medical technology assessment. Photic stimulation—standardization of screening methods. *Neurophysiol Clin* 1999; 29:318–324. Several colleagues of our original group (Rubboli G, Martins da Silva A, Wilkins A, Covanis A, Harding G) and, in addition, other IPS knowledgeable colleagues (Seri S, Hirsch E, Parra J, Elia M, Capovilla G, and Stephani U) came forward to update and revise these past 1999 guidelines; the newer 2012 standards can be found at https://www.ilae.org/files/ilaeGuideline/PhoticStimulation-2012-.1528-1167.2011.03319.pdf or in *Epilepsia* 2012 Jan; 53(1):16–24

Fig. 8 Workshop in 2000 on Visual sensitivity in Aix-en-Provence, France; encircled are from left to right, the key figures: Pierre Genton and Colin Binnie, Alberto Tassinari, Fred Andermann, me, Eva Andermann, Renzo Guerrini, and Michelle Bureau

Over time, I, together with Pierre Genton and Renzo Guerrini (see Fig. 8), organized more international workshops in France and The Netherlands, which led to animated discussions and subsequent publications on visual sensitivity and JME (40% of JME patients are photosensitive). The Aix-en-Provence workshop entitled "Visual Sensitivity in the Modern Environment" led to consensus on terminology and classification of clinical and EEG phenomenology in photosensitivity (*Epilepsia* 2001 May; 42(5):692–701) and key lectures were published in *Epilepsia* 2004; 45, Supplement 1.

An European Consortium on the "Genetic Analysis of Photosensitivity and Visual Sensitive Epilepsies" was started in 2002 in close collaboration with Utrecht University; even today, it is active in dealing with other issues in photosensitivity as well. Together with Bobby Koeleman and Dalila Pinto, we collected many DNA samples in combination with clinical information of photosensitive patients from the practices of Giuseppe Capovilla, Mantova, Italy, Thanos Covanis, Athens, and Bosa Jocic-Jacubi, Nis, Serbia. Finding "a gene" for photosensitivity is far more difficult than expected and taught us that the underlying epilepsy type or syndrome is prominent, as shown nicely in the publications of Dalila Pinto and Carolien de Kovel (de Kovel CG et al. Whole-genome linkage scan for epilepsy-related photosensitivity: a mega-analysis. *Epilepsy Res* 2010:286–94; D Pinto et al., Explorative two-locus linkage analysis suggests a multiplicative interaction between the 7q32 and 16p13 myoclonic seizures-related photosensitivity loci. *Genet Epidemiol* 2007:42–50)

I willingly and eagerly accepted invitations to lecture and visit universities all over the world; this undoubtedly strengthened the photosensitivity network (Fig. 9).

The Nintendo videogame reports on provocation of seizures led to the sponsoring by Nintendo through the Japanese Epilepsy Foundation of a workshop on 'Electronic Screen Games and Seizures' in London (*Epilepsia* 1999; 40; Supplement 4, co-edited with Binnie and Harding) and an European study on videogames with the collaboration of Italian, Portuguese, and Dutch colleagues (Kasteleijn-Nolst Trenite DGA, Martins da Silva A, Ricci S, Rubboli G, Tassinari CA, Segers JP. Videogames are exciting. *Epileptic Disord* 2002: 121–128).

Fig. 9 With Takahashi, Sendai, Japan, known for his work on low luminance red light and dot patterns

Then, I became more and more involved in teaching and doing research with my Italian colleagues through invitations by Alberto Tassinari and Guido Rubboli in Bologna and by Raffaele Canger from Milano to regularly lecture in his Gargnano masterclass school. Invited by child neurologist, Maurizio Elia, from the Oasi Institute, Troina, Sicily, we organized a workshop on "Reflex Epilepsy," including, of course, photosensitivity, in 2005. Very important and esteemed speakers included the above-mentioned Italian colleagues as well as Bobby Naquet (France), Heinz Gregor Wieser (Switzerland), Dieter Janz (Germany), and Benjamin Zifkin (Canada).

Invitations by Mario Brinciotti (known for his research on pattern) and especially Stefano Ricci (see Fig. 7, second from left) led me to Rome. Unfortunately, Stefano Ricci passed away. It was his pupil, Marta Piccioli (see Fig. 11a), who asked for my help to finish Stefano's paper on videogames and make her neurology residency at Sapienza University a success. Marta and I worked on research data from Bambino Gesù (including holidays, since it was fun!), together with the head of Child Neurology, Federico Vigevano (later also nice collaboration with Nicola Specchio). These efforts encouraged me to apply for an European Grant in collaboration with my Roman colleagues.

