which apply to PCMs. In reconstructing the past, there are (at least) three specific sources of uncertainty that are worthy of special attention.

**Tree uncertainty.** There is uncertainty from the building of the phylogeny. Tree-building methods are not perfect and often are used with data constraints, especially limited sampling of both genomes and species. As such, there is always uncertainty about phylogeny. Species can be misplaced in a phylogenetic tree, ancestral nodes can be wrongly inferred, or more subtly, but more commonly, branch lengths are incorrect. If we are interested in species diversification and what traits promote or inhibit such diversification, it is not difficult to see how these mistakes in phylogenetic trees can influence our inference.

**Trait uncertainty.** For most PCMs, we use trait values representative for particular species. However, traits are measured with error. In addition, what constitutes ‘representative’ is a difficult issue. Often, a value from a single population is used and, not uncommonly, some trait values come from a single observation. Another relevant point is that trait variation within species can be very large. Think of our own species — what is a representative value for human height?

**Model uncertainty.** When we investigate trait evolution, we assume a certain model of evolution — most often, the Brownian motion model. However, a trait can evolve quite differently from such a simple model and there may be heterogeneity in the tempo and mode among the branches of the tree. Although approaches are now available to test among competing models and to represent process heterogeneity in a limited way, there is no guarantee that any of the current generation of models are adequate in capturing the true complexity of trait evolution through space and time.

To have the appropriate confidence in our ability to infer events and processes from the deep past, we must both estimate and combine these uncertainties properly. However, dealing with all of these uncertainties simultaneously is still beyond the scope of the current generation of methods, with a few notable exceptions. That said, the appeal of the lofty goal — the promise of explaining key aspects of the evolution of life — will drive the field forward. Although we are still a long way from achieving this goal, it is nonetheless an exciting time for PCMs. Further, these shortcomings have not stopped PCMs from providing us with important new insights into the evolutionary secrets of life, including the history of mankind.

**FURTHER READING**


**Correspondence**

**Gamma oscillations and photosensitive epilepsy**

Dora Hermes1,4,5,* and Dorothée G.A. Kasteleijn-Nolst Trenité2,5, and Jonathan Winawer3,5,*

Certain visual images, even in the absence of motion or flicker, can trigger seizures in patients with photosensitive epilepsy. As of yet, there is no systematic explanation as to why some static images are likely to provoke seizures, while others pose little or no risk. Here, we examined the neurophysiology literature to assess whether the pattern of neural responses in healthy visual cortex is predictive of the pathological responses in photosensitive epilepsy. Previous studies have suggested that gamma oscillations (30–80 Hz) measured in human visual cortex may play a role in seizure generation [1,2]. Recently, we and others have shown that increases in gamma band power can come from two very different cortical signals, one that is oscillatory (with a narrow peak between 30 Hz and 80 Hz), and another that is broadband [3]. The oscillatory signal arises from neuronal synchrony in the local population, while the broadband signal reflects the level of asynchronous neuronal activity, and is correlated with multunit spiking [4]. These two responses have different biological origins and different selectivity for image properties. Here, we followed up on the previous proposals [1,2] to ask whether the image features that increase seizure likelihood in photosensitive epilepsy are linked to narrowband gamma oscillations specifically, or are associated with any kind of increase in visual activity. Based on published work, we compared pairs of image classes on a number of dimensions, and show that the type of image that elicits larger narrowband gamma oscillations in healthy visual cortex is also more likely to provoke seizures or pre-seizure activity in patients with photosensitive epilepsy. In contrast, images that elicit larger broadband, multunit, or fMRI responses are much less predictive of seizure activity. We propose that a risk factor for seizures in patients with photosensitive epilepsy

