approaches aimed at identifying alternative therapeutic strategies targeting cilia-dependent signaling pathways to reverse the multiple detrimental manifestations of mTOR in the CNS.

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Parallel Processing of Negative Feedback: E Unum Pluribus

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How do canonical computational elements interact to shape neural circuit function? In this issue of *Neuron*, Drinnenberg et al. (2018) show that parallel processing converts unitary negative feedback at the first synapse of the retina into diverse output signals to the brain.

Neural circuits, like their electronic counterparts, combine canonical elements in myriad ways to achieve diverse signal transformations. Although the local functions of individual elements (e.g., negative feedback) are relatively well understood, how multiple components interact to shape the overall input-output transformation of neural circuits remains mostly unknown. In this issue of *Neuron*, Drinnenberg et al. (2018) address this question in the retina.

At the first synapse of the retina, photoreceptors provide glutamatergic input to horizontal cells and bipolar cells. In mice, cone photoreceptors (cones for short), which mediate vision in bright light, receive negative feedback from a single horizontal cell type and pass signals on to 15 bipolar cell types (Figure 1). Bipolar cell types differ in their contrast preferences (ON versus OFF) and temporal tuning, extracting different components of their shared input signal (i.e., parallel processing) (Euler et al., 2014). In the inner retina, specific combinations of bipolar cells innervate approximately 50 types of interneurons (i.e., amacrine cells) and more than 30 types of retinal ganglion cells, the output neurons of the eye (Helmstaedter et al., 2013). Thus, the retina converts light-evoked photoreceptor inputs into more than 30 parallel outputs, each conveying different information to the brain.

To understand how negative feedback at the first synapse and parallel processing downstream shape the input-output transformation of the retina, Drinnenberg et al. (2018) suppress the light responses of horizontal cells while monitoring the light responses of large ensembles of retinal ganglion cells. Naively, one might expect that feedback from a single horizontal cell type to the single functional cone type driving light responses in this study would have uniform consequences across all retinal outputs. Drinnenberg et al. (2018) reveal this intuition to be spectacularly wrong and provide a simple quantitative explanation for how parallel processing converts unitary feedback into diverse, sometimes opposite, changes across different retinal outputs.

Drinnenberg et al. (2018) suppress the light responses of horizontal cells chemogenetically. Injecting adeno-associated viruses (AAVs) optimized for systemic delivery and broad neuronal tropism (Deverman et al., 2016) into a cell-type-specific transgenic Cre line, they achieve complete and selective expression of the pharmacologically selective actuator molecule (PSAM) in horizontal cells. PSAM is a chloride channel activated by an exogenous ligand, the pharmacologically selective effector molecule (PSEM) (Magnus et al., 2011). Application of PSEM clamps the membrane potential of PSAM-expressing horizontal cells near the reversal potential for chloride, which is slightly more depolarized than their potential in darkness when glutamate release from cones is high. Therefore, in the presence of PSEM/PSAM, feedback from horizontal cells to cones, which involves unconventional mechanisms (Thoreson and Mangel, 2012; Kemmler et al., 2014), is expected to be high and unmodulated by light.

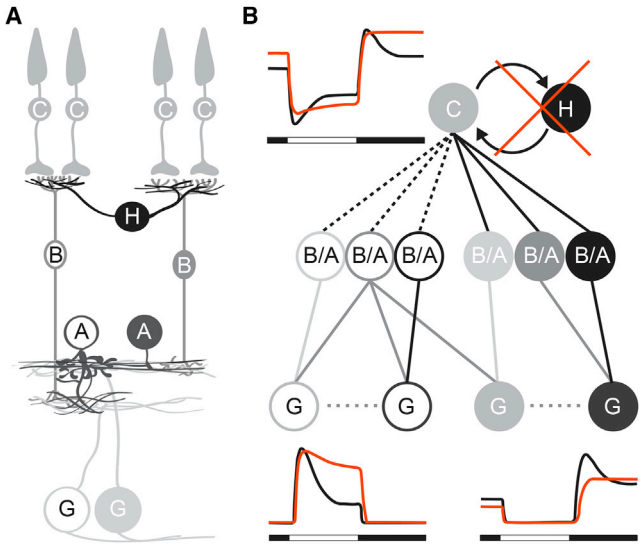

Figure 1. Parallel Processing of Negative Feedback in the Retina

(A) Schematic of the retina depicting cone photoreceptors (C), horizontal cells (H), bipolar cells (B), amacrine cells (A), and ganglion cells (G). The somata of cells that depolarize to light increments (i.e., ON responses) are outlined, whereas somata of cells that depolarize to light decrements (i.e., OFF responses) are filled in.

(B) Diagram of information flow across a simplified circuit model of the retina. Cells are labeled as in (A), with bipolar and amacrine cells combined (B/A). Shading in the bottom two layers indicate differences in temporal filters. Effects of chemogenetic suppression of horizontal cells on the light responses of cones (voltage) and two ganglion cell types (spike rates) are shown in orange compared to control responses in black.

