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Retinal Circuits for Seeing in the Dark

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How can we relate processing in the retina to an animal's behavior? In this issue of *Neuron*, Smeds et al. (2019) report that when "every photon counts," mice trade sensitivity for reliability to master visual tasks.

How behavioral decisions arise from activity in a neural circuit is a key question in systems neuroscience, as well as one of the most difficult. This question is addressed in the recent work of Smeds et al. (2019), in which they investigate which retinal circuits provide the information used to perform a visual behavioral task in the dark. At low light levels, the retina is exclusively driven by rod photoreceptors. Their signals reach the retinal ganglion cells (RGCs), the eye's output neurons, through the "rod pathway," a circuit of specialized interneurons (Field et al., 2005). The rod pathway piggybacks on the circuits that process cone photoreceptor signals and thereby provide information to both ON and OFF RGCs, which fire in response to an increase or decrease in light, respectively. Specifically, Smeds and coworkers test whether mice rely on an RGC channel that provides the maximal information about the given behavioral task or pool information across different RGC channels.

To link neural circuits to animal behavior, a valuable approach is genetic targeting of specific neurons or circuits. By measuring performance of a behavioral task both before and after selectively altering a specific neural circuit (e.g., by eliminating a neuron type), the role of this circuit for the tested behavior can be revealed. However, with increasing complexity of the animal's nervous system, interpreting the results of a specific manipulation becomes more difficult, and selectively targeting the sets of neurons involved while avoiding undesirable (behavioral) side effects is quite challenging. Moreover, defining a sufficiently complex but well-measurable behavioral task becomes demanding, with the risk of oversimplification.

Smeds et al. (2019) have employed a genetic approach, but they have elegantly "circumvented" many of these challenges. First, instead of eliminating specific types of neurons (from the retina) in a piecemeal fashion, they "turned down" the responsiveness of rod photoreceptors to see how circuit responses and behavior are affected. To this end, they made use of an existing transgenic mouse line, called the OPN1LW ("OPN") mouse, carrying a mild but well-characterized genetic modification that results in rod photoreceptors displaying responses with smaller amplitude to single photons (Fu et al., 2008). With this modification, Smeds et al. (2019) introduced a useful imbalance (see below) into the otherwise unaltered retinal circuits. Second, they conducted the behavioral experiment in near-complete darkness, where the mice had to rely on single-photon stimuli to find a hidden platform in a water maze. This configuration enabled the authors to use the same metrics—sensitivity as a function of stimulus intensity—to compare performance at the circuit level with that at the behavioral level and, hence, to determine which retinal circuit's output

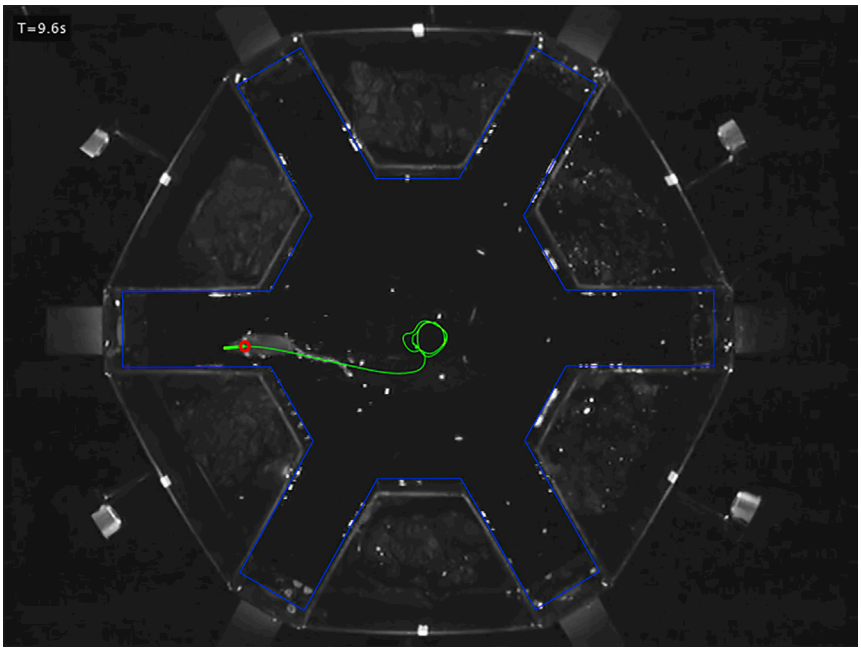

Figure 1. Behavioral Paradigm Used by Smeds et al.
Six-arm water maze viewed from above, with mouse swimming toward the hidden platform marked by the visual cue, a dim spot of light. Maze walls (blue) and trajectory (green), as well as head of mouse (red circle), are indicated. Picture courtesy of P. Ala-Laurila.

limits behavioral performance at the threshold of vision.

Smeds et al. (2019) started by measuring the light sensitivity of the RGCs by presenting dim light spots of increasing intensity to the isolated mouse retina and recorded spikes in individual cells using patch-clamp electrodes. By recording many neighboring RGCs, they first confirmed that the so-called "sustained alpha" RGCs, which receive strong synaptic input via the rod pathway, are by far the most light-sensitive cells among the approximately 40 different RGC types in the mouse (Baden et al., 2016). The light sensitivity of sustained ON (ON-S) and sustained OFF (OFF-S) alpha cells was approximately 30-fold higher than that of the average mouse RGC.