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1,2 In this study, we used the published work of other researchers to assess whether the pattern of neural responses in healthy visual cortex is predictive of the pathological responses in photosensitive epilepsy. Previous studies have suggested that gamma oscillations (30–80 Hz) measured in human visual cortex may play a role in seizure generation [1,2]. Recently, we and others have shown that increases in gamma band power can come from two very different cortical signals, one that is oscillatory (with a narrow peak between 30 Hz and 80 Hz), and another that is broadband [3]. The oscillatory signal arises from neuronal synchrony in the local population, while the broadband signal reflects the level of asynchronous neuronal activity, and is correlated with multunit spiking [4]. These two responses have different biological origins and different selectivity for image properties. Here, we followed up on the previous proposals [1,2] to ask whether the image features that increase seizure likelihood in photosensitive epilepsy are linked to narrowband gamma oscillations specifically, or are associated with any kind of increase in visual activity. Based on published work, we compared pairs of image classes on a number of dimensions, and show that the type of image that elicits larger narrowband gamma oscillations in healthy visual cortex is also more likely to provoke seizures or pre-seizure activity in patients with photosensitive epilepsy. In contrast, images that elicit larger broadband, multunit, or fMRI responses are much less predictive of seizure activity. We propose that a risk factor for seizures in patients with photosensitive epilepsy
is engagement of the circuitry that produces gamma oscillations. Photosensitivity, defined as an abnormal response in the electroencephalogram (EEG) triggered by light stimulation, is common and is found in 0.3–3% of the population [5]. Photosensitive epilepsy, where light stimulation causes seizures, has a prevalence of 1 in 10,000 individuals (or 1/4,000 between ages 5–24) [5]. Highly provocative stimuli can occur in the natural environment, on TV and in computer games. In the Pokémon incident in 1997, for example, one Pokémon episode resulted in seizures and hospital visits for 685 people in Japan. In a separate incident, a video for the 2012 Olympics was removed from the website because it caused seizures. Patients with photosensitive epilepsy are advised to avoid provocative stimuli.

Neuroscientists and neurologists have started to detail the visual input that can trigger a seizure. Repetitive flashes are well known for their potential to induce seizures, but stationary patterns can also elicit seizures in about 30% of patients with photosensitive epilepsy [5]. Large, high contrast gratings of 2–4 cycles per degree are most provocative to elicit abnormal, epileptiform, responses in the EEG signal, the photoparoxysmal response (PPR, which is the clinical marker for photosensitivity); looking at these gratings for more than 500 ms can trigger a seizure. Several image features influence the degree to which a stimulus is provocative (Table 1). The likelihood that a PPR is induced by viewing a grating can be reduced by decreasing the size of the grating, by reducing the contrast, by superimposing a second grating to create a plaid or checkerboard, or by superimposing noise. Both sine and square wave gratings are provocative whereas chromatic contrast alone (isoluminant gratings) is not.

A comprehensive overview of the neurophysiology literature indicates that the same image properties that can trigger seizures also elicit gamma oscillations in the local field potential in visual cortex. Gamma oscillations are most strongly driven by large, high contrast gratings and can be reduced in amplitude by decreasing the size of the grating, by reducing the contrast, by superimposing a second grating to create a plaid or checkerboard, or by superimposing noise [7]. In addition, gamma oscillations in visual cortex peak at a spatial frequency around 2–4 cycles per degree, sine and square wave gratings both induce gamma oscillations, and isoluminant gratings induce little or no gamma oscillations [8]. These stimulus features are highly similar to those that are provocative to induce seizures in photosensitive epilepsy (Table 1; additional references from the original reports are in Table S1 in Supplemental Information, published with this article online).

Importantly, the stimulus manipulations that increase both gamma oscillations and PPRs differ from those that increase multifractal firing rates [7] and the fMRI Blood Oxygen Level Dependent (‘BOLD’) response (Table 1). For example, gamma oscillations increase with larger stimuli, while the level of local neuronal firing and BOLD amplitude decrease (due to surround suppression). When a grating is converted to a plaid by overlaying additional orientations, gamma oscillations decrease, while increasing neuronal population firing rates and the BOLD signal. Superimposing white noise on a grating decreases gamma oscillations while not influencing firing rates. Chromatic contrast (e.g., an isoluminant grating) elicits high firing rates and a large BOLD response, but does not elicit a large gamma oscillation [8]. The stimuli that are most provocative in photosensitive epilepsy therefore match the stimuli that strongly drive gamma oscillations, and do not match the stimuli that strongly drive the overall level of neuronal firing or the metabolic demand as measured by BOLD fMRI.

