misexpression, they delineate the regulatory interplay between these genes, as well as analyze their roles in neuronal subtype specification in the Type II lineages. This reveals an intricate interplay between these genes, where Svp triggers opposing gradients of Imp and Syp to move the Type II NBs through different competence windows, with accompanying differences in neuronal subtype specification (Figure 1). The continued mapping of Type II NBs (DM1 and DL1 in this case), the identification of 81 genes with temporal expression profiles, and the elucidation of the genetic interplay between some of these both provide novel insight into temporal patterning in large neural lineages and sets the stage for future studies on this system.

In spite of the progress in decoding Type II NBs, in this and related studies, there are still several interesting and outstanding issues that justify further investigation. First, Ren *et al.* describe a genetic interplay between five genes, centered on generating opposing gradients of Imp and Syp. However, Type II NBs undergo some 40 divisions, all of which may indeed bud off an INP with distinct competence. How are these 40 windows programmed to be temporally unique? Second, recent studies have identified temporal patterning also along the INP sub-lineages [14]. Do the Imp and Syp gradients influence also the temporal patterning along each INP sub-lineage? Third, how many cell fates are really present in the Type II lineages; are all 400 cells unique? Fourth, a wealth of studies demonstrate that most if not all larval NBs are generated already in the embryo, and this presumably applies to Type II NBs as well. But what is their identity with regards to the embryonic NB map, what is their behavior like in the embryo, and how does embryonic spatial and temporal patterning influence their subsequent larval behavior? Finally, temporal patterning in *Drosophila* NBs, with the exception of Hh acting in a lineage paracrine manner [18], is not known to involve extrinsic signals. It would be very interesting to learn if such cues do indeed exist, as they would help form a more apparent bridge between *Drosophila* NB biology and mammalian neurogenesis.

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Neuroscience: When a Single Image Can Cause a Seizure

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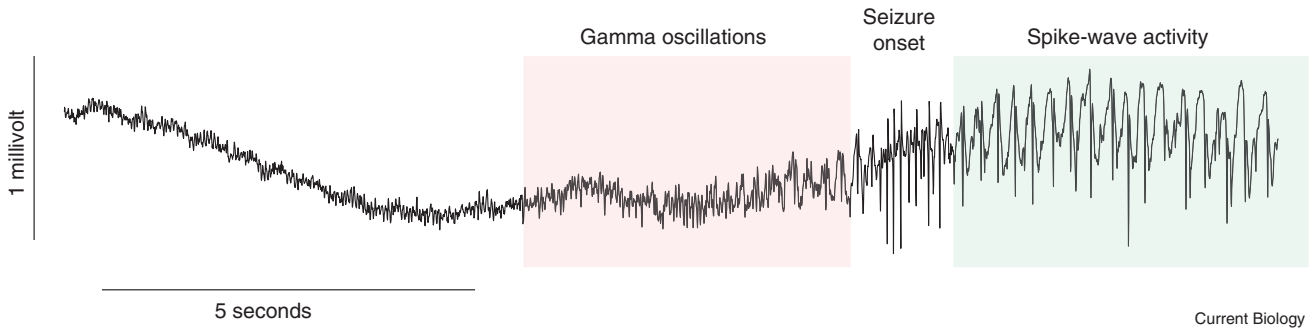

Figure 1. Gamma oscillations preceding a seizure.
An example of oscillatory gamma-band activity in the build-up to a seizure. This voltage trace was recorded from an intracranial electrode overlaying the somatosensory neocortex.

It has been known since classical antiquity that viewing particular images can trigger seizures in some individuals. Now we have a clue to the mechanism, as many of these images amplify 30–80 Hz rhythmic activity in the visual brain.

Most of us have been warned that flashing lights can drive rhythmic energy into our brains, cascading into the uncontrolled activity of a seizure. But seizures can also be triggered by images in which nothing is flashing. As early as the 2nd century, the Roman author Apuleius noticed that viewing a potter's wheel could induce giddiness in some and seizures in others. Many people imagine that Apuleius was referring to a flickering light emanating from the potter's wheel, but the original Latin does not mention any flicker [1]. So, if not flicker, then were the seizures driven by a spatial pattern in the scene? Was there something special about the symmetry of the potter's wheel, or the arrangement of shadow in the studio, or the circular clay residues on the wheel's surface? How could any of these features unravel the coordinated action of our brains?

The pictures that most often induce seizures or visual discomfort have some common features. Photosensitive individuals are warned of backlit window blinds and meshes, backlit pine trees, and striped garage doors: large, high-contrast images with intermediate spatial frequencies and symmetry. But other kinds of images, such as colored paintings or reflections on a wall, can also act as triggers, and so it remains a puzzle which features should be avoided and why. Solving this puzzle would immediately benefit the population of people with photosensitivity (who experience discomfort or vertigo from visual patterns) and also the smaller group with photosensitive epilepsy (in whom seizures can reliably be elicited by images). In a recent issue of *Current Biology*, Hermes *et al.* [2] describe a possible mechanism linking images to seizures. They propose that when images induce strong rhythmic 30–80 Hz activity in the visual circuits of our brains, this activity can become uncontrolled, and sometimes develop into a seizure.