With great joy I indeed received the prestigious European Grant within the FP6 EU Research Program to become one of the few "**Marie Curie Excellence Chairs**." I was appointed at the Neurology Department (head: Cesare Fieschi) of Sapienza University at St Andrea Hospital, Rome, Italy from 2006 to 2009 (see Fig. 10). This grant (MEXC-CT-2005-24224: Visual Sensitivity) comprised two main elements: (1) exchange of knowledge and training of advanced and other medics, paramedics, and lay people and (2) research.

Fig. 10 Driving from my apartment at the Via Flaminia Nuova to my work in St. Andrea Hospital, Sapienza University, Rome, Italy, 2006

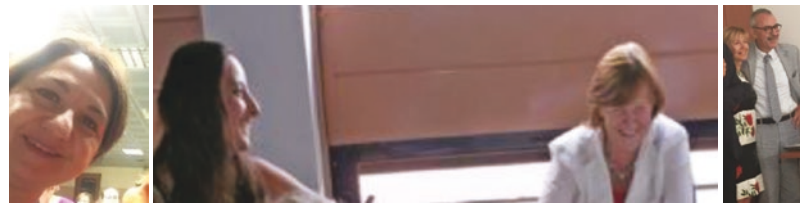

Fig. 11 (**a**) Marta Piccioli, (**b**) Laura Cantonetti at work with me, (**c**) Maria Pia Villa and Pasquale Parisi

This pivotal Marie Curie Grant successfully promoted further research on photosensitivity, culminating in:

- 18 peer-reviewed articles plus 3 book chapters
- 23 abstracts for posters and presentations at Italian and international congresses
- education and dissemination of knowledge about photosensitivity and epilepsy to the public at large through the Italian press, an Italian videogame software editing organization, including lectures for lay people and two workshops in Rome (one together with Alberto Spalice with contribution of pharmacologist Janet Mifsud from Malta, vice president of the IBE) and another on visually induced seizures in 2008 with Carla Buttinelli.

My PhD students Marta Piccioli (adult neurology) and Laura Cantonetti (child neurology) and pediatricians Pasquale Parisi and Maria Pia Villa were all instrumental to the success of the EU grant (see Fig. 11a, b, c). Many young colleagues are inspired and active, and for sure, our wonderful collaboration on photosensitivity, epilepsy, and migraine is ongoing.

Neurologists Luiz Barreto Silva (Teofilo Otoni, Brazil) and Paul Timmings (Hamilton, New Zealand) crossed my path at international epilepsy conferences, and thanks to regular (email) contact, they both received their PhD degree at the universities of San Paulo and Auckland, respectively, on studies on photosensitivity.

Pleasant and fruitful collaboration with Ronald C. Reed started in 2005, while he worked in 2005 at Abbott Laboratories, Neuroscience Research and Development, Chicago (see Fig. 12), in a photosensitivity study with IV VPA (performed at Vanderbilt University, Nashville, with Bassel Abou-Khalil). Since then, we have undertaken many AED-related studies (recently at St. Louis with William Rosenfeld) and scientific university projects.

Thanks to lectures and a very lively masterclass in Moscow and especially a wellorganized nationwide inventory of knowledge and attitude of neurologists/pediatricians toward photosensitivity, all organized by child neurologist Kira Voronkova from Moscow (see Fig. 13), it became more clear what future paths are necessary to give practicing colleagues the information they need.

I also have had wonderful collaboration with researchers conducting EEG studies in photosensitive *animals*: baboon studies of Akos Szabo, San Antonio, Texas; Rhodesian Ridgeback dogs of Gerhard Kluger, Vogtareuth, Germany; and rats of Daniel Uhlrich, Madison, Wisconsin, USA (see Fig. 14).

Overall, my international projects, collaboration, and friendships still continue today. I am currently academically appointed in the Department of

Fig. 12 Ronald C. Reed

Fig. 13 Kira Voronkova

Fig. 14 Photosensitive animals studied under the sensitive care of colleagues Szabo, Kluger and Uhlrich

Fig. 15 This fulfilling life with wonderful research and colleagues keeps me young-at-heart and smiling

Neurosurgery and Epilepsy, Utrecht University. I wish to acknowledge Peter van Rijen, Frans Leijten, and Cyril Ferrier, who have all helped me to further form an integral view on epilepsy; more importantly, they have helped and encouraged me to support young scientists (especially Dora Hermes with her work on gamma waves and patterns sensitivity) and young physicians and technicians to experience the special role photosensitivity can play in deciphering epilepsy (Fig. 15).