This review focuses on the link between photosensitive epilepsy and gamma oscillations induced by spatial
features of images. Narrowband gamma oscillations are highly dependent on the visual stimulus [3,7] and these oscillations are associated with engagement of specific types of cells and circuitry in visual cortex. We hypothesize that engagement of this circuitry is a factor that increases the likelihood of seizure activity, perhaps because this circuit does not self-stabilize in some patients with photosensitive epilepsy. Stroboscopic (mean field) flicker across many frequencies (3 Hz to 60 Hz) can also be highly provocative in photosensitive epilepsy (Table S2). Periodic stimuli elicit periodic responses; however, it is unclear whether these stimuli also engage the same specialized circuitry that produces induced (non-stimulus-locked) gamma oscillations. Hence the mechanism by which flicker induces seizure activity remains an important topic for further exploration.

We still know little about the underlying mechanisms of photosensitive epilepsy, in part because there is no animal model that translates well to humans and because there is no experimental paradigm for studying risk factors for photosensitive epilepsy in healthy human subjects. In contrast, neither of these limitations applies to gamma oscillations. The circuitry involved in gamma oscillations in visual cortex is extensively studied at the cellular level in animal models, at the systems level in healthy human subjects, and at the level of computational modeling. In particular, studies at all of these levels propose that the interaction between excitatory neurons and inhibitory interneurons is important for the generation of gamma oscillations [3] and fast spiking basket interneurons have resonant properties in the gamma frequencies and are hypothesized to play a role in gamma oscillations. Moreover, animal recordings have shown that large stimuli compared to small stimuli increase the power of gamma oscillations, and drive fast spiking interneurons more strongly [10]. Competing computational models (reviewed in [9]) have different implications for the type of stimuli and neuronal states that are likely to modulate the level of gamma oscillations in healthy visual cortex. If our conjecture is correct, then a critical question to address is why engagement of this circuitry leads to seizures or atypical responses in the EEG in some people, but not in others. Therefore, the tools used to study gamma oscillations — at the computational, cellular, circuit, and systems levels — might be marshaled to explain not only why gamma synchrony occurs, but also how excessive synchrony can occur in epilepsy.

SUPPLEMENTAL INFORMATION

Supplemental Information contains two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2017.03.076.

REFERENCES


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Supplemental Information: Gamma oscillations and photosensitive epilepsy

Dora Hermes, Dorothée G. A. Kasteleijn-Nolst Trenité, Jonathan Winawer

Contents

- **Table S1**: an extended version of Table 1 in the main manuscript. Table 1 shows how four types of brain signals change as the visual input changes in a systematic manner. Table S1 provides a selection of references for each of these observations. The references in this table are not exhaustive, but are representative examples from the literature. Note that various aspects cannot be presented in this brief overview, such as, for example, interactions between stimulus size and the orientation of the surround and interactions between color and spatial frequency.

- **Table S2**: temporal stimulus features
Table S1: an extended version of Table 1

