NEVILLE SANJANA: So Jerry started the ablation studies of the visual system, and the reason why I'm not picking up where he left off is because Jerry is really the specialist in this. In fact, you'll see in our textbook that his work is cited, his 1969 paper is cited for some of the ablation that he did to the superior colliculus. It's classic work, so he really is the one to talk about that. Not only that, I don't do lesion studies, so another good reason for me not to. So I am like a physiologist, and I work mainly in the hippocampus, but hopefully that will transfer to the retina nicely for today.

So this is today's topic, and Jerry had this kind of very large outline with lots of slides, so we're probably only going to talk about the retina, and maybe get to talk about the different cell types, the ganglion cell types, and I don't if everybody has done the reading or whatnot, but I'll try and introduce you, just starting with the eye, and then moving down to the retina, and then looking at the retina inside, so we'll probably tackle these first two things. So we'll start with the vertebrate retina.

So there's a lot of information here on this slide, and we're going to be going through it one by one, so don't get too overwhelmed right here. We're first going to be talking about the different cell types. I'm just going to introduce you without telling you too much about them, and then I'm going to tell you about what is the really interesting cells in the retina, which is the photoreceptors, which is kind of the input end of the retina, and the retinal ganglion cells, which is several levels back, a minimum of two synapses back, and that's the output end of the retina. So those are the interesting phenomena. We're going to look, hey, what do the photoreceptors do, what do the retinal ganglion cells do, and then, once we know what the input-to-output transformation is, we're going to talk about electrophysiological studies, and the mudpuppy-- and I'll tell you what the mudpuppy is, if you don't know, soon-- we'll talk about electrophysiology that does that transform in between input and output.

So let's get started with cell types. Where is the retina? This is the eye right here. We'll start with this. The retina is right here. It's this thin layer. It's just a couple hundred microns thick. That's really small. That's like a razor blade, really, really small. And there's all these cells that we're going to learn about today, and they're just in this very, very small piece of tissue. So something to keep in mind.

Just, I guess, I'll give you some basics here. The cornea is this thing that does most of the refraction, refraction focusing the rays of light onto the back visual plane of the eye, and the lens, also, which can adapt with these ciliary muscles. It also does some work in focusing too, but the retina is this back plane right here, and you can see the optic nerve exiting. The retina. And this optic nerve are considered central nervous system, unlike sensory receptors, like touch receptors, or like, in the ear, the cochlea. Those are peripheral. So this is central nervous system.

So there's five cell types we're going to be talking about today, and here they are kind of roughly in order from input to output, photoreceptors, horizontal cells, bipolar cells, amacrine cells, and lastly, retinal ganglion cells. So here's a picture. Again, this is about as thick as a razor blade. So the first thing, I don't know if I have a better slide of this--- no, I don't? OK, well, we'll see this more later, but the retina has this kind of inside-out organization, in that the photoreceptors, what's drawn here as R, is actually furthest back, and what is first is the ganglion cells. So the light actually has to go like this, boom, and then the information is processed in this inside-to-out fashion, and then the ganglion cells all connect to that optic nerve and goes back. So here are the different cell types with their initial letters. We'll get into this more. No need to worry about details right now.

So Jerry also says this nice picture based on EM, a much finer electron micrograph look, and you can see here synapses and how contacts are made. H is like a horizontal cell. These are the receptors again. Light is going this way. I'm speeding up here because I'm going to slow down a lot and talk about each cell individually.

[INAUDIBLE]

Yes?

[INAUDIBLE]

Sure. So what I mean by inside out is that, well, think about this way. If you're designing something like a video camera, where are you going to put the CCD or something? Are you going to put that behind all the electronics and stuff? Or, you know, say you had made the electronics out of clear plastic or something? Still, you'd worry about, you know, light getting bent and things like that. It makes more sense to put the CCD's focal plane right out there, right, so you'd see it, or so that the light would be incident on that before it's incident on electronics, and controls, and things like that. But here that's kind of reversed. All the electronics, and controls, and processing stuff is here. The light is coming from here, into the retina, and hitting the photoreceptors.

