PRIMARY VISUAL CODING

The last lecture was concerned primarily with phototransduction--how a rod or cone catches a photon and transmits a signal about it from the outer segment to the synapse. Today we will consider the subsequent processing of information by the retina. The retina is not simply a bank of photodiodes. It contains a variety of internal circuits, which compress and shape information before transmitting it to the optic nerve. At the end of the last lecture we saw one example. In the central retina, one cone drives one bipolar cell which drives one ganglion cell: this creates a region of maximal acuity. In fact, the acuity in the central retina reaches the theoretical maximum, which is limited by the packing density of individual cones. In the peripheral retina there is major convergence of rods and cones upon ganglion cells, such that acuity is traded for sensitivity and for economy in the number of optic nerve fibers.

SIGNALING BETWEEN RODS, CONES AND BIPOLAR CELLS

How do rods and cones signal to the subsequent neurons? In general, the answer is: just like any other neurons. However, there are some unusual features. One was encountered in the previous lecture. Rods and cones hyperpolarize in response to light, and there is no sign of action potentials in them. It turns out that the synapses of rods and cones release neurotransmitter, in just the same way as any other cell. When the cell hyperpolarizes, less neurotransmitter is released by their synapses. Why do they not make action potentials? The reason is that rods and cones are very tiny cells. A garden variety neuron of the brain – say a cortical pyramidal cell – might extend for around 2 millimeters. A rod or cone spans only 20-30 microns from tip to base. Since the rod does not have to transmit information very far, there is no need for action potentials. The electrotonic decrement between the end of the outer segment and the base of the synapse is so small, that no regenerative activity is required.

The same is true for retinal bipolar cells, horizontal cells, and many amacrine cells, which are equally tiny. The cells of the outer retina do not need to make action potentials, because electrotonic decrements are very small. In contrast, the retinal ganglion cell must send an axon several centimeters to the brain. There, action potentials <u>are</u> required.

RESPONSES TO LIGHT AND DARKNESS

When a rod or cone hyperpolarizes, it releases less neurotransmitter. What effect does this have on the subsequent cells? At this point--the synapse between rods or cones and bipolar cells--a major divergence in the handling of information is created. Different bipolar cells contain different kinds of neurotransmitter receptors. The neurotransmitter released by rods and cones is glutamate. Some bipolar cells contain kainate-type glutamate receptor, which gates a cation channel. When glutamate falls on this receptor, the cation channel is opened. Ions, predominantly sodium, flow into the bipolar cell. The bipolar cell will thus follow fairly faithfully the activity of the rod or cone. When the cone is very hyperpolarized it releases little

neurotransmitter. The bipolar cell cation channel is thus mostly closed, and the bipolar cell also remains relatively hyperpolarized. When the photoreceptor cell depolarizes, the bipolar cell also depolarizes. Accordingly, this synapse is sign-conserving: when light falls on the rod or cone, the bipolar cell hyperpolarizes (because the photoreceptor hyperpolarizes).

However, there is a second class of bipolar cell, which contains a different type of glutamate receptor. This receptor is a metabotropic glutamate receptor, MGluR6. Binding of glutamate to the receptor activates a g protein.   Through its downstream effectors (still incompletely known) it holds a cation channel closed. The net effect is that the synapse is sign-reversing. When the concentration of glutamate is high, the channel tends to stay closed. When the concentration of glutamate is low, the channel opens. When light hyperpolarizes the rod or cone, the concentration of glutamate in the synapse falls, the channel opens and the cell depolarizes. Thus are created two major classes of bipolar cell. One depolarizes when light falls on the rods or cones and the other hyperpolarizes. These are conventionally called ON and OFF bipolar cells.

The neurotransmitter released by bipolar cells onto ganglion cells is also glutamate. The synapse of bipolar cells upon ganglion cells are not understood in as much detail as those of rods and cones on bipolar cells, but it is certain that they are sign-conserving synapses. As a final consequence, two classes of retinal ganglion cells are created. One responds to light with depolarization and one with hyperpolarization. Ganglion cells generate action potentials; when the cell is depolarized above a certain threshold, regenerative sodium spikes are caused. The net result is that one class of ganglion cells fires action potentials at an increased rate down the optic nerve to the brain, while the other decreases its rate.

The dichotomy between ON and OFF responses is a central one in the early stages of vision. About half of the cells in the early visual system respond to light by increasing their rate of firing and half by decreasing it. One may imagine the situation as being a push-pull one. Retinal ganglion cells have fairly restricted rates of firing. Their operating range is from around 0 to around 1,000 Hz. The cells that are inhibited by light (OFF cells) tend to have a higher level of spontaneous activity in the dark. They fire steadily even in the absence of a stimulus. This means that they have a working range at "negative" rates of firing--rates below their resting rate. One interpretation is that the overall range of signaling is thus expanded by having cells that work in two directions.

Another way to think about it is to consider the situation at an edge between a light and a dark zone. What the visual system really cares about is transitions between light and dark. Uniform areas of illumination carry little information; it is the points of change where information if contained. If one has a light-dark edge, is the information contained in the lightness or the darkness? It's a glass that might be half empty or half full. Information is contained in both lightness and darkness and the visual system respects each equally.