I am grateful for the wonderful contributions of so many esteemed colleagues to this book, with whom I worked together and am confident that this book will further stimulate interest and research in this specific phenomenon of epileptiform EEG discharges that can be evoked by visual stimuli to the benefit of all patients with epilepsy. And for those who might wonder if I myself are photosensitive, I have been exposed to so many flashes and striped patterns over the years, that I know, confirmed via EEG, that I do not have (photosensitive) epilepsy.

Utrecht, The Netherlands Dorothee Kasteleijn-Nolst Trenite

Introduction

Commentary and Insight on the Importance of the Respective Chapters, as Stated in This Book Titled: *The Importance of Photosensitivity for Epilepsy*

What can we look forward to in this new book? Each chapter provides a sentinel summary of past knowledge plus an abundance of new information concerning each topic. The chapters in this book have been grouped into various themed sections, for which I have provided both commentary and insight, herein, plus, I have hopefully provided a similar keen annotation for each individual chapter, written by experts, as well.

Overview of Part I: Has Photosensitivity Changed Over the Years?

Yes, photosensitivity has changed over the years:

- Provocative factors in our indoor and outdoor environment have increased enormously and became diverse. Recognizing sensitivity for a particular visual stimulus has thus become much more difficult.
- Home video and cellphone pictures of suspected provocative situations and devices are helpful in diagnosing photosensitive epilepsy.
- Deep red monochromatic flashing lights are being used in many modern videogames, advertisements, and cartoons and have been proven to be extremely provocative.
- Routine IPS methodology is less rigorously performed with technically flawed photic stimulators. Many physicians consider thus visual sensitivity as a condition that has disappeared or is less relevant.
- Instead of classifying photosensitivity as a "stand-alone" entity in epilepsy and pathophysiology, it is nowadays more considered as an integral part of the epilepsies.
- *The* epilepsy photosensitivity gene has not yet been discovered, but many candidate genes of syndromes and epilepsies that are connected with PPR have been found.

Chapter #	Short title	Corresponding author	Editor's commentary
1	*Epidemiology*	Barreto da Silva	Detailed descriptions of methodology and outcome of the various studies performed in healthy and epilepsy populations since 1949 are given. In nearly every study, a female preponderance is found in those sensitive to intermittent photic stimulation while this is not found in those with sensitivity to striped patterns, regardless the methodology used. Pattern sensitivity is, to date, never shown in healthy subjects; photosensitivity seems to be a trait that can stay sub-clinically in healthy children with normal background EEG. See also Chap. 7 on prognosis.
2	*Provocative factors*	Striano	Visual sensitivity, being the most important reflex type of epilepsy, typically has recognizable provocative factors in daily life. Best known for its seizure provocation are these situations: flickering sunlight, disco lights, electronic screens, and videogames; patterns and fluorescent lighting are much less known for their provocation. New, potentially provocative devices (e.g., curved, HD television screens and high-intensity LED lamps) need to still be investigated in the EEG laboratory. In this chapter, special emphasis is put on the outcomes of EEG studies in photosensitive patients of the different visual stimuli and its meaning for understanding epilepsy in general.
3	*History*	Genton	Ancient medical traditions recognized the influence of natural visual stimuli as a seizure-provoking factor. In the twentieth century, EEG technology made it possible to "visualize" this sensitivity: in Europe, the USA, and South Africa, many famous epileptologists built (simple) photic stimulators and studied the effect of flashing lights on brain waves in epileptic and psychiatric patients. Colleagues in Japan and India followed soon afterwards. It is fascinating to learn about the origin and development of photic stimulation before it was implemented as a routine method in EEG diagnostics. See also Chaps. 18 and 19 for the historical role of animal research.
4	*Photosensitivity within the classification systems*	Appleton	In the latest ILAE 2017 classification, photosensitivity-related items are found only in focal non-motor onset (sensory) and generalized non-motor (eyelid myoclonia, EMA) seizure types. EMA is one of the most debated epilepsy types; it is still unclear if it should belong to the absence or myoclonic types of epilepsy. This very easy-to-read chapter describes the place of photosensitivity in historical classifications, goes into detail in its position within the various syndromes, and concludes that, at this moment, a separate classification of photosensitivity is unnecessary and impracticable. However, in the editor's opinion and as we discover more, it is important to have a specific axis for those who are photosensitive—a JME patient with a PPR needs other advice than a non-photosensitive JME patient.
5	*Genetics*	Bebek	Although it has never been doubted that PPR is a genetic trait, it is yet not clear which genes are involved. Some genes have been discovered to play a role in a variety of syndromes connected with PPR. Further research for PPR genes is necessary; this chapter gives a complete overview of our current knowledge and understanding of PPR genetics and is valuable for clinicians and researchers alike.