So what's interesting is then evolution has done some things, and I didn't really want to get into this. But I'll very briefly say, to compensate for this, one of these things is these cells, all these rights here, are unmyelinated. So cells in there which are unmyelinated are-- cell bodies are, by themselves, clear. If you look in a microscope at cell cultures, say, in our lab, you'd see that. So the myelin coating can cause more of a diffraction of light.

Another thing is, behind the photoreceptors right here, there's a pigment epithelium, which is like this black layer. And what it does is it absorbs anything that the photoreceptor does not absorb. You'll see later, the photoreceptors are tuned to certain colors of light, say, and-- tuned to certain frequencies of light, I should say. And what's not absorbed, you can imagine, if you had a reflective surface, it would go boop, and then bounce back. And that would cause some kind of interference in your-- in your sensing. So here there's like this black pigment epithelium. So I don't know if that really answered your question. That was an attempt.

Going to talk now about the phenomenology of the interesting stuff, the photoreceptors. How do they do their amazing job? And what's the end part of the transform? What are we getting out of the retina? What are the retinal ganglion cells-- those output cells, what do they send us? What are they sending back to cortex, and superior colliculus, and all those interesting areas?

So we're going to start with the photoreceptors. That is a photoreceptor right there. So here is a very nice-- can you see this? Yeah, you can see well. So I'm lucky to have some friends in vision science here who gave me these great photos. This is a scanning electron microscope picture of rods and cones. And you can see the rods, these thin rods, and these larger cones. Actually, we'll get into a little bit about why these are here. I just want you to observe the structure and how nice the organization is, actually.

So why this rods and cones stuff? So here's the question. How do you design a visual system that can respond to high illumination levels during the daytime and low light levels at night? And there's actually a few different things that are in the visual system to answer this question. But there's one big one. Does anyone know what it is? I kind of just gave it away on the last slide by my poor organization of slides. Mumbling, mumbling-- yes?

AUDIENCE: You have two different kinds of photoreceptors.

NEVILLE SANJANA: You have two different kinds of photoreceptors. That's exactly right. So one is for scotopic vision, which is the word that denotes low-light vision. That's rod-dominated vision. And the other one is for photopic, which is high light levels. And that's cone-dominated. So let's get into a little bit more about these two luminance regimes and the things associated by them.

So here is what you see with if you're just looking at cones. And here's what you see if you're looking with rods. And what's the big difference here between these pictures? Don't look at the text. Just look at the pictures. What is the difference between this and that?

Right, you see all the little spots here. And here's really the huge like, wow, look at this. Only one quanta is needed to stimulate a rod receptor. So that's amazing. That one quanta can lead to-- if you read in your textbook, it explains a little bit more about how photoreceptors work. But it can lead to this huge phosphorylation cascade that involves, like, thousands of cyclic GMP molecules.

And that's-- don't write that down. It's not needed to know that. But just if you're interested, look in the book. It's an amazing thing, one quanta of light phosphorylating all those molecules.

So OK, what is the distribution of receptors in the eye? Why are receptors distributed this way? And what does it imply about vision? Those are a lot of questions.

But there are two main regions to the eye. In this central portion, which we call the fovea-- I don't if everybody's familiar with that-- you can see it there's just cones, these hexagonal cones. There's no rods there. And that's because these-- you have this fine-- so in the fovea, when you fixate on something, you have this fine, high-acuity color vision.

But here, out in the periphery, you have cones interspersed with rods too. And so this is another important point. So here you have high color acuity. Now what do you think having this buys you? What is something you can tell me in terms of-- so if I want to look at some fine color detail, fovea is good. But what might this be good for? Contrast, OK. That's partially it. Anyone? Bueller? Bueller?

So right, so rod's are for scotopic vision, right? So that's like the low light levels, the night vision. So have you ever noticed that when you look out on a starry night or something, if you're trying to see a star that's kind of dim, have noticed that it's not better to actually look right at it, but just kind of go a little bit away, like move your eyes a little bit away? And you can see it kind of in a-- not quite peripheral, but near the periphery?

No? Am I making it up? Yes, one guy agrees with me. Good, that's enough to go on to the next slide.

So what do these different cones and rods-- so these different photoreceptor types, we distinguish them by the frequencies that they're tuned to. So you might hear me refer to these-- the cones as blue, green, and red. But that's, for obvious reasons you can see on this graph, incorrect. It's better to refer to these as short-wavelength, medium-wavelength, and long. You can see this. Somebody called this red. It would be more really green-yellow.

