

This paper serves as an introduction to the following papers, which were presented at a colloquium entitled "Vision: From Photon to Perception," organized by John Dowling, Lubert Stryer (chair), and Torsten Wiesel, held May 20–22, 1995, at the National Academy of Sciences in Irvine, CA.

Vision: From photon to perception

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A National Academy of Sciences colloquium entitled "Vision: From Photon to Perception" was held at the Beckman Center of the Academy in Irvine, California, on May 20–22, 1995. The meeting was organized by John Dowling, Lubert Stryer (chair), and Torsten Wiesel. The aim of the colloquium was to bring together leading scientists and students from different disciplines of vision research ranging from physics to psychology to define and explore the most challenging questions in the field. One hundred forty scientists participated in the colloquium. We are indebted to Silicon Graphics, Inc., and the Ruth and Milton Steinbach Fund, Inc., for generous grants that helped bring graduate students to the meeting.

The major topics discussed were as follows.

- (i) How is light converted into a nerve signal?
- (ii) How are the outputs of rod and cone cells processed by the retina?
- (iii) How does the visual system develop and how did it evolve?
- (iv) How do we perceive color, depth, and motion?

The colloquium began with a spirited opening lecture by David Hubel on the process of discovery in vision research. The first session, "From Photon to Nerve Signal" (chaired by Lubert Stryer), focused on transduction processes in vertebrate and invertebrate photoreceptor cells. The second session, "Development and Circuitry" (chaired by John Dowling), dealt with the development of the retina and lateral geniculate nucleus and with signal processing. Higher-order processes occurring in the visual cortex were considered in the third session, "Representation and Perception" (chaired by Francis Crick). Torsten Wiesel gave a reflective closing lecture on the pursuit of knowledge and the future of research in neurobiology.

Denis Baylor (1) began the first session by providing an account of how the absorption of a photon by a retinal rod or cone cell leads to the generation of an amplified neural signal. Photoexcited rhodopsin triggers the activation of transducin, a G protein, which in turn stimulates a cyclic GMP phosphodiesterase. The consequent hydrolysis of cyclic GMP directly closes cation-specific channels in the plasma membrane. The resulting hyperpolarization is sensed at the synapse, where it decreases the rate of transmitter release. This light-triggered cyclic GMP cascade is one of the best understood signal transduction processes in nature. The challenge now is to elucidate the molecular events mediating recovery of the dark state and adaptation to background light. The remarkable reproducibility of the single-photon response also needs to be understood in molecular terms. Investigators are now focusing on the negative feedback actions of the light-induced fall in the cytosolic calcium level. Baylor presented several incisive recent experiments comparing phototransduction in normal and transgenic mouse rods harboring mutant genes in the deacti-

vation pathway. A rich harvest is being reaped from the concerted use of electrophysiological and molecular genetic techniques.

A workshop entitled "Amplification in Phototransduction," chaired by Trevor Lamb, further explored the cyclic GMP cascade of vertebrate vision. Lamb (2) presented a stochastic simulation of the photoactivation of the cyclic GMP phosphodiesterase. The simulated rising phase of the photocurrent agrees closely with the response of intact rods as measured electrophysiologically. This modeling approach will be useful in testing our emerging grasp of how the cascade is deactivated. New experimental methods too are enriching our understanding of the early events in vision. Minh Vuong (3) demonstrated a highly sensitive microcalorimetric technique for measuring the heat released by cyclic GMP hydrolysis. This approach provides a window on the kinetics and gain of the initial steps in phototransduction. Joe Noel (4) vividly displayed the three-dimensional structure of the α subunit of transducin, the first amplified intermediate in vision.

Invertebrate vision too begins with the activation of a G protein by photoexcited rhodopsin. As was discussed by Charles Zuker (5), the cascades of vertebrates and invertebrates then diverge. In *Drosophila*, the activated G protein stimulates a phospholipase C rather than a cyclic GMP phosphodiesterase. Another major difference is that, in *Drosophila*, light opens channels and depolarizes the photoreceptor membrane. How does phospholipase C activation lead to channel opening? Inositol trisphosphate, calcium, and cyclic GMP have been implicated in the process but the actual messenger has eluded detection. Zuker outlined three genetic approaches that have led to the identification of more than 50 genes in phototransduction. Electrophysiological studies of mutants generated by these approaches and laser scanning confocal microscopic studies of photoreceptor cells show that localized changes in the calcium level play a key role in switching off the photoreponse. The major task now is to complete the molecular characterization of the light-sensitive channel and, most important, to learn how it is gated.

