

Visual Thought Stopping for Pain Stress and Depression

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Signal Processing in the Retina

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Summary: Fred Rieke wants to understand the biophysical mechanisms that underlie perceptual and behavioral function. This issue is particularly tractable in sensory systems, largely because the performance of several such systems reaches or approaches fundamental physical limits. This performance serves to focus questions about the underlying processes and challenges our understanding of sensory transduction, synaptic transmission, and neural coding.

Visual sensitivity is striking. In starlight, only about 1 rod in 10,000 absorbs a photon during the ~0.2-sec integration time of rod signals. To complicate matters, all of the rods generate noise that threatens to obscure the signals in the few rods absorbing photons. Cone vision is similarly impressive. Our everyday visual experience relies on detecting subtle changes in contrast, spatial position, and color. But vision does more than detect near-threshold inputs, and the amplification required to detect weak inputs presents a risk of saturating neural responses as lighting conditions change. Such saturation is prevented by a diverse set of adaptational mechanisms. Our broad goal is to understand how biophysical mechanisms operating in the retina contribute to the sensitivity and dynamic range of vision.

The challenges visual performance poses for our understanding of neural function recur throughout the nervous system. Other sensory systems must discriminate weak input signals from noise and accurately represent a wide range of input signals. The auditory system, for example, can detect sounds producing movements of the hair cell stereocilia similar in magnitude to those produced by Brownian motion and yet avoid saturation for sounds thousands of times louder. The retina provides an excellent opportunity to study these general issues because the signal and noise properties of each cell type can be measured and the stimuli can be precisely controlled.

Photon Detection and Rod Vision

The dark-adapted visual system can detect absorption of just a few photons. This performance places strict constraints on how absorbed photons are converted into electrical signals by the rod photoreceptors and how the rod signals are processed.

The challenges include generating a reproducible, macroscopic elementary response from a single active receptor molecule, reliable transmission of small synaptic signals, and separation of a signal of interest from cellular noise. We are investigating how these challenges are met.

Behavioral measurements are often interpreted to show that rod vision is limited by statistical fluctuations in photon absorption—i.e., the physics of light itself—and spontaneous photon-like noise events in the rod photoreceptors. Uncertainty in both rod and behavioral experiments makes this conclusion tenuous. Furthermore, previous work focuses on the ability to detect the presence or absence of weak stimuli, while essentially nothing is known about how accurately stimulus timing is represented. We are currently determining the limits that noise in primate rods imposes on the detection and temporal sensitivity of dark-adapted vision; we are comparing these limits with the sensitivity of retinal ganglion cells, in collaboration with E. J. Chichilnisky (Salk Institute). At stake in this comparison is our qualitative view of the retinal circuitry: if the ganglion cells reach the limit set by the rods from which they receive input, the retina must process the rod signals efficiently and noiselessly.

One source of rod noise of particular interest is trial-to-trial variations in the rod's single-photon responses; these variations are much smaller than expected for signals produced by single molecules—e.g., the charge flowing through an ion channel during its open time. Thus reproducibility also presents a molecular design problem: how is the response produced by a single rhodopsin molecule regulated so that its variability is so much less than expected? The answer seems to be that rhodopsin shuts off through a series of 10–15 steps, a substantial departure from conventional models for the shutoff of single molecules. Rhodopsin is one of many G protein–coupled receptors; thus a similar strategy may decrease variability in signals controlled by other G protein cascades. We are investigating the mechanisms responsible for reproducibility by characterizing single-photon responses produced by rods from mice in which the phototransduction cascade has been altered genetically.

Cones and Cone Vision

The approach to rod signaling described above builds on years of work relating rod and behavioral sensitivity. We know much less about cones and the retinal readout of the cone signals. What limits does cone noise place on the fidelity of cone vision? How much of retinal adaptation to changes in mean light intensity is due to adaptation in the cones themselves? These are fundamental issues for our understanding of cone vision. They have gone unanswered because only a few studies have been made of the sensitivity of primate cones, and none under

conditions that allow direct comparison of cone sensitivity with the sensitivity of behavior or downstream retinal cells.

Most of us go through each day blissfully unaware of the limitations of cone vision. Indeed, cone vision, quantified in behavioral measurements, is impressive. For example, humans can discriminate changes in the wavelength of a monochromatic light of a few nanometers, about 50 times less than the width of the cone spectral sensitivity curves. Noise in the cone responses poses a fundamental limit to this acuity. We do not know, for any property of cone vision, how close behavioral performance comes to the limit set by cone noise. We have recently started experiments that will establish the limits the cone signals place on the sensitivity of cone vision. By comparing these limits with the sensitivity of retinal ganglion cells, we will test whether the cones or downstream events limit the sensitivity of the retinal output.

This comparison, like that for the rod signals described above, is fundamental to how we view retinal processing: if ganglion cell sensitivity reaches limits set by the cones, retinal processing must be efficient and effectively noiseless; if ganglion cells fall short of the cone limit, retinal processing must introduce additional noise.

Our vision operates from starlight to bright sunlight, conditions that differ by 10^{12} in mean light level. As cones account for the majority of this dynamic range, adaptation is of paramount importance for cone vision. Nonetheless, we have a primitive understanding of the sites and mechanisms controlling the gain of cone-mediated signals. For example, we do not know how much of the dynamic range of cone vision is due to adaptation in the cones themselves and how much is due to adaptation in post-cone processing. We recently started experiments that will identify the relative contributions of cones and post-cone retinal processing to adaptation of cone signals. These experiments are still in their infancy, but we are now able to compare the effect of light intensity on cone-mediated signals from all major retinal cell types. Once we have identified where adaptation occurs, we will investigate the mechanisms responsible, using a combination of electrophysiology and two-photon imaging to monitor events in pre- and postsynaptic processes.

Absolute visual sensitivity has motivated 20 years of work that has made the rods the best understood of the many G protein cascades in biological systems. It also has had direct medical benefits, as we now understand the mechanisms and have potential treatments for several forms of stationary night blindness. The long-term aim of our work is to bring a similar clarity to our understanding of cone phototransduction and of the retinal processing of rod and cone signals.

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