So here are the spectral sensitivities. And there's a lot of-- if you take some of the vision classes here, the undergrad vision classes, they'll tell you a little bit about thinking about this from an engineering point of view. You know, why are these two so close together and this one far apart? What's the optimum way to design this? And I encourage you, if your interested and those kind of things, to take those classes. But you can see the rods are kind of here in the middle.

So this is some recent work, which is just absolutely amazing neuroscience going on. And these are the first images that were taken of the human-- I guess-- I think it's the fovea. I'm not sure. So the fovea-- the foveal region just has cones. But what's amazing about these images is can distinguish the different cones. The short ones are labeled blue, the medium wave ones here are green, and the long are red.

And the only thing that-- well, what's stressed in this paper and the one thing to notice here, which is interesting, is that the blue cones are relatively less here. And I'm not going to really explain why. One explanation that's been proposed has to do with chromatic aberration, the fact that you can't focus all colors at the same time really, no matter what kind of lens you have. And that blue by itself-- the way the human visual system is designed, blue is getting blurred anyways.

So evolution was like, hey, well, blue is getting blurred. I don't need to sample it as finely. And that's why you have this kind of regular pattern of blue with relatively regular spacing. Whereas red and green are just kind of random.

What's interesting is, in this paper, they had two male subjects. And the ratio of medium to long-lens cones between subjects differs by 4 to 1. So it's like this huge difference in what-- but they both-- and both subjects reported normal color vision, just a fun fact for you.

So the other kind of cell that we should talk a little bit about the phenomenology-- and back to the receptor cell for a second. The actual transduction cascade is not covered in this lecture because it's in the textbook. So if you're interested in how the light signal becomes an electrical signal, look there.

So there's two basic types of retinal ganglion cells. And one is an on-center cell, and the other is an off-center cell. And we're going to be seeing something in the second to make this a little bit clearer. But in the on-center cell, when a bright spot moves toward the center-- so there's photoreceptors in the center, and then there's photoreceptors in the circular surround region, and the retinal ganglion cell pulling information from all of those.

And when the spot passes through, this bright spot, the on-type cell fires. And when this bright spot passes through with an off-type cell, it's inhibited. So the off-center cell-- or the off-- yeah, off-center cell-- prefers a dark patch on a light circle, whereas this one prefers a light patch on the dark circle. So retinal ganglion cells in action, right?

So there are some classic movies that I was able to acquire of some of this work. And I guess one thing I should say, just for those of you who look into this more, these recordings are not exactly from the retina. But they're not exactly from retinal ganglion cells. But they are from cells that display similar receptive field properties. So when I use the word "receptive field," I mean something like bright spot on a dark patch, or dark spot on a bright patch, the optimal stimulus there. Sure.

AUDIENCE: [INAUDIBLE].

NEVILLE SANJANA: Oh, that's showing-- just denoting the time. So when the spot hits the center, the on-type cell-- so this is time right here. This is saying the direction of travel. So here it's not in the center. There it gets into the center. There it leaves the center, OK, the center of this circle right here, which is the center of its receptive field.

OK, so we're going to look at some-- so put that small caveat I gave you about the movie-- don't worry about that. We're going to look at how experimenters, neuroscientists experimentally recording from-- I think this is in cat, but I'm not sure-- how they show that a cell truly is on-center, off-surround versus off-center, on-surround. So let's get to the movies. Is this going to stay here?

OK, so it's kind of blurry. OK, so what are you going to be listening to? So what you'll be hearing is they hooked up the amplifier that's-- OK, electrode in the cell, right, recording from the cell-- hooked the amplifier up to a speaker. You're going to be hearing action potentials, like pop, pop, pop. That's going to be action potentials. And what you're seeing is what the experimenter is moving around with the retina is being exposed to this stimulus right here. So you'll get it in a second.

Hear that? That's a cell, one cell. Bright spot, kind of dark background. So he's trying to find where is the maximal response rate? Where is the-- did you guys see that? So diffuse illumination over everything excites it a little bit, but not a lot. So this is not as much as directly on its receptive field with a dark surround.