Overview of Part II: Does Photosensitivity Matter; Clinical Relevance?

Yes, photosensitivity clearly does matter:

- In particular, when PPRs, being either generalized or focal, are accompagnied with (subtle) clinical symptoms during IPS testing, the likelihood that the patient has epileptic seizures in daily life is very high; thorough clinical history taking is important.
- Insight into their own clinical symptoms and signs during PPR helps patients to detect their individual provocative factors in daily life and thus learn to avoid these.
- When photosensitive patients unwittingly encounter visual stimuli, e.g., flashing programs on TV, sunlight, or LED lamps in tunnels during driving, immediate covering of one eye with their hand prevents a seizure. Every photosensitive patient should get this advice.
- Measuring the photosensitivity ranges as biomarker of sensitivity helps to determine the risk of seizures at different ages and to monitor efficacy of antiepileptic drug treatment.
- The highest prevalence of photosensitivity, as well as the highest sensitivity (ranges), are seen in adolescent females: girls not needing treatment yet might need more protection some years later. Clinical follow-up with IPS-EEG (photosensitivity ranges) is necessary.
- If withdrawal of anti-epileptic drug (AED) is intended in (seizure free) photosensitive patients, regular IPS-EEG before, during, and after complete withdrawal can reveal that the photosensitivity returns or increases. Re-installment of the AED regimen can thus prevent occurrence of GTCS or even status (personal data).
- PPR at an early age (e.g., in Dravet syndrome) gives a worse prognosis in epilepsy in general. Interaction of different underlying mutated genes might be the cause.
- PPR certainly occurs also in focal epilepsies, and therefore, *the epilepsy of a PPR patient should not be automatically classified as generalized*. Classification has its implications for further diagnostic workup, prognosis, and treatment.
- Photosensitive children and adults (even those with generalized epilepsy) can have a visual aura and headache complaints; this should not be mistaken for migraine.
- Discomfort to flickering lights, striped patterns, and TV screens is reported not only in patients with photosensitive epilepsy but also in those with headache disorders, brain tumor, panic disorders, and after brain trauma.

Chapter #	Short title	Corresponding author	Editor's commentary
6	*Correlation EEG and clinic*	Capovilla	Photoparoxysmal EEG responses (PPR) can be focal (Waltz grade 1 and 2, usually over the parieto-occipital area of the brain) or generalized (Waltz grade 3 and 4). It is useful to diagnose syndromes and monitor treatment. PPR are found in many different epilepsies, ranging from the catastrophic epilepsies to the benign focal epilepsies. In this chapter in particular, there is an impressive collection of PPR examples with concomitant clinical information.
7	*Prognosis*	Steinhoff	Prognosis is a difficult subject in epilepsy, in general, and even more in photosensitive epilepsy or epilepsy with a PPR. Age, treatment, and underlying epilepsy syndrome/comorbidity play a role. We need standardized and repeated photic stimulation, with the determination of ranges as follow-up study clinically. PPR, as isolated phenomenon, is especially seen in female adolescents and seems to disappear in about 30% around 30 years of age. However, in a recent study in healthy school children, it appeared that one female of the seven PPR-positive children developed later epilepsy: focal epilepsy with a temporal focus (see Chap. 1); thus, it might be that she has inherited traits for temporal epilepsy and PPR and that the interaction caused seizures. A study in children with generalized epilepsy and a PPR suggested that seizure freedom (77%) was independent of disappearance of the PPR (37%). However, the IPS methodology is not clearly described and testing included only the eyes closed condition. It is, in addition, imperative to recognize that while abolition is important, *diminishment of photosensitivity ranges is definitely known to reduce the risk of having seizures and could therefore contribute to seizure freedom.* An extensive survey is given of the various aspects of prognosis. The case report of a patient, who responded favorably during a controlled Proof-of-Concept trial to a single oral AED dose, but did not react anymore when in long term steady-state, is intriguing; is this a difference between acute and chronic treatment or lack of compliance in a possibly self-inducing woman? Unfortunately, blood AED levels have not been measured during the EEGs at steady state.
8	*Special syndromes*	Franceschetti	PPR occurs in many epilepsy subtypes (10–92%) and is found in patients with chromosomal abnormalities (e.g., Down syndrome) as well. While myoclonic seizures are provoked during IPS, occipital seizures occur as well, dependent on the type of epilepsy it is connected with. In encephalopathic epilepsies of infancy, it is remarkable that the PPR appears to be an early marker of severity, yet is also a transient phenomenon. A nice and comprehensive overview is given of the different aspects of PPR that appear in the various syndromes from infancy to adulthood.

