Visual Neuroscience: A Retinal Ganglion Cell to Report Image Focus?

Tom Baden[1,2,*], Frank Schaeffel[2], and Philipp Berens[2,3,4]
[1]School of Life Sciences, University of Sussex, Brighton, BN1 9QG, UK
[2]Institute for Ophthalmic Research, University of Tübingen, Otfried Müller Strasse 25, 72076, Tübingen, Germany
[3]Bernstein Center for Computational Neuroscience, University of Tübingen, Otfried Müller Strasse 25, 72076, Tübingen, Germany
[4]Center for Integrative Neuroscience, University of Tübingen, Otfried Müller Strasse 25, 72076, Tübingen, Germany
*Correspondence: tom@badenlab.org
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A recent study describes a mouse neuron projecting from the retina to the brain that exhibits exquisitely high sensitivity to high spatial frequency patterns presented over an unusually large receptive field: could this cell be a (de)focus detector?

The retina is our window to the world, and its entire output is carried by a highly diverse set of projection neurons called retinal ganglion cells. The many different types of retinal ganglion cells each form an approximately complete mosaic across the retina and thus visual space. Each type informs the brain about a particular aspect of the visual scene, such as motion, edges or chromatic content. How many of these retinal ganglion cells there are in any one species, and perhaps more importantly, what they all do, has been a major focus of vision science for decades [1]. Recent functional and anatomical approaches agree that, at least in mice, the number is certainly above 30 and perhaps as high as 50 [2,3] (see also museum.eyewire.org for the current state of anatomical classification). However, we still only have a rudimentary understanding of what most of these retinal ganglion cell types compute and what circuit mechanisms underlie their computations. Addressing these questions requires taking the cell types one at a time, which, for some, has been done with great success. These include the four types of alpha cells [2], several populations of direction-selective [4] and orientation-selective types [2,5], contrast-suppressed [6] and edge-detecting cell types [7], as well as chromatic [8] and intrinsically photosensitive cell types [9]. Together, these barely account for half of the diversity that is thought to exist. What do all the other types do?

In this issue of *Current Biology*, Mani and Schwartz [10] add a rather intriguing member to the list. This cell, dubbed the 'On-delayed' retinal ganglion cell, responds to a step of light in an 'On' fashion, that is, it increases its firing as the intensity of the light falling in its receptive field increases, and it does this in a delayed fashion relative to the responses of other retinal ganglion cell types (Figure 1A). This delay can be as large as 700 milliseconds, which is almost an order of magnitude longer compared to the fastest responses in visual cortex [11]! What is more, this delay systematically decreases with the spatial extent of the stimulus as it grows beyond the borders of the cell's dendritic field: the larger the stimulus, the smaller the delay. At the same time, the cell also continues to increase its spike rate as stimulus size increases well beyond its dendritic field instead of showing the strong surround suppression that is characteristic to most other retinal ganglion cells.

The new study of Mani and Schwartz [10] suggests that these effects are generated through the interplay of multiple lateral inhibitory circuits formed by amacrine cells (Figure 1B). It appears that one group of amacrine cells directly inhibits the On-delayed retinal ganglion cell, but these amacrine cells are in turn inhibited by yet another group that acts over a wider special scale. Accordingly, the larger the stimulus, the more of the second group of amacrine cells is recruited. This leads to stronger disinhibition of the On-delayed retinal ganglion cell, allowing it to depolarise more rapidly and hence to spike earlier and more vigorously. This size encoding remained stable over a wide range of luminances.

What might be the function of such a cell? As stimulus size increases, it reliably emits more spikes and at shorter latency. The cell might thus support both a spike rate as well as a latency code to encode the spatial scale of the stimulus, a fundamental property of visual coding. Latency coding has intrigued computational neuroscientists for a long time, and it has been shown that, in the salamander retina, latencies are informative about the phase of a grating even if it cannot be inferred from the spike rates [12]. The issue with such proposals has always been the reference frame: latency is always relative and in the natural world there is no notion of stimulus onset. Instead, the visual system might use motor commands from saccades to trigger the latency computation [12], but this may solve only part of the problem in a highly dynamic world with moving objects. The work of Mani and Schwartz [10] provides an intriguing example of a cell that may actually support the computation of a robust latency code for a spatial aspect of the stimulus: one could easily decode stimulus size by using the activity of another 'On' cell that responds over wide spatial scale, but the response latency of which is largely stimulus size invariant (like that of the On-alpha cell) as the reference for computing the latency of the On-delayed cell.