<table>
<thead>
<tr>
<th>Stimulus characteristic</th>
<th>Stimuli exemplars</th>
<th>I. Stimulus provocativeness (#PPR responses)</th>
<th>II. Gamma oscillation in V1/V2</th>
<th>III. Spiking activity in V1/V2</th>
<th>IV. BOLD in V1/V2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Size</td>
<td><img src="image1" alt="Size Stimuli" /></td>
<td><img src="image2" alt="Green Up" /> [S1]: Figure 8 [S2]: Figure IV.8.3.3</td>
<td><img src="image3" alt="Green Up" /> [S3]: Figure 1 [S4]: Figure 2</td>
<td><img src="image4" alt="Red Down" /> [S3]: Figure 1 [S4]: Figure 2</td>
<td><img src="image5" alt="Red Down" /> [S10]: Figure 3 [S11]: Figure 7 [S12]: Figure 5</td>
</tr>
<tr>
<td>2. Contrast</td>
<td><img src="image6" alt="Contrast Stimuli" /></td>
<td><img src="image7" alt="Green Up" /> [S1]: Figure 7 [S13]: Figure 4</td>
<td><img src="image8" alt="Green Up" /> [S4]: Figure 2 [S6]: Figure 4 [S14]: Figure 6</td>
<td><img src="image9" alt="Green Up" /> [S4]: Figure 2 [S6]: Figure 4 [S14]: Figure 6</td>
<td><img src="image10" alt="Red Down" /> [S17]: Figure 3,5,7 [S16]: Figure 2 [S18]: Figure 4,7</td>
</tr>
<tr>
<td>3. Number of orientations</td>
<td><img src="image11" alt="Number of Orientations Stimuli" /></td>
<td><img src="image12" alt="Red Down" /> [S1]: Figure 3 [S19]: Table 3 [S20]: Figure 3</td>
<td><img src="image13" alt="Red Down" /> [S21]: Figure 2 [S19]: Table 3 [S20]: Figure 3</td>
<td><img src="image14" alt="Green Up" /> [S21]: Figure 2,1,3 [S22]: Figure 4,1,3</td>
<td><img src="image15" alt="Green Up" /> [S17]: Figure 3,5,7 [S22]: Figure 6 [S23]: Figure 3</td>
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<tr>
<td>4. Luminance (\rightarrow) chromatic</td>
<td><img src="image16" alt="Luminance Stimuli" /></td>
<td><img src="image17" alt="Red Down" /> [S19]: Table 3 [S24]: Figure 3 [S25]: Figure 1</td>
<td><img src="image18" alt="Red Down" /> [S19]: Table 3 [S24]: Figure 3 [S25]: Figure 1</td>
<td><img src="image19" alt="Red Down" /> [S24]: Figure 3 [S26]: Figure 3</td>
<td><img src="image20" alt="Red Down" /> [S24]: Figure 3 [S26]: Figure 3</td>
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<tr>
<td>5. Spatial frequency low to middle (1-4cpd)</td>
<td><img src="image21" alt="Spatial Frequency Low to Middle Stimuli" /></td>
<td><img src="image22" alt="Red Down" /> [S1]: Figure 1 [S13]: Figure 6</td>
<td><img src="image23" alt="Green Up" /> [S7]: Figure 12 [S27]: Figure 3</td>
<td><img src="image24" alt="Red Down" /> [S15]: Figure 2,12 [S7]: Figure 12</td>
<td><img src="image25" alt="Red Down" /> [S28]: Figure 4 [S29]: Figure 6</td>
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<tr>
<td>6. Spatial frequency middle (1-4cpd) to high</td>
<td><img src="image26" alt="Spatial Frequency Middle to High Stimuli" /></td>
<td><img src="image27" alt="Red Down" /> [S1]: Figure 1 [S13]: Figure 6</td>
<td><img src="image28" alt="Red Down" /> [S7]: Figure 12 [S27]: Figure 3</td>
<td><img src="image29" alt="Red Down" /> [S15]: Figure 2,12 [S7]: Figure 12</td>
<td><img src="image30" alt="Red Down" /> [S28]: Figure 4 [S29]: Figure 6</td>
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<tr>
<td>7. Sinusoidal (\rightarrow) square wave</td>
<td><img src="image31" alt="Sinusoidal to Square Wave Stimuli" /></td>
<td><img src="image32" alt="Red Down" /> [S19]: Table 3 [S30]: Figure 2</td>
<td><img src="image33" alt="Red Down" /> [S19]: Table 3 [S30]: Figure 2</td>
<td><img src="image34" alt="Red Down" /> [S30]: Figure 2</td>
<td><img src="image35" alt="Red Down" /> [S19]: Table 3 [S30]: Figure 2</td>
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<td>8. Increasing noise</td>
<td><img src="image36" alt="Increasing Noise Stimuli" /></td>
<td><img src="image37" alt="Red Down" /> [S32]: 8 Study 5</td>
<td><img src="image38" alt="Red Down" /> [S32]: 8 Study 5</td>
<td><img src="image39" alt="Red Down" /> [S32]: 8 Study 5</td>
<td><img src="image40" alt="Red Down" /> [S32]: 8 Study 5</td>
</tr>
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</table>