That's like the optimal stimulus. It's these circular, center-surround fields. Let's see if he does anything else interesting, or if that's going to be-- ah, that's good. So it's quiet all of a sudden. Because that darkness is so-- it's like the opposite of the skin. The [INAUDIBLE] is bright on black. So black on bright is the max incondition.

OK, this has been exciting for long enough. So let's now go to off-center. OK, that's not looking too happy. Let's look at that. And yeah, I can just open it again. Oh, it's black? Is that right? Yeah.

Think this one takes a little longer for them to figure out what's going on here. So it fires when it goes away. You can see that. They're still trying to figure it out here.

So this is like the optimal stimulus. So now they're trying to find where the center truly is. So background rate when it's just all dark, it likes that, but it likes this more.

I guess here, they're just mapping this around. But this video isn't as good. The first one is kind of the one to keep in your mind, I guess. This one isn't as impressive.

OK, so the question now is, how do we get-- from the photoreceptors to the retinal ganglion cells, how do we get just from something that's light-sensitive to actually be center-surround-- be center-surround fields, this kind of opposition? And what are the electrophysiological properties of all those cells in the middle, horizontal, bipolar? How do they produce this transformation?

So right, so the part we're going to be interested in now-- again, here's the photoreceptors back here, inside out organization. And here's the ganglion cells up here. We're going to be interested in this part in the middle here. Just another picture of that, I guess. So I actually don't know about these until Professor Schneider told me that the classic studies, the first recordings of all the different cells in the retina and seeing what they're doing simultaneously, was by Werblin and Dowling here. And they were classical studies in the mudpuppy.

Does anybody know what a mudpuppy is? Yeah, I didn't either. My office mate knew what it was instantly, and I was like, whoa. But this is the mudpuppy.

So the mudpuppy is like this salamander. And it's got this crazy set of gills that come out of it like that. And here's the eye. I think the reason it was chosen is the cells are large in its retina and can be easily-- this is before finer techniques such as patch clamp electrophysiology were developed. So large electrodes could easily put in these cells.

So starting with the photoreceptors, the main electrophysiological property to know about in the photoreceptors-- and I'll show you some current traces in a second so you can see this-- is that in response to light-- I mean, you'd think that neurons, when they get their stimulus, they fire, right? But when the photoreceptors have light impinging on them, they hyperpolarize. They actually go more negative.

So is everybody familiar with those terms? Hyperpolarize is more negative. Depolarize is positive. That's just the electrophysiologists' convention there. And hyperpolarizing means that the photoreceptors, when they make their synapse with the next cell in the chain, they're going to be-- they're going to be releasing less glutamate, right? Because in their natural state, they tend to be more polarized, closer to firing. Firing means releasing glutamate. So the only thing that's inverted is their response to light from what you might think. They hyperpolarize.

So another kind of interesting difference here is that the photoreceptors don't use action potentials. They don't fire. They use these graded potentials. They just slowly change their membrane to gradually more depolarized, and then gradually more hyperpolarized as they see light. So this is a complex diagram. We're going to go over it bit by bit here.

But this is just to show you that-- look at the ganglion cells down here. This is what we were listening to, right? Those spikes, you hear those-- blip, blip, blip. That's firing, like spikes like this. And here you can see there's no real spiking. It's kind of just like woozy, kind of going down and up, you know? So this is the graded potentials. This is a very different regime. This is analog. This is very digital, to take an engineering perspective

So what do we know about these now? We know that they hyperpolarize in response to light, and when they hyperpolarize, that is when there's light there, there's less glutamate. OK. How does this get us closer to center-surround organization that's found down here in ganglion cells? Well, the next kind of important cell in the chain is these bipolar cells, which form a bridge literally between the photoreceptor and the retinal ganglion cell.

So add to our little store of information here, bipolars come in two major types. For the most part, we should have said two major types. There are some others too but they're not nearly as significant as these. And they're either hyperpolarizing or depolarizing. So, right. So just let's look-- right now don't worry about the interpretation of that, but look at this.

So here, both photoreceptors are hyperpolarized and they're going more negative in potential. Both of them are. This one to not such a degree. But look at these bipolar cells. One of them is hyperpolarizing in response to this hyperpolarization, the other one is depolarizing. So here you have two bipolar cell types, either hyperpolarizing or depolarizing. And we'll talk about what they do.