9	*Focal epilepsy General overview*	Brandt	Photosensitivity can be found in up to 20% of focal epilepsies, the most frequent type being occipital lobe epilepsy. In the recent review by Kasteleijn et al. on focal epilepsy and PPR (Epil Res. 2017; 133: 113–120), it was also found that "focal epilepsy" AEDs are effective both in the "Human Photosensitivity Model of Epilepsy" and in real life in photosensitive patients. A clear overview is given of the position of photosensitivity in relation with focalities within the new classification of epilepsies. See also Chap. 6 and the following Chaps. 10 and 11.
10	*Focal epilepsy EEG perspective*	Martins da Silva	Modern techniques help in finding evidence of a local origin of the photo-paroxysmal EEG response, regardless the type of epilepsy it coincides with. It becomes also more and more clear that, even in generalized epilepsies, focal signs such as visual aura are not uncommon. Read also more about the use of gamma waves in photosensitivity research in Chap. 17!
11	*Focal epilepsy Clinical perspective*	Jocic-Jakubi	The prevalence of photosensitivity is not only age dependent (higher in younger age groups), but also the likelihood of finding photosensitivity in focal epilepsies is age dependent (higher in adults). Occipital seizures, especially present in children, are different: thanks to the slow generalization of the occipital discharges focal clinical features are much more easily recognized. In this comprehensive chapter, special focus is placed on the various occipital epilepsies and their overlap with generalized epilepsies.
12	*Various disease states*	Parisi	Few studies have addressed this subject. Some isolated cases have been published where clinicians encounter a combination of a specific disease with a PPR by coincidence. Links between the various disease states and epileptic photosensitivity exist however; for example, discomfort to bright (intermittent) light, striped patterns, and TV screens is reported not only in patients with photosensitive epilepsy but also in those with headache disorders, brain tumor, panic disorders, etc. High alpha EEG power and photic driving might be the reason of this discomfort. In posttraumatic epilepsy, both photophobia and PPR have been shown. Parisi and colleagues give us a fascinating view on the pathophysiological pathways that are involved in a hyperexcitable visual cortex.
13	*What to learn from a patient*	Timmings	Patients can recognize potentially provocative stimuli in their environment, such as use of faulty LED lighting. Fortunately, avoidance of triggers can be helpful in managing the condition. Measuring the photosensitivity ranges as biomarker of sensitivity helps to determine the risk of seizures at different ages and to monitor efficacy of antiepileptic drug treatment. Critical analyses of several studies on AED effect on PPR are given.

Overview of Part III: Abnormal Electroencephalographic Response to Photic Stimulation in Humans and Animals

Studying EEG responses to IPS in humans and animals has taught us the following:

- Distinction must be made between the diverse PPR waveforms with its various locations of onset of PPR and physiological normal evoked responses.
- Gamma oscillations seem to be highly correlated to the provocativeness of visual stimuli.
- The connections between the occipital cortex and motor brain areas are strong and explain why clinical signs during PPR are, in the majority of cases, of myoclonic nature.
- Cortical and sub-cortical brain connections have been shown during a PPR. A PPR is thus part of an epileptic brain network and can help elucidate the very nature of epilepsy.
- Three animal species (baboon, chicken, and dog) are known with naturally occurring photosensitivity: this raises hypotheses about natural selection (advantage/disadvantage on being photosensitive) and gives clues on pathophysiology and genetic transmission.
- Differences in EEG reaction to visual stimuli are noticed in different rat strains: albino rats have more and larger photically induced after discharges than pigmented rats.
- Sprague Dawley rats can be photo-sensitized with extreme flashing, while baboons with a PPR decrease their sensitivity on repeated stimulation. Both these observations are however not seen in humans.
- Genetic research in homozygous photosensitive Ridgebacks (dogs) gave us the PPR-connected gene DIRAS1.

