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 guite 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 that 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.

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Gamma oscillations and photosensitive epilepsy

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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 multiunit 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, multiunit, 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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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 [6]. 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,

Table 1. Image features provocative in photosensitive epilepsy also induce large gamma oscillations.

Feature	Exemplars	I PPRs	II Gamma	III MUA	IV BOLD
Size: small → big	$() \rightarrow ([])$	1	1	4	Ψ
Contrast: low → high	$\bigcirc \rightarrow ()$	1	1	1	1
Orientations: 1 → multiple	$\bigcirc\!$	4	4	1	1
Contrast: luminance → chromatic	$\longrightarrow \longrightarrow$	4	V	-	1
Spatial frq: low → middle (1-4cpd)		1	1	1	1
Spatial frq: middle (1- 4cpd) → high		4	4	4	4
Grating: sinusoidal → square wave	$()\rightarrow ()$	-	-	4	-
Noise: absent → present	$(\text{ll})\rightarrow (\text{l})$	4	4	1	•

The response pattern of PPRs (I) and gamma oscillations in V1/V2 (II) is similar for stimulus size and contrast, number of orientations, luminance v chromatic contrast, spatial frequency, sine wave v square wave, and presence of noise. The pattern differs for multiunit activity, (MUA; III) and the fMRI BOLD response (IV). Arrows indicate increases or decreases, and a desaturated arrow indicates partial evidence. Dashed lines indicate no change. For (II-IV), responses refer to neural populations representing the stimulus center, not the signal pooled over all of visual cortex. The table includes image features for which all four measures have been made. (More details in Tables S1 and S2.)

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 multiunit 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

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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 [9] 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.

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