So, right. OK. So if you're using graded potentials, this should be an obvious statement right here. There's no action potentials. Actions at the synapse don't require action potentials. As I said, it's a gradual change in the amount of neurotransmitter released. So it's just another figure Jerry gave me so I used it.

You see in the photoreceptor and the horizontal cells, these slow graded- or the bipolar cells, excuse me, these slow graded potentials. But then, by the time you reach ganglion cells and some cells that are right before them, amacrine cells, action potential. So we just want to make this difference really clear, that you can look at this recording and see if you've got one of these graded potential neurons or one of these action potential neurons.

So, right. So let's talk now about receptive field. So bipolar cells connect to multiple photoreceptors. And this slide, I guess, is just to say that they have a circular receptive field. So they're organized in terms of their connections, such that they basically connect to a similar amount of photoreceptors in any direction from that cell. The photoreceptors here are a little bit above this central area and a little below, so you imagine the bipolar cell's kind of in the middle of this receptive field.

So here's the experiment that we're going to show the results for in a second. In the spot of light, the experimenter moves. And what is that? OK. What is this? If there's an annulus flashed. Not sure. OK. So let's just look at this right here. So there's going to be just-- yeah, this makes sense now.

So there's going to be, in the receptive field, the first thing the experimenter does is places this annulus of bright light on a dark background. And then what happens is the spot of light is just going to be moved across. And you're going to see what happens when the bipolar cell, that's hooked up to the photoreceptors that give it this input from these areas, what it does.

So if you do this experiment, that exact experiment I showed you, the bright spot of light through that annulus, and you can see here's dark bright and spots going to move across. Move across. There's two types of bipolar cells. And in the on-center bipolar cells, the spot is going to cause a depolarization. And so we turn this so there's multiple ways and this gets a little confusing to think about this. But previously, I've said that, here, if you have something like this, a bright spot here, that these depolarize.

So I'm going to confuse things even more here by saying the photoreceptor, when it sees a bright spot, what does it do? Right. Hyperpolarize. And when it hyperpolarizes, that means that the synapse, what's happening? More glutamate, less glutamate? Less glutamate. And the depolarizing bipolar is going to hyperpolarize or depolarize? Depolarize.

So less glutamate depolarizes, which is the opposite of what we think in central synapses, right? I mean, most central synapses, more glutamate, it depolarize and we go toward the action potential. We go positive, we depolarize. So this is kind of like a strange cell.

And we term this cell either a depolarizing bipolar or an on-center cell. And then we say on-center because when a bright spot of light is put there, it depolarizes. It takes a while to sink in. Just deal with it.

So same thing over a hyperpolarizing bipolar. OK. So we get on the bright spot of light, less glutamate, right? Bright spot of light, less glutamate, the synapse. And that leaves this type of cell because of it. And why? I mean, why do we have arbitrarily these different cell types? It has to do with the channels, the ion channels. They're different channels so they react differently in the presence of glutamate.

One type of cell drives the potential one way. That is, say, it opens channels, right? So in the presence of-- let's try and get it straight here. So a bright spot of light is going to be less glutamate, right? And that's going to cause this one to depolarize. So we know that this kind of cell, when it's exposed to glutamate, it closes its channels. It closes it.

And I don't know how much Jerry's talked about this before but in these cells, it's metabotropic, which means that the receptor is not next to the ion channel. Actually, the receptor grabs on to the glutamate, and then there's some intracellular processes that happen that force an ion channel down the road to close just a little bit further from it on the membrane.

Here, what happens is the opposite. Glutamate links on. And these are actually, to fully confuse you, these are ionotropic, but don't worry about it. Doesn't matter. Glutamate links on right here and the ion channel opens, causing sodium to rush in. So I should say in both cases. When I say ion channel, I mean sodium ion channel. So if sodium goes in, depolarizes. So here, glutamate causes sodium to come in and will depolarize the cell. Yes.

AUDIENCE: [INAUDIBLE]

NEVILLE SANJANA: OK. So let's get terminology here. So photoreceptors are always the same. They're depolarizing to light. There's no on and off center range because the photoreceptors are just the fine pixels of space. So they're the sampling guys. They're the ones who are sampling the environment.

