function of outer retinal signals for resetting the circadian clock is not yet clear, although it is possible that rod-cone signaling also increases the sensitivity of the SCN to light.

The results of this study suggest that, at least in rodents, the visual and nonvisual ganglion cells comprising the optic nerve are anatomically discrete and that segregation is correlated with melanopsin expression. Loss of the melanopsin-dependent nonvisual pathway results in the loss of nearly all signaling to nonvisual brain centers. The extent to which melanopsin-based signaling contributes to visual responses is less clear. At least in mice, it appears that these cells do not project to visual centers in the lateral geniculate[5], and the current study suggests that visual acuity is not lost with the ablation of this pathway. In primates, however, it does appear that a subset of melanopsin-expressing cells project to the lateral geniculate nuclei[14], although their role in visual processing is still unclear. Recent studies have suggested that melanopsin pathways remain intact in humans with severe outer retinal degeneration[15]. Light is able to influence pupillary responses, sleep and cognitive behavior, even when the patients are unable to perceive the light. This suggests that, in humans, as well as other mammals, nonvisual photoreception operates as a functionally independent system, one that influences our behavior without our awareness. Future studies will no doubt extend the range of behaviors influenced by light through this pathway.

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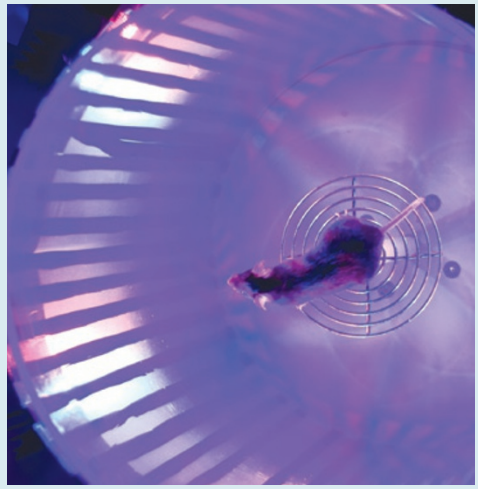
Visual enlightenment

Genetically targeted optical control of neuronal activity is one of the more exciting and important techniques in the study and manipulation of neural circuits. Now, on page 667 of this issue, Lagali *et al.* demonstrate that light-activated channels could also be used therapeutically by restoring photosensitivity to a visual circuit in a rodent model of retinal degeneration (*rd1*) with channelrhodopsin-2 (ChR2). In a separate study on page 631, Zhang *et al.* expand our repertoire of optogenetic tools, reporting a new channel that not only increases the usefulness of light-driven channels, but could also extend the rescue of functionality that is described by Lagali *et al.*



Lagali *et al.* targeted ChR2 to 'ON' retinal bipolar cells of *rd1* mice, using *in utero* electroporation to specifically label the inner plexiform layer containing the ON cells (referred to as e-*rd1* mice). Previous strategies that were designed to rescue visual function in rodents after photoreceptor loss (such as electrical stimulation of retinal neurons or nonselective expression and activation of optical neuromodulators) suffered from a lack of specificity. With these earlier techniques, both ON and OFF cells were activated in response to light, which produces ambiguous signals and can negatively influence the flow of information to higher-order integrating centers. Lagali *et al.*, by specifically stimulating the ON cells, removed this potential for signal cancellation.

After confirming that light-evoked bipolar neuron spiking produced subsequent ganglion cell activity *in vitro* and fully characterizing the circuit organization in the 'ChR2-repaired' retina, Lagali *et al.* then examined the animals' *in vivo* behavioral responses to light. Similar to wild-type animals, e-*rd1* animals responded to light with increased locomotor activity, whereas light exposure did not alter the behavior of control *rd1* animals lacking retinal function. Interestingly, e-*rd1* animals could respond to moving light gratings, recapitulating the normal optomotor responses that are typically lost in animals lacking retinal function. Although the response was only observed under conditions of high illumination, this strongly suggests that the behavioral reflex is indeed light-dependent and that e-*rd1* animals are light responsive.

This strategy of targeting ChR2 expression as a means of restoring retinal function suggests an alternative to electrical stimulation in human patients suffering from retinal degeneration. Although exclusive activation of ON cells allows for more physiological responses by the rest of the retinal circuit, high-intensity light is needed to properly drive behavioral responses, which may damage the retina. Using more photosensitive modulators could avoid this potential photodamage, while retaining similar light-evoked responses. In addition, the current strategy would only rescue black and white vision, and would not provide color-based information. Zhang *et al.* may have a potential answer to this problem.

Zhang *et al.* identified a previously unknown channelrhodopsin from the alga *Volvox carteri* (VChR1). This channel is similar to ChR2, except that its action spectrum is substantially red-shifted, providing a method for activating neurons with longer wavelengths of light. In theory, ChR2 and VChR1 could be used together in the same experimental preparation to independently stimulate separate populations of neurons that individually express one channel or the other. However, more work may be needed to further optimize this separation, as VChR1 retains some minimal responsiveness to the same blue-light wavelengths that robustly activate ChR2. Using longer wavelength light will facilitate several *in vivo* applications of optogenetic control, as red-shifted light can penetrate more deeply into tissue, increasing the types of cells that can be accessed and reducing the light intensity needed to drive action-potential firing.

Targeting ChR2 or VChR1 to different populations of bipolar cells examined by Lagali *et al.* could present a potential strategy for recovering some color processing. Expressed in bipolar cells dedicated to transferring color information, VChR1 might allow cells to respond more strongly to certain red-shifted wavelengths, whereas other bipolar cells, expressing ChR2, could better detect the shorter, blue-shifted spectrum. Although this strategy has yet to be tested, it is clear that we are rapidly approaching a time when the therapeutic use of light-activated channels, with one or more types of channels, may become commonplace.

Noah Gray