To test the effects of their manipulation on cones, Drinnenberg et al. (2018) express a genetically encoded calcium indicator from a novel cone-specific AAV promoter. Two-photon imaging reveals that PSEM application in PSAM-expressing retinas (1) reduces baseline calcium levels in cone terminals, (2) makes light-evoked calcium transients more sustained, and (3) eliminates the preference of cones for small stimuli. These observations confirm that in the presence of PSEM, feedback from PSAM-expressing horizontal cells is high (1) and unmodulated by light (2 and 3).

Having confirmed the local effects of their manipulation, Drinnenberg et al. (2018) next analyze its influence on the overall input-output transformation of the retina. Toward this end, they record thousands of retinal ganglion cells on complementary metal-oxide-semiconductor (CMOS) microelectrode arrays. PSEM/PSAM-induced changes fall into six categories (Figure 1), enhancing or suppressing ganglion cell responses early or late during ON or OFF stimuli. PSEM/PSAM expands or compresses the response range of the respective ganglion cells. Importantly, all effects are reversible upon washout of PSEM; PSEM has no effect without PSAM and vice versa. When Drinnenberg et al. (2018) group ganglion cells into five broad classes based on their responses to full-field stimuli, PSEM/PSAM-induced changes are limited to a subset of cells in each class. This could be either because PSEM/PSAM effects are unreliable or because they are restricted to a few specific ganglion cell types.

To distinguish between these possibilities, Drinnenberg et al. (2018) design a short visual stimulus that enables them to cluster ganglion cells recorded on CMOS arrays into 30 functional types. Using a clever chemogenetic tagging strategy, they confirm that this functional classification faithfully distinguishes genetically identified ganglion cell types. Analyzing responses of functionally identified ganglion cells on CMOS arrays and of genetically identified ganglion cells targeted for patch clamp recordings under two-photon guidance, Drinnenberg et al. (2018) then demonstrate that the PSEM/PSAM effects are consistent within a given ganglion cell type and disparate between them.

How is unitary feedback from horizontal cells to cones converted into diverse cell-type-specific changes in ganglion cell light responses? Drinnenberg et al. (2018) construct a simplified circuit model, in which parallel pathways with different contrast preferences (ON versus OFF) and temporal filters (fast, intermediate, and slow), resembling divisions among bipolar cell types (Euler et al., 2014), relay cone signals to ganglion cells. The output of each pathway is rectified by a threshold nonlinearity and can be excitatory, mimicking direct connections from bipolar cells to ganglion cells, or inhibitory, mimicking input from an intervening amacrine cell. Because of their rectification, pathways communicate either ON or OFF responses of cones, while the different temporal filters isolate changes in the baseline activity (i.e., the slow pathway), the baseline-subtracted cone response (i.e., the intermediate pathway), or the differential of the cone response (i.e., the fast pathway). Combining input from one or two pathways per cell, the model reproduces the six categorical changes observed in ganglion cells when light-evoked feedback from horizontal cells to cones is removed. Furthermore, the model makes new predictions about synaptic inputs underlying the changes in ganglion cell responses, which Drinnenberg et al. (2018) validate experimentally. Thus, the model explains how parallel processing converts unitary negative feedback from horizontal cells to cones into diverse cell-type-specific changes in retinal output signals.

The study of Drinnenberg et al. (2018) is a remarkable technical achievement. It combines advances in viral engineering (Deverman et al., 2016) with chemogenetics (Magnus et al., 2011) to suppress the light responses of horizontal cells selectively, completely, and reversibly. It introduces new AAV promoters to monitor and manipulate the activity of cones and ganglion cells without the need for transgenic intersection. It records spike trains of thousands of ganglion cells on large-scale CMOS arrays. The precision of their manipulation and the scale of their observations, enable the authors to provide a comprehensive account of the contributions of horizontal cells to visual processing in the retina.

Horizontal cells are best known for mediating lateral inhibition in the outer retina where their negative feedback reduces photoreceptor responses to large stimuli (Baylor et al., 1971). Lateral inhibition in the outer retina is thought to shape antagonistic receptive fields surrounds of ganglion cells in the inner retina (Thoreson and Mangel, 2012). Drinnenberg et al. (2018) confirm that horizontal cells are preferentially activated by large stimuli and mediate lateral inhibition in the outer retina. However, horizontal cell contributions to ganglion cell surrounds appear to be minor and uniform across cell types. Instead, Drinnenberg et al. (2018) discover that the dominant vertical consequences of horizontal cell function are cell-type-specific changes in response dynamics and response range of ganglion cells (Chaya et al., 2017; Ströh et al., 2018). Their model explains how this diversity arises through parallel processing of negative feedback.

Finally, the study of Drinnenberg et al. (2018) highlights how quickly interactions of canonical computational elements can produce complex and counterintuitive results, suggesting that studies of similar experimental precision and scale, and theoretical acumen, will be needed to understand the input-output transformations of circuits throughout the nervous system.

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Are We There Yet? Identification of Reward-Selective Cells in the Hippocampus

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Navigation to a previously visited reward site requires a reliable and accurate spatial memory. In this issue of *Neuron*, Gauthier and Tank (2018) use two-photon calcium imaging to uncover a discrete hippocampal subpopulation specialized for encoding reward location.

An animal's ability to navigate back to a previously discovered food or water source is critical to its survival. In order to locate such a reward successfully, the memory of the reward location must be precise, reliable, and updatable, particularly when the reward location or the surrounding environment changes. Furthermore, this memory must include detailed