Table S1: The image features that are most provocative in photosensitive epilepsy (expressed as photo-paroxysmal responses (PPR) in the EEG), are also the most likely to
induce large gamma oscillations. The first two columns show example image pairs, differing in size, contrast, number of orientations, luminance v chromatic contrast, low v mid spatial frequency, mid v high spatial frequency, sinusoidal v square wave, and level of superimposed noise. The following columns describe how four brain signals change according to these image properties:

I. **Stimulus provocativeness in photosensitive epilepsy.** The number of PPR responses measured with EEG in photosensitive epilepsy.

II. **Gamma oscillations in V1/V2.** The amplitude of gamma oscillations measured with intracranial electrodes in cat, macaque or human V1/V2 or measured with magnetoencephalography (MEG) in human visual cortex.

III. **Spiking activity in V1/V2.** Single or multi-unit activity measured in cat, macaque or human V1/V2.

IV. **BOLD in V1/V2.** The amplitude of the BOLD response measured with fMRI in macaque or human V1/V2.

The arrows indicate whether the signals increase or decrease with the feature difference (Upward arrows indicate greater responses for the images feature on the right). A desaturated arrow indicates that the evidence is variable within or across studies. The critical finding is that signal I (the number of PPRs in photosensitive patients) changes in the same way as signal II (the amplitude of the gamma oscillations). Signals III and IV (spiking activity and fMRI BOLD signal) show different patterns. Abbreviations: cpd = cycles per degree. The bracketed numbers and figure number indicate the reference and figure providing the supporting evidence.

Notes:

**Row 1. Stimulus size.** Spiking activity and BOLD responses decrease with increasing stimulus size, assuming the stimulus does not get smaller than the population receptive field size.

**Row 3. Number of orientations.** If the MUA comes from a cortical column tuned to just one plaid component, then the addition of the second component will lower the response due to cross-orientation suppression, but the summed response across a hypercolumn will tend to increase.

**Rows 5 & 6. Spatial frequency.** Signal changes reflect responses in the fovea.

**Row 7. Sinusoidal \(\rightarrow\) square wave.** Neurons in V1 are more selective for sinusoidal gratings than square wave, and have increased firing at the optimal frequency of sinusoidal gratings compared to the optimal width of square waves [S31].

**Row 8. Increasing noise.** The increases in stimulus provocativeness with increasing noise is only noted for visual discomfort, not for the number of PPRs [S32].

**Not included in the table because the data are incomplete: Single colors.** Red flicker may have a larger chance of evoking PPRs compared to other colors (reviewed in [S37]). There is evidence that relatively more cells in visual cortex are tuned to red [S38]. The effect of single colored stimuli on the level of gamma synchrony is not yet well described.
Table S2: Temporal stimulus features