While this idea will be tantalising for those interested in neural coding, there may even be more to the On-delayed cell. Natural visual stimuli are rarely well defined homogenous spots of light or darkness, but instead, typically intermingle large and small-scale
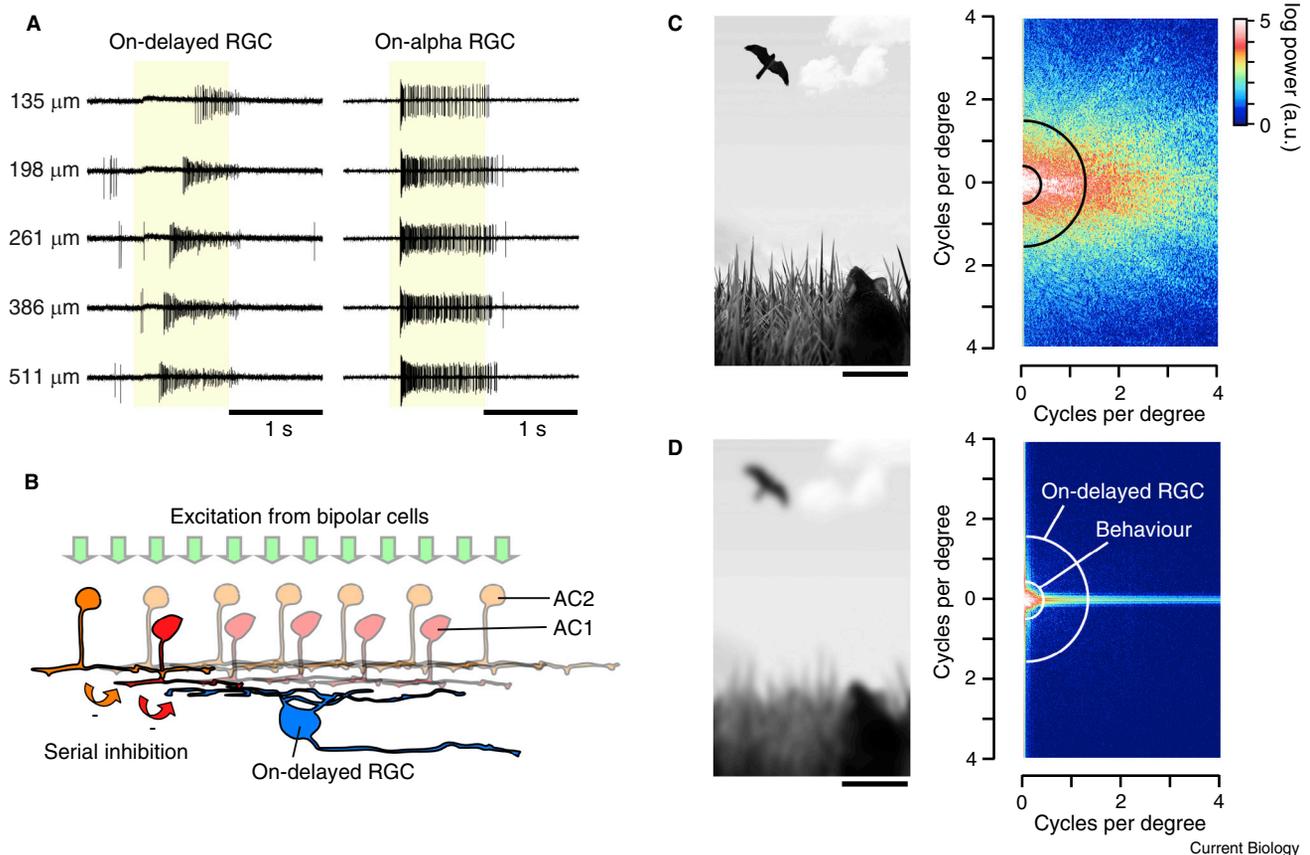
Figure 1. The ON-Delayed retinal ganglion cell — an image-blur detector?
(A) Spike responses of the On-delayed retinal ganglion cell (left) and another, well studied On-type retinal ganglion cell called On-alpha to 1 s spots of light of increasing diameter as indicated (yellow shading). Traces kindly provided by Mani and Schwartz [10]. (B) Simplified proposed circuit that may underlie the size dependency of On-delayed retinal ganglion cell spike responses. Amacrine cell (AC) group 2 inhibits AC1s which in turn inhibit the On-delayed cell. All are excited by bipolar cells. (C) 'Naturalistic' image (left) and its Fourier spectrum, with higher frequencies indicated in warmer colours (right). (D) Blurring the image in C results in a loss of high spatial frequencies. Approximate spatial frequency limits of behaviour and of the On-delayed cell indicated. Scalebars: 5 degrees.