These are the first level of cells that are connected to multiple photoreceptors and integrate those samples and try and make some sense of it. And that is the first receptive field organization, right? I mean, even climate photoreceptors have a receptive field but it's literally just, is there light there or not? I mean, it is a receptive field, but this is the first what we would call a higher level organization in a receptive field.

So I'm going to move on. We'll see how far we get here. Oh, we're going to talk more about bipolar, so it's good. OK. So we saw this already in the retinal ganglion cells, that there is this antagonistic effect by the surround. So in this previous slide, we're just looking at one thing. A bright spot of light in the center. And what does it do? What does it cause?

And here we're not having-- oh, right. Here we're going to talk about the surround effect. And I'm to show you the experiment. It's kind of hard to read from these slides what the experiment is. So here's the experiment here. Can everybody see that? There is just a bright-- so it's a dark background and you just flash this bright annulus of light. And again, here's this whole area is the receptive field with photoreceptor.

So it's first dark and then just this bright annulus is flashed. OK. So now let's look at the results. So for the off-center, the one I called off-center but it's the hyperpolarizing bipolar, when we add the annulus in there, it-- what happens here? It depolarizes, right? That's right. It depolarizes.

But the on-center, when we add the bright annulus, so it wants on-center. It wants light in the center. We add the brightness on the outside. We see that this does not-- it goes down. It does not go closer to releasing more glutamate. Again, when it goes up, we're releasing more glutamate.

So basically, the take-home message here is this right here-- sorry, it just keeps flashing but, OK, imagine there's that bright thing again-- that's the optimal stimulus for which type of cell? on-center or off-center? Off-center, right. Yeah, that's right. Because it's bright on the outside and dark on the inside. So that's why this guy depolarizes and that's why this guy hyperpolarizes. Let it sink in.

So we're going to backtrack for just a second. You might have noticed that in going from photoreceptors to bipolars, I just kind of skipped over the cell right here, the cell type the horizontal cells. And horizontal cells are the ones that are responsible, actually, for creating that inhibitory surround. You can see the bipolars, even though they have kind of some dendritic branching here going over a few photoreceptors, you can see that the horizontal cells have a much, much more-- I mean, they're horizontal. They branch, right? OK.

And basically, they're the ones that create the inhibitory surround. And I'm not going to explain too much about the mechanism there. And I don't know actually how much of it is fully known. But these are inhibitory cells for the most part, and they're the ones responsible for creating that inhibitory surround, the on-center off surround or off-center on surround.

OK. Before we get to the ganglion cells, the next cell type is amacrine cells. So, right. Curious slide here. On-center amacrine cell. So let's just back up for a second. So one question you might be asking is, well, the bipolar cells have this center surround organization, and when you showed those videos of the retinal ganglion cells, they also had basically center surround organization. So what is all this? I mean, why don't we just have the bipolar cells going out to the brain? I mean, what is all this? Why do you need all this other machinery?

And the reason is that, though I didn't show you it fully in those movies, the ganglion cell is actually more complex. It adds, in addition to just this center surround thing, it can add some temporal response properties. And what adds those is really these amacrine cells.

And now we're going to enter into the digital domain. The graded potentials are over. We're now going to start talking more about action potentials. So let's see here. What's being done here is-- this is a very confusing diagram-- but I think that what's being done here is this spot is being moved across right here of this on-center amacrine cell. On-center means the optimal stimulus is bright light at the center, right? OK. So this is bright light moving toward the center.

And what you see here, what these arrows indicate-- look first just at this one graph. It's only moving this direction. Well, look at this. During the time that it's over the middle area, which you might say is this whole period right here, like there's this whole block right here, well, it's not that the response is up the whole time. It's not like an elevated response the entire time. It's actually interestingly a super increase in response just as it enters the central part of the on-center cell, enters the central portion.

So it's like it's got its preference to fire right when it enters. And you can see at the same-- you can prove this to yourself by doing the experiment, starting the spot on this side and going that way. And that's what this-- unfortunately, this is overlaid both directions. But you can make out this trace is the same as this trace, the one in this direction.