Chapter #	Short title	Corresponding author	Editor's commentary
14	*How to interpret EEG results?*	Guerrini	Photoparoxysmal responses are often considered to be only generalized, rhythmical, and consisting of spike and waves: this interpretation is incorrect, because PPR can consist of different waveforms and localization, just as in focal epilepsy. Furthermore, spikes, one of the variations in PPR, should not be confused with the normal visual evoked responses that are phase-locked to the flash. Sleep deprivation and spontaneous sleep thereafter have an important impact on occurrence of PPR. PPR is part of a genetic trait or an epileptic disease and nice examples are given of PPR in different epilepsy syndromes.
15	*Motor manifestations*	Rubboli	There is evidently a strong connection between the occipital cortex and the motor regions as seen in the clinical symptomatology of the majority of photosensitive epilepsies and in its explicit form in eyelid myoclonia with absence seizures. A thorough, thoughtful, and very interesting insight is given in the various aspects of eyelid myoclonia, including self-induction and pathophysiological mechanisms.
16	*The basics*	Koepp	The different functional studies show altered connections within networks in photosensitive patients and during PPR: cortico-cortical, including visuo-motor, and cortico-subcortico-cortical connections (via thalamus and callosum) are involved. Excitability at rest and during a PPR might be key in understanding basic underlying mechanisms of photosensitivity. The latest developments in unraveling the pathophysiology of the PPR are given in this important chapter.
17	*Gamma oscillations*	Avanzini	Gamma oscillations (30–100 Hz) have been studied more intensely since the past two decades when advanced digital EEG and MEG software became available. In this fascinating chapter, hypotheses are given about how various provocative visual stimuli can inhibit, destabilize, or synchronize the circuits in human visual cortex. In other words, what triggers the PPR?
18	*What can we learn from animals?*	Szabó	Photosensitivity (clinical history and PPR) has been studied extensively in three natural animal species: Papio Papio and other baboon subspecies, Fayoumi chicken, and lately Rhodesian Ridgeback and other dog species. Although there are similarities to human photosensitivity (familial congregation of PPR, Juvenile Myoclonic Epilepsy or Progressive Myoclonic Epilepsy phenotype), there are also differences: response to anti-epileptic drugs (AEDs) is not exactly similar, and repeated IPS can reduce photosensitivity in the baboon. Genetic research has been successful: the new gene DIRAS1 was found mutated in homozygous Ridgebacks. This chapter gives an excellent overview of clinical, neuro-physiological, and neuro-pathological outcomes of animal studies, thus enriching our knowledge on the photosensitivity trait.
19	*Photo-sensitivity in rats*	van Luijtelaar	Similar to human research, there is an especially great variability in latency and amplitude of the early components of visual evoked potentials (VEPs) found in rats due to different methodologies. Also, strain differences are seen: albino rats have more and larger photically induced after discharges (PhADs) than pigmented rats. The PhADs are of special interest because they are enhanced by (a) quiet animal behavior, (b) the proconvulsive agent PTZ, and (c) GABA antagonists; alternatively, they are suppressed by the anti-seizure drugs ESM, VPA, DZP, that are effective in human photosensitivity as well. In the genetic absence rats, VEPs can be elicited, but they become much more aroused by photic stimulation than humans with strong suppressive effect on the spike and wave discharges (SWDs) as a result. To date, no PPR has been recorded in rats, although Uhlrich et al. (J Neurophysiol. 2005; 94: 3925–37) managed to sensitize rats gradually to flicker with chronic IPS. Studies mentioned in this very informative and absorbing chapter gives us insight into pathways of photosensitivity and SWDs.

Overview of Part IV: Peculiarities of Photosensitivity in Diagnosis and Treatment

Photosensitive patients do indeed have their peculiarities:

- Prevalence rates of PPR differ among ethnicities, indicating that there is an important genetic factor involved.
- Very specific for photosensitivity is a systematic overrepresentation of females (2:1) in a healthy normal population or in epilepsy.
- In adolescence female preponderance in PPR-positives is maximally with also the biggest photosensitivity ranges in the EEG, suggesting an important role of X-linked genes and sex hormones.
- Dravet syndrome children show a peculiar type of photosensitivity: PPRs occur already at the very start of the disease and in time even before the spontaneous EEG discharges occur. Furthermore, the photosensitivity comes and goes, which cannot be explained easily by (changes in) antiepileptic drug (ASM) treatment.
- Dravet syndrome patients are more often pattern sensitive and self-inducers of seizures ("sunflower syndrome").
- PPR can be used as a biomarker for efficacy testing of AEDs, for all types of epilepsy. This has led to the human "Phase IIa Photosensitivity Model in Epilepsy" proof-of-concept study for novel potential AED/ASM development.
- Higher prevalence rates of epilepsy in general are found in the developing countries; it is possible that head trauma, perinatal injury, and CNS infections, all more seen in those countries, could result in a higher incidence of photosensitive epilepsy than expected.