Brain circuit oscillations in the 30–80 Hz range are referred to as 'gamma' oscillations. Gamma oscillations can have distinct roles and origins in different parts of the brain, but in the cerebral cortex they are believed to arise from a feedback loop involving the two main classes of neurons [3,4]. When excitatory neurons fire (typically releasing the neurotransmitter glutamate) they increase the chance of firing of other neurons. If those other neurons are all excitatory, then this chain of excitation can potentially lead to an uncontrolled positive feedback loop. However, excitatory neurons also activate inhibitory neurons. If a large enough group of inhibitory neurons is active, their release of the neurotransmitter γ-aminobutyric acid (GABA) can usually provide a negative feedback that prevents runaway excitation, a particularly important mechanism for curtailing seizure spread in the context of seizures [5]. By 'quenching' the activity of many neurons at once, inhibitory neurons can push the network into a state in which excitatory and inhibitory neurons fire (or do not fire) at the same time. If many excitatory neurons fire at once, this will be followed by a volley of counteracting inhibition, and the network falls into a synchronized rhythm: excitatory neurons increase their firing rate, are quenched by inhibition, then increase again after 20–40 milliseconds. In this way, the combined activity of excitatory and inhibitory neurons waxes and wanes with a frequency in the 30–80 Hz range.

Gamma oscillations are associated with the onset zone of seizures [6] and have been specifically linked to seizures or aberrant circuit events in photosensitive epilepsy [7,8] (Figure 1). However, the presence of this correlation does not determine whether gamma oscillations are a cause of seizures, or a byproduct of the abnormal brain wiring that leads to seizures. Hermes *et al.* pursued an analysis with a straightforward logic: if gamma oscillations increase the likelihood of seizures, then visual features that increase the amplitude of gamma oscillations should also increase the likelihood of eliciting a seizure. To test this hypothesis, it is necessary to know which kinds of images will most strongly drive gamma oscillations.

Gamma oscillations can be elicited by many visual stimuli [9], but the magnitude and frequency of the oscillations vary across images [10,11]. The largest gamma oscillations are elicited by high-contrast, black-and-white images

Figure 2. Image properties that elicit gamma oscillations.
The top half of the forest scene (A) is monochromatic and symmetric with a dominant orientation, and it has higher contrast than the bottom of the scene (B). Therefore, the top half of this forest scene is expected to produce larger gamma oscillations in the visual neocortex, and may also be more likely to elicit a seizure. However, the magnitude of gamma oscillations is also modulated by other image properties that are less well understood: the top car image (C) drives robust visual gamma oscillations while the bottom car (D) does not. Vehicle images are adapted from [11] by permission of Oxford University Press.

in sharp focus, with intermediate spatial details organized around a single dominant orientation (Figure 2). As it happens, each of these visual properties is also associated with eliciting seizures.

Why do large, high-contrast, oriented stimuli drive strong gamma oscillations? Inhibitory connections within the visual cortex are organized in a way that is believed to enhance the spatial precision of neural responses (by suppressing responses of neurons of similar selectivity). At the same time, driving inhibitory neurons is an extremely effective means of inducing gamma-band oscillations [12]. So, the firing of particular combinations of inhibitory neurons (each sensitive to distinct regions in space) can be elicited by images that present the right combination of spatial features. The precise mechanism remains uncertain, but the spatial organization of inhibitory connections in the visual cortex will be an important place to look.

Why would gamma oscillations increase the risk of a seizure only in some individuals? One idea is that gamma oscillations are a challenging test for the feedback control processes in our brains. If the brains of people with photosensitive epilepsy have impaired feedback control processes, then they may not be able to control the response to all forms of visual stimulation. Under this proposal, inhibitory (GABAergic) neurons would play a central role [13]. Large GABA releases are measured near the beginning of a seizure, which can cause GABA receptors on excitatory neurons to become overactive. This overactivity leads to a buildup of potassium outside the cell [14] and chloride within cells [15], especially if chloride pumping mechanisms are impaired [16]. These changes in potassium and chloride would not only shift neurons closer to their firing threshold, but could also switch GABAergic neurotransmission to become an excitatory signal. In this way, the overall excitatory drive within the circuit would be dramatically increased. Consistent with this hypothesis, recent optogenetic studies have shown that brief [17] or sustained [18] activation of inhibitory neurons can trigger seizure onsets in animal models. So, when a neural process such as a gamma oscillation produces a large release of GABA, the negative feedback loops in a photosensitive brain may sometimes switch into positive feedback loops, leading to uncontrolled neuronal firing.

If the hypothesis presented by Hermes *et al.* proves true, then a series of follow-up questions present themselves. Are the spatial characteristics of images transformed into gamma oscillations via the lateral connections between location-selective inhibitory neurons? What proportion of visual neurons need to be involved in a gamma oscillation in order for that oscillation to constitute a seizure risk? Can gamma oscillations in visual cortex directly transfer to become gamma oscillations in the medial temporal lobe, an area with a distinct set of circuit and cellular timings? We do not yet know the answers to these questions, but the hypothesized connection between image properties, gamma oscillations, and seizures is already a compelling proposal. People living with photosensitive epilepsy are often mystified by the origins of their own seizures: how could a seizure be induced by a forest scene or by a potter's wheel? It is not only an exciting possibility, but also a comforting one, to be able to point to the patterning of light: space transformed into a temporal resonance.

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