But you see the arrow going in that direction? That direction. That one, you see a spike of the maximum response is right as it enters this area. So here you have this beautiful temporal kind of characteristic. So Jerry is saying right here, compare this with the photoreceptor, the horizontals on the bipolar cell. And what this shows is here the arrow is going each way and the take-home message here is, look, you put a spot-- oh, this is kind of nice. You see the photoreceptor? Why are these circles different sizes? Anyone? Is?

AUDIENCE: Horizontal [INAUDIBLE].

NEVILLE SANJANA: That's right. It's got that huge dendritic authorization, whereas the photoreceptor, hey, it's just sticking out there looking at light, right? So it's got its one little area. So what this shows here is that, look, you go in one direction or the other direction, the photoreceptor is going to have the same neural response. This is neural response, right? Light comes in and it's going to depolarize, hyperpolarize. OK. Hyper, so it's going down, right?

And then horizontal cell, same thing. Bipolar cell, same thing. You see this kind of bumps here but it's basically the same response. It's not nearly as peaked as this. So the amacrine cell adds this temporal complexity.

AUDIENCE: [INAUDIBLE]?

NEVILLE SANJANA: So the on/off organization starts at the level of the bipolar cell, so no on the receptor and horizontal cell.

AUDIENCE: But the horizontal [INAUDIBLE]?

NEVILLE SANJANA: Actually, I'm not too sure about the receptive field of the horizontal cell. Yeah, let me backtrack on that. I've not seen recordings of it. Well, there are probably some here. Let's look at it afterwards. It's not terribly important. But in your handout, probably a few slides back, there's the summary. But that doesn't have this exact experiment. Let's talk about this maybe offline because I'm not sure. I haven't really seen good recordings of horizontal cells.

So, right. I made that comparison. So direction selectivity in ganglion cell. Right. Oh, so Jerry wants to show you a model that's been proposed of how this might work. So again, this direction selectivity, which I showed you right now in an amacrine cell, is also found in certain ganglion cells. She's asleep. OK. In certain ganglion cells.

So I'm going to show you how one model of this has been proposed, how the amacrine cell can lead to this directional selectivity. And this is, again, one of these models with lots of synapses so let's just try and keep this simple. So there's a preferred direction and a null direction.

So preferred direction, we can imagine the spot moves this way. So what would happen is this bipolar gets the spot. Let's just assume all the bipolars are on-center to keep my lights in focus. Yeah, I think that's a valid assumption. Let's do that.

So this one fires, right? OK. So what we're trying to do is excite this ganglion cell when something's moved this way and not excite it when it's moved this way. So this one fires. And what it does is it also makes a synapse onto this amacrine cell, which-- why is this not a touch screen right now? Right. OK. So it makes a synapse on one of these amacrine cells, which also synapses onto the ganglion cell.

And you can see that if you-- so here this fires, then this fires. But you can see by this one firing here, it also induced this neuron to fire down here, right? This synapse is excitatory, excites this one. And this one is also excited simultaneously from the bipolar cell because we're moving the stimulus this way. That bipolar cell excites the next amacrine cell, and that one makes it easier to fire because then the stimulus is also here.

So what's happening is that there's the kind of sequential excitation in this direction. Whereas, if you move in this direction, when this bipolar cell fires, this synapse-- and you can see, it's by the asymmetry, these amacrine cell synapses. This one fires, it makes it easier for this one to fire, but-- makes it easier for this one, right, but this one makes an inhibitory synapse onto this amacrine cell. So this one is less likely to fire by the time the stimulus reaches this bipolar cell.

So all you need to observe here is that it's the asymmetry in these connections that make it easier for this direction than for that direction. Easier to excite this cell. If you find this confusing, the way to do this is think at time 0.1 this gets excited, at time 0.2 this gets excited, time 0.3 this gets excited. And then just trace. OK, if this is a plus connection that means this guy is easier to excite. And well, then he's also getting a connection from this because at time 0.2, the stimulus is here. And that's what's going to prefer this direction.

So there's a way to kind of work through these diagrams synapse by synapse. And think that the conduction time from one synapse to another is it's much shorter, actually, than the conduction time for most stimuli, I would think, going across. So you can assume that, even though it has to traverse a synapse, it's already made it over there by the time that bipolar cell fires the next one in there, in the line.