LATERAL INHIBITION

As we have just seen, there is a partitioning of information into two distinct pathways at the synapse between photoreceptors and bipolar cells. At the same level, a second computation occurs: lateral inhibition sharpens the contrast between neighboring regions of illumination.

In the outer retina is located a horizontally conducting cell, called, not surprisingly, a horizontal cell. Horizontal cells receive synaptic input from rods and cones, and make synaptic output back onto rods and cones. The neurotransmitter of horizontal cells is GABA. Notice that the lateral extent of the horizontal cell is much greater than the size of the individual rods, cones, or bipolar cells. An individual rod or cone outer segment is around 2 μm in diameter. A horizontal cell may be 500 μm.

Because the neurotransmitter of horizontal cells is inhibitory, because the horizontal cell feeds back onto the rods and cones, and because the horizontal cell has a wide spatial extent, this cell can spatially sharpen the response of retinal ganglion cells to small stimuli. In effect, when a small stimulus falls on the retina, regions around it are inhibited by the horizontal cell. One way to think of this is that the horizontal cell creates a region of "hyper-darkness" around a small stimulus. Light falling on a small patch of retina causes hyperpolarization of the rods and/or cones directly stimulated by the light. In neighboring regions, though, negative feedback from the horizontal cells causes the rods and/or cones to be depolarized. To understand the sign of these changes, one must slowly walk through a long series of sign reversals. This is clearly diagrammed in the chapter on the retina by Kandel, Schwartz and Jessell.

The effect of this for information processing in the retina is that regions of change between light and darkness are accentuated. When light falls on a patch of retina there is a region of excitation surrounded by a trough of inhibition. In the absence of lateral inhibition, two neighboring stimuli tend to blend into one. A central "detector", located in the brain must discriminate a narrow trough of excitation. Lateral inhibition occurring in the retina sharpens the difference between two nearby stimuli.

PHASIC AND TONIC RESPONSES

A second form of signal processing occurs deeper in the retina. It is mediated by amacrine cells. The net result of the processing is that the responses of some retinal ganglion cells become phasic, which means that the cells are sensitive primarily to changes in illumination rather than simply its ongoing level.

Amacrine cells occur in a horrifying diversity--there are approximately 30 different kinds of amacrine cells, each of which does something different. For present purposes, we will consider only one of their functions. Some amacrine cells contain an unusual synaptic arrangement, called a reciprocal synapse. A bipolar cell synapses on the terminal of the amacrine cell. The amacrine cell in turn immediately synapses back onto the axon terminal of the bipolar cell. The neurotransmitter released by the bipolar cell is glutamate. The neurotransmitter released by the amacrine cell is GABA. When the bipolar cell depolarizes, it releases more glutamate onto the terminal of the amacrine cell. However, when the amacrine cell is

depolarized by the glutamate, it in turn releases its neurotransmitter, GABA, back onto the terminal of the bipolar cell. The effect is to return the bipolar cell to a more hyperpolarized level – i.e., to truncate the output of the bipolar cell.

The same bipolar axon that contains the reciprocal synapse with an amacrine cell also synapses on the ganglion cell. There, it also releases glutamate. The release of glutamate by the bipolar cell onto the ganglion cell is truncated by the amacrine cell feedback. Since the overall output of the bipolar cell is truncated temporally by the amacrine cell feedback upon its terminal, the response of the ganglion cell is also truncated. The effect is that a train of action potentials is generated by the ganglion cell immediately after the onset of the stimulus, but it is soon reduced by the amacrine cell feedback onto the bipolar cell. These ganglion cells are thus phasically active, firing a burst of action potentials immediately after the onset of a stimulus but fewer as the stimulus continues.

OVERALL CODINGS OF THE RETINAL OUTPUT
Thus far you have heard about four kinds of processing of the visual input that occur within the retina: 1) The convergence of cones and rods on retinal ganglion cells. 2) The splitting of the photoreceptor output into separate ON and OFF channels. 3) Lateral inhibition, occurring at the level of the horizontal cell, which sharpens contrast between neighboring retinal regions and 4) the action of amacrine cells to temporally sharpen the responses of some retinal ganglion cells. How are these combined at the level of the retinal ganglion cell?

The answer is that they are mixed and matched to create distinct types of ganglion cell outputs. Each type is associated with a distinctive morphological type of cell, so that these are discrete, parallel informational channels.

One type of cell, termed in the primate a "midget" cell, has a small receptive field. Its center can be ON or OFF. Midget cells are generally quite tonic in their responses – they show a sustained increase in their rate of firing (for an ON cell) or decrease in their rate of firing (for an OFF cell). They have center-surround antagonism, so that an ON cell is excited by stimulation of the receptive field center and inhibited by stimulation of the receptive surround.

