Comment on "Emergence of Novel Color Vision in Mice Engineered to Express a Human Cone Photopigment"

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Jacobs *et al*. (Reports, 23 March 2007, p. 1723) reported that plasticity in the mammalian visual system permitted the emergence of "a new dimension of sensory experience" in mice genetically engineered to express a human long-wavelength–sensitive cone photopigment. However, neither neural plasticity nor a new dimension of sensory experience is required to explain their results.

The neural plasticity of the visual system reported by Jacobs *et al*. (*1*) has broad implications for the evolution of sensory systems, for the mechanisms of neural development, and for the treatment of visual abnormalities and disease. However, these conclusions about plasticity are not justified by the evidence.

Jacobs *et al*. introduced a new visual pigment into the mouse retina by replacing the DNA coding sequences for normal mouse pigment with cDNA for a human pigment. They had also shown that mice with the new pigment can discriminate stimuli that normal mice cannot. This replicates their earlier finding (*2*) that the new pigment is so situated that in response to illumination it generates electrical signals that can be observed electroretinographically. They also showed that signals from the new pigment propagate at least as far as the ganglion cells. What is new here is that these signals propagate to the brain as well, and that they are in a form that provides a basis for behavioral responses. Jacobs *et al*. go on to conclude that "[a]n inherent plasticity in the mammalian visual system thus permits the emergence of a new dimension of sensory experience based solely on gene-driven changes in receptor organization." However, their experiment demonstrates neither plasticity nor a new dimension of sensory experience.

Cones with the human pigment will of course respond either more or less to any given monochromatic stimulus than cones with the mouse pigment (except when the stimulus is at the unique wavelength to which the two classes of cones are equally sensitive). This leads to a spatial variation in excitation across the retina corresponding to the distribution of the two classes of cones, even when the stimulus is spatially homogeneous. If the pigment expression is stochastic and independent in each cone, as Jacobs *et al*. hypothesize, the spatial variation will contain all spatial frequencies and will cause variations in the excitation of different ganglion cells even if their receptive fields are large. The pattern of excitation would be identical to that caused in the retina of a normal mouse by a monochromatic field with random variations in luminance, that is, one that could be described as of blotchy luminance but of uniform chromaticity.

If the only difference between these knock-in mice and normal mice is the difference in pigment contained by some of the cones, without any changes in neural connections, then one might suppose that a homogeneous, monochromatic field would look blotchy to the knock-in mice and homogeneous to the normal mice. If one changes the wavelength, the blotches must change contrast; wavelengths on opposite sides of the wavelength that excites both classes of cones equally must produce blotches of opposite contrast.

One may question how visible these blotches are, for the visibility of patterns that have fixed locations on the retina, such as these, tend to fade over time. However, the visibility of all such images does recur, though the conditions under which they are visible depend on whether they are formed by artificially stabilized images (*3*, *4*), by the production of afterimages (*5*, *6*), or by entopic images such as the shadows of the retinal blood vessels (*7*, *8*), for these various images have different properties. The properties of the blotchy patterns formed by the new pigment likewise differ from those of other retinally fixed patterns, so one cannot predict the conditions under which they will be visible.

If these blotchy patterns are visible to the mice at all, as is probable, then the mice could make all the color discriminations in the behavioral tests reported by Jacobs *et al*. solely on the basis of the contrast of the blotches. No plasticity of the nervous system is required, nor any new dimension of sensory experience. Neural plasticity of the sort described by Jacobs *et al*. remains to be demonstrated, and its far-reaching implications must be held in abeyance until it is.

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