Gerald Jacobs (6) reviewed recent advances in our understanding of color vision in primates and discussed their evolutionary implications. The number of dimensions of color vision as determined by perceptual color matching tests is usually the same as the number of types of cone visual pigments in the retina of a primate. Four patterns of primate color vision are evident. Old World monkeys, apes, and humans are trichromatic. New World monkeys were once thought to be dichromatic, but the actual situation is more complex and interesting. Males are always dichromatic, whereas females can be either dichromatic or trichromatic depending on whether their X chromosomes contain the same or different alleles of the long-wavelength pigment gene. This potential polymorphism is absent in diurnal prosimians, who are uniformly dichromatic. The situation is even simpler in nocturnal primates, who are monochromatic because they possess only one functional cone pigment. These findings pose

two intriguing questions: (a) What were the selective pressures underlying the evolution of partial trichromacy in the New World lineage and uniform trichromacy in the Old World lineage? (b) How did the retinal circuitry for color vision coevolve with the establishment of a second visual pigment locus on the X chromosome in the emergence of trichromacy in Old World monkeys?

The next set of papers dealt with the circuitry and development of the retina. Human color vision begins with signals from three types of cones that combine antagonistically to form blue–yellow and red–green opponent pathways. Dennis Dacey (7) showed how the circuits underlying opponency are being deciphered. The macaque monkey retina can be studied *in vitro*, and photoresponses can be recorded from cells identified by their morphology and binding of specific fluorescent markers. Blue–yellow opponency is mediated by a small bistratified ganglion cell that receives depolarizing inputs from a blue-sensitive “on” bipolar cell and a summed red and green-sensitive “off” bipolar cell. A different kind of circuitry underlies red–green opponency, which is signaled by midget ganglion cells. Dacey proposed that the receptive field centers of these cells get a simple cone input (either maximally red- or maximally green-sensitive), whereas the surround gets both types. This mixed-surround model provides a simple basis for the evolutionary transition from dichromacy to trichromacy.

The determination of cell fate in the vertebrate retina was discussed by Constance Cepko (8). Distinctive cell types are born in overlapping order. In the mouse, ganglion cells, cones, amacrine cells, and horizontal cells arise early in development. Rods come later, followed by bipolar cells and Müller glial cells. Retroviral vectors have been used to insert genetic tags (such as the β -galactosidase gene) for lineage analysis. The significant finding is that retinal progenitors are multipotent. As many as six cell types have been seen to arise from a single precursor. The overlapping birth order of retinal cell types and the multipotency of progenitor cells imply that extrinsic cues play key roles in directing cell fate in the vertebrate retina. Cepko proposed that retinal progenitors undergo a series of state changes that are accompanied by alterations in competence to respond to environmental cues to produce particular cell types. Each state of competence is transient and is endowed by expression of a combination of transcription factors.

The remarkable diversity of ganglion cell properties and the precision of their programming stimulated Jeremy Nathans (9) to pose a set of questions concerning the underlying molecular mechanisms: (a) What determines the synaptic specificity, neurotransmitter type, and dendritic field of each class of ganglion cells? (b) What are the guidance mechanisms that lead ganglion cell axons to precise locations in the midbrain and lateral geniculate nucleus? (c) What are the genetic regulatory circuits specifying ganglion cell type? There is much interest now in identifying transcription factors that control ganglion cell development. Four POU-domain transcription factors (homeodomain proteins) are attractive candidates because they are expressed in subsets of ganglion cells. One of them, Brn-3b, is abundant in P-type but not in M-type ganglion cells. P-type (parvocellular-type) cells have high spatial resolution and exhibit color opponency, whereas M-type (magnocellular-type) cells have high temporal resolution and can respond to small changes in contrast but are achromatic. The importance of Brn-3b is evidenced by the finding that retinas lacking the gene have 70% fewer ganglion cells than do normal retinas.

Ganglion cell axons from the two eyes terminate in adjacent but nonoverlapping eye-specific layers in the lateral geniculate nuclei of adults. By contrast, the inputs are intermixed in development. Carla Shatz (10) presented experiments that provide insight into how neural activity contributes to the emergence of eye-specific layers. Segregation takes place *in*

utero before vision is operative but requires ganglion cell signaling. How is this accomplished? Spontaneous action potentials arising from as many as 100 ganglion cells were simultaneously recorded by use of a multielectrode array. The surprising finding was that neighboring cells fired in a concerted manner. Their action potentials occurred within 5 sec of each other, followed by a silent period of up to 2 min before firing resumed. The ganglion cell activity comprised a wave that swept across the retina. Optical recordings monitoring changes in intracellular calcium levels suggested that amacrine cells and ganglion cells act together in generating spontaneous synchronous activity in the developing retina. Shatz proposed that activity-dependent wiring may be generally used in the developing nervous system to help refine early neural connections.