structure (Figure 1C). This means that an individual retinal ganglion cell will be typically driven by a mix of local bright- and dark-evoked events that must be integrated across its receptive field. If the encoding is perfectly linear, a cell does not respond at all to a balanced light–dark pattern of sufficiently fine spatial scale, as positive and negative inputs cancel. On the other hand, nonlinearities in a retinal ganglion cell's synaptic input will activate that retinal ganglion cell even at spatial scales that are substantially smaller than its dendritic field [13]. Could this be also going on in the On-delayed cell? Its spatio-temporal response profile makes it an ideal candidate as it can integrate over both a huge amount of space and time to thus yield a very low-noise response, potentially required for being sensitive to fine spatial detail. This may make the cell

able to inform about any systematic deviates thereof, for example during image defocus.

To test this idea, Mani and Schwartz [10] recorded the response of several different types of retinal ganglion cell in the mouse retina to balanced and random light–dark patterns that were blurred to different amounts, thus attenuating higher spatial frequencies (Figure 1D). As expected, many retinal ganglion cells did not show any appreciable response to this type of stimulus, likely as they integrate approximately linearly as discussed above. However, the remaining cells, which also contained the On-delayed cell, did respond, most more vigorously so with increasing blur. Where it got interesting is at the fine end of the spatial scale. The authors found that the On-delayed cell stood out as the

last cell to cease responding as blur decreased. In other words, by comparing the degree of firing of the On-delayed cell to large field patterned stimulus to that of other cell types, one could reliably extract information about the amount of high spatial frequencies contained therein.

A brain cell differentially driven by inputs from the On-delayed cell and a suitable reference cell should be the first to notice as the image gets out of focus. Besides its immediate utility in informing the rapid adjustment of the lens, such a 'defocus' signal could also play an important role in regulating eye growth in the course of development [14]. Of course, to what extent signalling of On-delayed retinal ganglion cells in the mouse retina is sufficient and/or necessary to trigger corrective responses remains to be seen, but the idea is

certainly tempting. What is noteworthy also is that the spatial scales concerned here are quite substantially beyond the behavioural resolution limit of the animal (Figure 1C,D) [14]. This would imply that the retina could pre-emptively detect defocus long before it becomes behaviourally relevant.

Whether the presumed defocus signal is actually used anywhere in the brain requires further study, for example on the projection patterns of this type. As the spatial sensitivity goes beyond the behavioural limit of the mouse, we might expect these cells not to project to the visual thalamus and cortex, where pattern vision is thought to be formed. Instead, they may project to midbrain structures like area pretectalis, where accommodation is controlled (although like many other small mammals, mice do not accommodate with their huge lenses [14]). Nevertheless, the On-delayed cell might still contribute information for "visual control" of eye growth. Previous work showed that the retina by itself can determine imposed defocus in the projected image, including its sign [15] (which the suggested circuit would presumably not attain). It is therefore conceivable that such a pathway may then signal to adjust axial eye growth rates during emmetropisation [16]. Interestingly, information about the sign of image focus, though present in the retina, is not available when e.g. we try focussing a microscope. Instead, we experience that accommodation uses a trial and error approach which also argues in favour of these type of signals not being part of the 'conscious' visual experience. In any case, the new study [10] adds to a growing body of well-characterised retinal output channels in the mouse and thus provides one more puzzle piece in our overall understanding of vision in vertebrates.

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Insect Navigation: What Backward Walking Reveals about the Control of Movement

Matthew Collett[1], Paul Graham[2], and Thomas S. Collett[2]
[1]Psychology, College of Life and Environmental Sciences, University of Exeter, Exeter EX4 4QG, UK
[2]School of Life Sciences, University of Sussex, Brighton BN1 9QG, UK
Correspondence: m.collett@exeter.ac.uk (M.C.), paulgr@sussex.ac.uk (P.G.), t.s.collett@sussex.ac.uk (T.S.C.)
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Ants often walk backwards to drag large prey to their nest. New experiments show how they can use information from retinotopically encoded views to follow visual routes even while moving backwards. The mechanisms enabling ants to decouple body orientation and the control of travel direction are likely to be shared with other, flying, insects.

Driving a car backwards is a tricky business that many of us find difficult even with the aid of mirrors. Ants also move backwards, not to park in tight spaces but when dragging home items of food that are too large to carry. Until last year backward navigation in ants was uncharted territory. Now, three papers on desert ants of the genus *Cataglyphis* [1–3] and one on *Myrmecia*

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