Chapter #	Short title	Corresponding author	Editor's commentary
20	*Genetic (ethnic) differences*	Shiraishi	Typical for photosensitivity, there are clear differences in prevalence of PPR with or without epilepsy among multiple nationalities and ethnicities. Based on a variety of studies, hypotheses to explain these differences are being discussed. A very interesting chapter!
21	*Gender differences*	Delanty	In nearly all epilepsy syndromes, patients with a PPR will show female preponderance (exceptions are childhood absence epilepsy and the progressive encephalopathies). Also, the likelihood of having epileptic seizures is greater in women with a PPR. More research needs to be done to elucidate the role of sex hormones and X-linked genes in photosensitivity. This chapter provides an excellent starting point!
22	*Age differences*	Seri	Photosensitivity, in general, is most prominent at childhood and adolescence and the question thus arises: "What role does maturation of the visual system and related networks play?" However, photosensitivity is also found at other ages and is dependent on the epilepsy type it is connected with. This very interesting chapter argues both type of hypotheses.
23	*Dravet syndrome*	Berten	A genetic etiology of Dravet syndrome (DS) is known since 2001 (*SCN1A* gene), and many phenotype–genotype correlations have been made. Early photosensitivity, often combined with pattern sensitivity and self-induction, is considered part of DS. Another typical provocative factor is elevation of body temperature. Rigorous analysis of clinical and EEG data of 58 patients with DS and comparison with available literature are described in this insightful chapter: it especially shows discrepancies in study results due to selection bias, IPS methodology, and differences in PPR definition.
24	*The Human Photosensitivity Model*	Reed	The PPR can be used as a biomarker for AED pharmacotherapeutic studies. Over the years, this Proof-of-Concept principle has led to a standardized human Phase IIa Photosensitivity Model in Epilepsy ("PMoE") with its successful detection of preliminary efficacy of single oral doses of new AEDs. If rapidity of brain entry or impact of small pharmacokinetic changes (both via IV infusions) need to be evaluated, adaptation of methodology is imperative. Such trial adaptations are described and explained with great knowledge and detail.
25	*Identification of geographic*	Mifsud	In the "early days," study sites were limited to the UK, USA, and France (see Chap. 3 on history). The authors of this chapter have documented, that studies on photosensitivity have been additionally performed in many other sites in European countries, South America and Asia. Interest in photosensitivity has thus grown, which is reflected also in the diverse geographical background of the authors in this book. A plea is made for further information on photosensitivity in developing countries.

Overview of Part V: How to Approach the Photosensitive Patient, the Caregiver, and the Surrounding

Photosensitive patients need the following:

- First of all, a good clinical history from caregiver and patient alike is instrumental for a proper diagnosis and a way to help the patient in deciding if avoidance is sufficient or that anti-epileptic drug (AED) treatment is necessary.
- A proper video-EEG with IPS (and provocative videogame), according to the guidelines, gives maximal information with a minimum of risk of provoking a GTCS.
- A combination of history and EEG allows an individual approach to optimally advise the photosensitive patient concerning avoidance of visual stimuli and/or use of different types of AED.
- Physicians are in need of clear protocols and flowcharts concerning detection and handling of photosensitivity.
- Patients need to be warned for new technologies (e.g., virtual reality [VR] glasses and high-definition screens [HD TV]) that could worsen their photosensitivity.
- Architects who are involved in building constructions and interiors need to get information from their professional organizations how to diminish provocative visual stimuli that can provoke seizures.

Chapter #	Short title	Corresponding author	Editor's commentary
26	*Optimizing the patient's history*	Brinciotti	In general, taking a good clinical history is very important, but certainly is the case for the diagnosis of potential visually induced seizures. The circumstances under which seizures happen need to be "dissected" with the help of cameras and drawings of perceived visual aura. Self-induction needs a special approach. The authors give a very clear, concise, and up-to-date overview of environmental provocative visual stimuli and stress that also the type of concomitant epilepsy/ syndrome must be taken into account.
27	*Maximizing EEG methodology*	Abou-Khalil	Proper EEG diagnostics confirm a clinical history of seizures that are (possibly) provoked by visual stimuli. It can also provide a measure of photosensitivity that predicts liability to seizures in daily life and allows follow-up of AED treatment effect. During AED withdrawal, PPR ranges can be monitored to predict likelihood of re-occurrence of seizures. But how do we best register an EEG that is maximally informative? In this chapter, the best methodology is simple and explained in detail with many examples, all according to the guidelines of the professional organizations IFCN, ACNS, and ILAE (European guidelines).
28	*Safety of EEG methodology*	Whitehead	EEG technicians are often reluctant to perform photic stimulation routinely; they never seem to forget a generalized tonic-clonic seizure that occurred unexpectedly during or shortly after intermittent photic stimulation of a patient. Studies, however, show a very low incidence rate of GTCS (<0.05%) provided modern guidelines are followed (see also Chap. 27). Authors show their great clinical (e.g., explain the IPS procedure to the patient to minimize "stress" and other practical advice) and study experience (benefits) with photic stimulation in combination with a thorough literature review.
29	*Treatment and prevention: When?*	Yacubian	About a third of photosensitive patients will not recognize clinical signs, such as eyelid myoclonia, absence or focal seizure, as can be observed during a PPR. When they are informed about this knowledge, they do recognize similar events evoked by visual stimuli in daily life. This helps the clinician and patient to set up preventive measures such as individualized avoidance of stimuli. If PPR is registered in combination with spontaneous epileptiform activity, a significant increase in history of visually induced seizures is found. A similar effect is seen when the sensitivity ranges are wide (more exposure to provocation). If PPR is part of a syndrome, the specifics of that syndrome must be taken into account as well, and AED medication is often necessary. In this chapter, a clear overview is given of the different situations in which patients with a PPR can be found with examples of the different scenarios. A plea is made to individualize preventive advice and AED treatment.