Next, they compared the sensitivity of the two alpha cells in wild-type and OPN mice. Unsurprisingly, they found that OPN ON-S and OFF-S RGCs were much less light sensitive than their wild-type counterparts. More strikingly, however, the OPN alpha cells lacked the symmetry between the ON and OFF channels. Whereas in wild-type mice the sensitivity curves of ON-S and OFF-S cells were quite similar, in the OPN mice, the ON-S cells were less sensitive than the OFF-S cells. Thus, this genetic mutation not only changed the sensitivity of the rod photoreceptors to light but also created an imbalance in different retinal circuits that could be involved in night vision. Smeds et al. (2019) propose that this difference arises from an asymmetry in the rod pathway, where the synaptic transmission into the ON, but not the OFF, pathway features a thresholding nonlinearity (Ala-Laurila and Rieke, 2014). Due to this thresholding, the smaller, single-photon signals from the OPN rod photoreceptors are more frequently discarded in the ON pathway, hence reducing the sensitivity of the ON-S cell.

What does this loss in light sensitivity at the retina level mean for the behavior of the OPN mouse? To address this question, Smeds et al. (2019) went on to test the behavioral performance in wild-type and OPN mice at the limit of light detection. They used a six-armed water maze (Figure 1) to measure and compare the behavioral sensitivity of these mice based on a forced choice paradigm. After being placed in the center of the maze, the mice had to locate, in darkness, a dim spot of light that marked the position of a submersed target platform. Throughout the experiment, trajectory and head orientation were tracked. As a metric for behavioral sensitivity, Smeds et al. (2019) used the probability of finding the correct maze arm as a function of light spot intensity. To ensure that this probability was solely a function of spot intensity, they carefully ruled out other factors that could have affected behavioral sensitivity, including general learning performance, pupil size, and strategy for finding the visual cue—none of which differed between wild-type and OPN mice. As expected, they found that OPN mice needed significantly brighter spots to perform the task. More strikingly, the behavioral threshold of OPN mice matched the sensitivity difference Smeds et al. (2019) previously established at the level of the On-S RGCs. Together, this suggests that, in darkness, mice do not pool signals across RGC channels but instead rely on the information from a single RGC type, the ON-S cell.

While this match is quite remarkable, the settings under which electrophysiological and behavioral data were acquired were certainly different (i.e., light spots presented to isolated retina versus swimming mouse searching for the visual cue), as Smeds et al. (2019) also discuss in their paper. To explore this, Smeds et al. next developed ideal observer models that had access to a population of ON-S or OFF-S cells (for both wild-type and OPN mice) which "saw" the visual cue based on recorded mouse trajectories and head positions from the real behavioral experiments. Notably, they found that the "behavioral performance" of the models mirrored the experimental findings, with the OPN ON-S model predicting the behavior of the OPN mouse.

In summary, the study by Smeds and colleagues suggests that in nearly complete darkness, when catching single photon is important, mice rely on a specific information channel from the retina—the one formed by ON-S alpha cells. Compared to its OFF-S counterpart, ON-S RGCs provide (through non-linear signal processing) a more reliable but somewhat less-sensitive readout of light spot intensity to the brain (Takeshita et al., 2017). Thus, it seems that the brain

prioritizes reliability over sensitivity—at least in these extreme conditions.

These findings raise interesting questions about the functional role(s) of alpha RGCs, which are considered to be a conserved cell type across mammalian species including primates (see Discussion in Krieger et al., 2017). The recent description of a fourth alpha cell type (ON-T) in mouse fosters the idea that ON-S and OFF-S, together with their transiently responding counterparts (ON-T and OFF-T), split the visual signal into four information channels arranged symmetrically with respect to response polarity and kinetics (Krieger et al., 2017). Interestingly, compared to the other alpha RGCs, OFF-S cells seem to tap into different retinal circuits, with their relatively slowly decaying light responses being largely mediated by inhibition instead of excitation (van Wyk et al., 2009). Likely as a consequence, driving OFF-S cells efficiently requires approximately 6-fold larger structures within their receptive field center compared to the other alpha RGCs (Krieger et al., 2017). These differences may explain why the mouse visual system in the behavioral paradigm by Smeds et al. (2019) relied on ON-S instead of OFF-S alpha cells. Here, it would be instructive to see if the outcome also holds for different stimulus sizes (i.e., larger stimuli) or structured, more "natural" stimuli, which may be more salient to the OFF-S channel.

At a more general level, the efficient coding theory suggests that "cooperation" between ON and OFF pathways is beneficial for encoding visual scenes under the constraint of limited energy consumption (Simoncelli and Olshausen, 2001); according to the data of Smeds et al. (2019), this seems not to be the case at very low light levels. If this is true, what is the functional role of the OFF pathways under these conditions? Following the signals from alpha RGCs to their downstream brain targets could provide some answers. Alpha RGCs project to the retina's main target areas in the brain, the superior colliculus, and the core region of the visual thalamus (Krieger et al., 2017). It would be interesting to see which pathway guides behavior in the single-photon regime and what becomes of the signals from the OFF pathway. Together, the study by Smeds and colleagues represents an elegant demonstration of how to connect neural circuits to behavior and a significant step toward a better understanding of a well-conserved retinal information channel.

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