The optic nerve is a severe bottleneck in visual signaling. All information captured by 125 million photoreceptor cells in humans is carried into the brain by only 1 million ganglion cell axons. How does the retina generate a highly efficient representation of the visual scene? Markus Meister (11) described recent experiments suggesting that the retina employs multineuronal coding to compress a large number of distinct visual messages into a relatively small number of optic nerve fibers. Simultaneous recordings of many ganglion cells with a multielectrode array showed that nearby ganglion cells have a pronounced tendency to fire synchronously (within 20 msec of one another). A particular ganglion cell can partake in several different concerted firing patterns. Hence, synchronous firing events, rather than individual action potentials, may be the fundamental symbols of the retinal code. A calculation based on a simple model shows that concerted firing conveys more information than does independent firing and therefore could be advantageously used to enhance spatial and temporal resolution. Meister suggested that multiplexed messages could be decoded in layer IVc of the visual cortex, which contains many more neurons than afferents from the lateral geniculate nucleus.

The last four papers considered higher-level processes in the visual cortex. Charles Gilbert (12) presented experiments showing that receptive field properties of cells in the cortex can be dynamically altered in times ranging from seconds to months. Focal retinal lesions were made at cognate positions in the two eyes to remove visual inputs destined for a particular area of the visual cortex. Over several months, the silenced cortical area regained functioning visual input by an expansion of the representation of the retinal region around the lesion. Furthermore, a transient blind spot could be generated by occluding part of a twinkling random dot pattern. This occlusion led within a few minutes to a reversible expansion of the size of the receptive field of the corresponding cortical cell. It will be interesting to learn the molecular mechanisms underlying this cortical plasticity. Gilbert suggested that experience-dependent changes in cortical function play essential roles in perception.

David Heeger, Eero Simoncelli, and Anthony Movshon conducted a workshop on “Computational Models of Cortical Visual Processing” (13). Their aim was to devise detailed quantitative models of neuronal function that capture the behavior of different classes of cortical neurons with a small number of measurable parameters. One of their models deals with simple cells in the primary visual cortex (V1), which are known to be selective for stimulus position, orientation, size, and direction of motion. The other model is concerned with pattern direction-selective neurons in the extrastriate visual area MT (V5), which have been shown to signal the movement of entire patterns by combining information from several orientations. Both models compute a linear combination of their inputs, rectify this sum, and then divide the neuron's response by a quantity proportional to the pooled activity of many neurons in the cortical neighborhood. Readers can

explore the models and carry out simulations by obtaining a Macintosh computer program over Internet (13). Movshon and coworkers proposed that each cortical area conducts calculations having the same basic form but using distinctive inputs.

William Newsome (14) presented experiments that probe the neural basis of decision making. What are the cognitive links between sensation and action? Neural responses in the lateral intraparietal area (LIP) of the cortex were monitored while alert monkeys discriminated the direction of visual motion. A monkey was required to judge the direction of coherent motion in a dynamic random dot pattern in which only a fraction of the dots moved consistently in one of two directions. After a delay of about a second, the monkey reported the direction of coherent motion by making an eye movement to one of two visual targets. The significant finding was that neurons in LIP generate signals that predict the decision a monkey will make. Newsome views neural activity in LIP as a window on the decision-making process in which weak, slowly arriving sensory information is integrated. Two fascinating questions arise: (a) What is the neural circuitry that links sensation to decision making to motor activity? (b) Which elements of this circuitry continue to be utilized when monkeys make decisions based on a different sensory attribute, such as the color of a random dot pattern?

In the final talk, Ken Nakayama (15) showed that stereoscopic vision plays a key role in the perception of surfaces. Because two-dimensional surfaces are often only partially visible, a three-dimensional interpretation is needed before two-dimensional information can be fully evaluated. The task is to distinguish between true boundaries and spurious ones caused by occlusion, to determine border ownership. First,

binocular disparity (the differential angular separation between pairs of image points in the two retinas) is used to sort edges and determine their ownership. Second, half-visible points (image points in one eye having no counterpart in the other because of occlusion) provide complementary information. The identity of the eye receiving the visual input needs to be known to form the correct image. This essential eye-of-origin information probably resides in the striate cortex (V1). The reader can explore relations between stereopsis and the perception of surfaces by looking at Nakayama's vivid stereoscopic illustrations (15).

1. Baylor, D. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 560–565.
2. Lamb, T. D. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 566–570.
3. Vuong, T. M. & Chabre, M. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 9813–9817.
4. Noel, J., Hamm, H. E. & Sigler, P. B. (1993) *Nature (London)* **366**, 654–663.
5. Zuker, C. S. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 571–576.
6. Jacobs, G. H. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 577–581.
7. Dacey, D. M. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 582–588.
8. Cepko, C. L., Austin, P., Yang, X., Alexiades, M. & Ezzeddine, D. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 589–595.
9. Xiang, M., Zhou, H. & Nathans, J. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 596–601.
10. Shatz, C. J. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 602–608.
11. Meister, M. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 609–614.
12. Gilbert, C. D., Das, A., Ito, M., Kapadia, M. & Westheimer, G. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 615–622.
13. Heeger, D. J., Simoncelli, E. P. & Movshon, J. A. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 623–627.
14. Shadlen, M. N. & Newsome, W. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 628–633.
15. Nakayama, K. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 634–639.