Chapter #	Short title	Corresponding author	Editor's commentary
30	*Treatment and prevention: How?*	Hogan	It is important to manage exposure to visual provocative stimuli. Individually tailored advice is necessary. Much information is given on the blue lenses and different types of anti-seizure medication that have shown to be effective in the photosensitive patients. Together with Chap. 32, a complete picture arises on the choices that must be made to serve the photosensitive patients.
31	*Diagnosis and treatment in daily practice*	Voronkova	How do neurologists-epileptologists use available knowledge on photosensitivity in daily patient care? Is it important to know if a patient has a PPR? These and other related issues have been investigated via a nationwide questionnaire in Russia. The vast majority of physicians are interested in the subject, and many ideas were given to improve detection of photosensitivity by patients (website, conferences) and by physicians (standards, algorithms and educational courses). Correlation with centers that are specialized in photosensitivity is encouraged (see Chap. 25).
32	*A guide for patients and caregivers*	Covanis	Sensitivity to visual stimuli in daily life such as flickering sunlight, TV screens, striped patterns, videogames, LED lamps, etc. is often not recognized as reflex type of epilepsy by patients, caregivers, or physicians. Sometimes patients are even referred to a psychiatrist. Awareness is crucial; it can help prevent seizures and tailor treatment. In this chapter, all current information is given to identify potentially provocative visual environmental triggers in detail and for the physician to understand why brain pathophysiology reacts to the various physical elements of visual stimuli from the environment, e.g., to distinguish strobe light from escalators. In Sect. 32.6, detailed and complete descriptions of new technologically developed hazards are given to make patients, caregivers, and also professionals aware of the difficult modern environment that people with (potential) sensitivity live in nowadays.
33	*Technical issues to prevent photosensitivie seizures*	Ferlazzo	Technological new developments (e.g., VR glasses) and daily use of electronic devices (e.g., computer/TV screens) unknowingly increase the likelihood of visually provoked seizures in those who are susceptible. Devices are provocative due to a combination of the countries mains frequency, program content (flashing images, patterns, colors), and emotional involvement. This chapter unravels, nicely, the different provocative elements that contribute to an unsafe environment for photosensitive patients. Furthermore, recommendations are given to videogame producers. Guidelines need to be designed also for architects who are involved in constructing buildings and interiors.
34	*Summary and observations for new Research*	Kasteleijn-Nolst Trenite	A point by point summary is given about the most important things that have been learned in the past decades about (the role of) photosensitivity in epilepsy. Then the focus is put on which observations and issues need more research in the near future.

Appendix

Photosensitivity (sensitivity to light) in epilepsy expresses itself as epileptic seizures of different severity (from eyelid flutter to GTCS) that are repeatedly provoked in a patient by visual stimuli in daily life (flickering sunlight, colored lights, TV, striped patterns). This genetically determined sensitivity can be diagnosed and quantified with IPS at different flash frequencies during EEG recording. The evoked epileptiform EEG responses are called PPR, and these can be accompanied by signs and symptoms that are recognizable by the patient.

Abbreviations that are regularly used in this book:

- EEG = Electroencephalogram
- IPS = Intermittent Photic Stimulation, a routine EEG method in epilepsy diagnostics
- ILS = Intermittent Light Stimulation = IPS
- Hz = Hertz = flashes per second
- PPR = Photoparoxysmal EEG Response (focal or generalized epileptiform reaction visible in the EEG when sensitive persons are being exposed to intermittent flashing lights or other visual stimuli)
- PS = Photosensitive = Photogenic = Photosensitivity = Photic Sensitivity
- GTCS = Generalized Tonic Clonic Seizure
- M = Myoclonus = Muscle jerk
- AED = Antiepileptic Drug
- ASM = Antiseizure medication (modern and more correct term for AED)

Dorothee Kasteleijn-Nolst Trenite

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