<table>
<thead>
<tr>
<th>Stimulus characteristic</th>
<th>I. Stimulus provocativeness (#PPR responses)</th>
<th>II. Gamma oscillation in V1/V2</th>
<th>III. Spiking activity in V1/V2</th>
<th>IV. SSVEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Flash frequency</td>
<td>Range: 3-60Hz</td>
<td>When 10-20 Hz flashes elicit a PPR, the harmonics in the gamma range (30-120 Hz) show increased phase consistency compared to when the flashes do not elicit a PPR [S40].</td>
<td>In cat, MUA respond at flash frequencies from 2-50 Hz, and harmonics [S41]. The biggest MUA response at the fundamental frequency is for flash rate ~ 20-30 Hz. These stimuli also produce large 1st harmonic responses (40-60 Hz).</td>
<td>SSVEP amplitude is largest for frequencies around 10, 18, and 50 Hz [S42]. SSVEPs are largest for frequencies near 10, 20, 40 and 80 Hz, and that stimulation at or near these frequencies can cause both subharmonic and harmonic responses [S43].</td>
</tr>
<tr>
<td>2. Reversing versus moving grating</td>
<td>Gratings that oscillate in space (&quot;reversing gratings&quot;) or that contrast reverse drive seizure activity more strongly than gratings that drift continuously in one direction [S44]. The most provocative temporal frequencies for spatially reversing or contrast reversing gratings are 10-20Hz (20-40 reversals per second).</td>
<td>An MEG study showed that a grating with an abrupt contrast reversal induced a larger gamma responses than a grating that moved smoothly [S45].</td>
<td></td>
<td>SSVEPs in response to contrast reversing grating patterns are the largest for 10-20 Hz (20-40 reversals per second) [S46].</td>
</tr>
<tr>
<td>3. Stimulus duration</td>
<td>Patterns presented for &gt; 500 ms can evoke seizures [S47].</td>
<td>Gamma oscillations are sustained during stimulus presentation [S48, 49]. Repeated exposure to a stimulus increase gamma oscillations [S50].</td>
<td>Firing rates often show an initial transient and then reduce [S51]. Repeated exposure to a stimulus decreases multiunit activity [S50].</td>
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</tbody>
</table>

Table S2: Temporal image features. Temporal stimulus changes can influence stimulus provocativeness, gamma synchrony, spiking activity and the steady state visual evoked response (SSVEP).

I. **Stimulus provocativeness in photosensitive epilepsy.** The number of PPR responses measured with EEG in photosensitive epilepsy,

II. **Gamma oscillations in V1/V2.** The amplitude of gamma oscillations measured with intracranial electrodes in cat, macaque or human V1/V2 or measured with magnetoencephalography (MEG) in human visual cortex.
III. **Spiking activity in V1/V2.** Single or multi-unit activity measured in cat, macaque or human V1/V2.

IV. **SSVEP in V1/V2.** The steady state visual evoked potential (SSVEP) amplitude measured with EEG or MEG in human V1/V2.

Notes:

1. **Stroboscopic flicker.** Stroboscopic flicker spanning a broad frequency range can elicit seizures. The peak tuning is similar to the peak tuning for SSVEPs in healthy subjects, but the tuning is much wider for PPRs than for SSVEPs. It is not known whether flicker drives the same circuitry implicated in induced gamma oscillations, or whether flicker and static patterns cause seizures by the same mechanism.

2. **Reversing versus moving grating.** Contrast reversing gratings at 10-20 Hz elicit large SSVEPs in healthy subjects, matching the temporal frequency tuning of spatially oscillating or contrast reversing gratings in triggering PPRs. The similarity in temporal tuning is intriguing and requires further study. For the comparison between PPRs and induced gamma oscillations, the stimuli used were quite different (prolonged oscillations for PPRs, a single contrast reversal for induced gamma). Hence, a strong connection cannot yet be made.

3. **Stimulus duration.** PPR responses are elicited by longer stimulus durations (>500ms). Similarly, gamma oscillations occur with a slight delay, and are sustained throughout the stimulus exposure. The MUA response differs from both PPR sensitivity and the time course of the gamma response: the MUA to a prolonged stimulus is initially large (a transient) followed by a low-level sustained response. These patterns are consistent with a tighter connection between PPRs and gamma oscillations than PPRs and MUs.

**Acknowledgements**

This work was supported by the Netherlands Organization for Scientific Research grant 016_VENI_178_048 (D.H.), the National Institutes of Health grants R00-EY022116 (J.W.) and R01-MH111417 (J.W.) and the EU program Marie Curie MEXCT-CT-2005-024224 “Visual Sensitivity” (DKNT).
References:


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