A second type of cell, the "parasol" cell, has a much larger – roughly 5-6 times the diameter – receptive field. These cells are phasically active; they fire a burst of action potentials (or suffer a burst of inhibition) when the light comes on, after which they return more or less to their resting rate. In the case of an OFF parasol cell, they fire a rebound burst of spikes when the stimulus goes off. (You should be able to predict this from the mechanism of the phasic response – can you?) For reasons that will be discussed in more detail later, the large receptive field area of the parasol cells means that the retina can use far fewer of them than of midget cells.

Here I have termed the cells "midget" and "parasol" cells. This is the traditional anatomical designation. There is also in use a second nomenclature, based on the CNS targets of the cells. In this system, the midget cells are called parvocellular, or "p" cells, because they

project to the parvocellular layers of the lateral geniculate body; and the parasol cells are called magnocellular or "m" cells because they project to the magnocellular layers. The physiological nomenclature (m and p) has weaknesses and will eventually probably fall from use. However, it is the nomenclature used in the textbook by Kandel, Schwartz and Jessell. Sorry about that. The simplest thing to remember is that the small cells project to the small-celled nucleus of the lateral geniculate body, and the large retinal ganglion cells project to the large-celled nucleus.

Midget cells represent around 60% of all retinal ganglion cells in the near-peripheral retina of the primate, and parasol cells slightly under 10%. What represents the remaining 30%? These are a heterogeneous class of cell with highly specific responses. One example is a ganglion cell with chromatic tuning. This neuron has a simple receptive field, with a single light-sensitive "center" region. Blue light falling on the cell's receptive field excites it; yellow light inhibits it. This antagonism is created by the pattern of synaptic inputs onto the cell. The cell receives excitatory inputs from blue cones, and inhibitory inputs (via a set of OFF bipolar cell) from the red and green cones (remember red plus green equals yellow). Thus, simply by looking at the output of this neuron, the brain can tell where on the spectrum from blue to longer wavelengths a stimulus lies. If the rate of firing of the cell is high, the stimulus lies toward the blue end; if the rate of firing is low, the stimulus lies toward the yellow end. Mixtures of colors would create intermediate firing rates. Note that this is a very efficient re-coding. The activity of two sets of cells is compressed, such that information sensed by two sets of cells is transmitted to the brain as a single number.

Other cells subserve vegetative functions and project subcortically. An example is a cell with a very large receptive field that appears to act as a simple light meter: it projects to the suprachiasmatic nucleus, which sets circadian rhythm. The cell does not need a sophisticated receptive field, since its only function is to sense the level of ambient illumination. (There are very few such cells--in the rodents where they have been studied, only a few thousand per retina.)

Another is the directionally selective retinal ganglion cell. As its name implies, the direction selective ganglion cell can report on the direction of movement of a stimulus falling within its receptive field. The cells have an inhibitory surround, as they must due to the action of horizontal cells in the outer retina. However, within their receptive field center movement of the stimulus causes an increase in firing while movement in the opposite direction inhibits firing. In fact, these cells can abstract movement independent of any local features of the receptive field. There are no inhibitory or excitatory zones that can account for this preference for motion. Indeed, the cell reports motion independent of its location within the receptive field or of the contrast of the stimulus--i.e., black on white or white on black.

The mechanism by which these computations are achieved is unclear. However one of their functions is known: the directionally selective cells provide an error signal for optokinetic tracking of moving stimuli. In lower animals, where these have been most studied, a directionally selective type of ganglion cell projects to the pretectal nuclei. One of these nuclei

is concerned with eye tracking. Optokinetic nystagmus is a test in which the animal is exposed to a large moving field. An everyday example is the visual stimulus created when one stares out of the side window of a moving car. This causes an irresistible following movement of the eyes. It is part of the mechanism by which gaze is stabilized when the animal moves through the environment. The direction selective ganglion cell provides a signal that says that the image is slipping on the eye, which then triggers a counter movement of the eyes. Evidence that similar mechanisms occur in primates, is that the optokinetic reflex survives massive combined lesions to the visual centers of the cerebral hemispheres and superior colliculus.

COVERAGE

Thus far we have been discussing cells one at a time. How do they behave as whole populations? Put in other terms, how do the different classes of retinal ganglion cell cover the visual world? It turns out that each class of retinal ganglion cell surveys the world efficiently. What this means is that receptive fields of a single type, cover the retina with little overlap--they "tile" the retinal surface.

This is true for each of the classes of retinal ganglion cell. Since the parasol cells have larger dendritic and receptive fields than the midget cells, it thus is necessarily true that they are far fewer--10% as opposed to 60% of all retinal ganglion cells. The tiling is efficient not only for the large classes (midget and parasol) but also for ON and OFF within the large classes. The retina is tiled, for example, by ON-parasol cells and independently by OFF-parasol cells. At every point on the retina every class of retinal ganglion cell is represented at least once. In the limit, where the tiling is perfectly efficient, every point on the retina would be covered once and exactly once by each class of retinal ganglion cell. This is the principle of parallel processing. At each point on the retina, many different features of the visual stimulus are being reported to the brain in parallel.

Reference: Kandel, Schwartz and Jessell, Chapter 26