Is that clear? Should I go over that more? I think I might even mumble that up more by going over it more though. OK. Let's keep moving. So this type of model is, I guess, also been supported by some experimental studies. OK. So this one's an easy one to explain. The amacrine cells are GABAergic cells because they make those inhibitory connections, right? So inhibitory neurotransmitter in the CNS, the primary one is GABA. And so if you block, if you use a block or a GABA antagonist in the retina, all of the directional specificity goes away. So this is a good argument for those amacrine cells.

I don't know what-- I think the summary of this here says that some people think that it might be happening even earlier, like horizontals and bipolars that might be causing directional selectivity. But the jury's still out on it.

So back to this. You saw this diagram before. Some of you. So this is the straight on and off center response. Standard stuff. And this is showing you that ganglion cells also, because of this neat wiring with the amacrine cells, can have these transient responses. So that they fire more right when the stimulus enters the central area. So like this, where it's uniform firing, when it's the stimulus is anywhere in that central area. But here it's only on entrance, it's a transient response.

OK. Direction selective cell maybe. [INAUDIBLE]. I did it again. Let's play this here. Yeah, not going to happen. Where are the buttons?

Does anyone notice that it only fires when you go in this direction, not when you go in that direction? So actually this light stick is way bigger than the receptive field, so he's going to try and figure out what the receptive field is. This is neuroscience in action, folks. Neuroscience in action in the 60s though, but still.

So see, it's much less when he goes the other way. Does everybody see that? It's much, much more in this direction. Oh, he figured it out finally. OK. OK, you got it. Yeah, experimenter.

AUDIENCE: So this is [INAUDIBLE]?

NEVILLE SANJANA: No, no, this is anesthetized preparation, I think. Actually, I'm trying to think. Maybe it could be X plant too. And this is-- no this might be [INAUDIBLE]. No, no, this is-- I wish I could give you a definitive answer. It is--

AUDIENCE: What's he writing on?

NEVILLE SANJANA: I am pretty sure this is single cell responses though. What is he writing on? So basically, the way, if this is done in an anesthetized cat, it's put into a stereotactic hold, which means it's basically immobilized and it's anesthetized so it's not going to really be moving too much anyways. And they make a recording from this area of retina and basically the cat is just-- the eye lids are held open and it's going to be staring at a screen. And the video camera is also focused on the same screen that the cat is staring at. So you're seeing it from the video camera sitting next to the cat or something. Something like that.

Man, the crazy things we used to do. OK. So this is kind of a nice general principle to know about the retina. And the idea that these cells kind of form these two cascades and that each cascade contributes to specific electrophysiological properties, specific receptive field properties that arise. So you can explain the response of the bipolar cells in terms of connections with the photoreceptors in the horizontal cells. That is, the photoreceptors here making the center and the horizontal cells making this antagonistic surround. Remember, surround is always the opposite, on versus off, off versus on.

And that you can do the similar kind of explanation with the ganglion cell responses and explain their properties in terms of connections with the bipolars and amacrine. And you should see the connections here. Horizontal and amacrine cells arborize. They branch dendritic trees. And receptors and bipolar cells are like the direct kind of input coming right down. But the amacrine cells and horizontal cells are able to take in the inputs of multiple bipolars or photoreceptors. And then send them down to the next level, which in this case is bipolar and this case is ganglion cells.

And what the result is here is that, hey, you already have the center surround organization, but what this basically does, it's a stronger definition, I guess is another way of putting it. It intensifies the center surround antagonism. It makes it even more pronounced. And it also adds those temporal properties that we saw. Oh, and these cascades are referred to often as-- this area here is the outer flex form layer. Outer meaning closer to the light sensing. And the inner flex form layer here is this inner, closer to the ganglion cells.

The retina is actually separated that way. And the natural question is, well, where do the bipolar cells fall? They're in both. Oh, wow, this really flew this time. So this is kind of an interesting analysis Jerry had in here. But the greater the complexity of the ganglion cell responses, the greater the ratio of amacrine cell synapses to bipolar cell synapses.

OK. Well, what would you think-- I guess you all have the slide so I can't do this, but what would you think? Do you think that you or a pigeon has more complex ganglion cell responses and hence a greater-- this ratio would be greater. You or the pigeon? Come on. You can't bet against yourself. It's the pigeon. The pigeon has a lot more. 10 points.

So this is the ratio, again, of amacrine to bipolar synapses, [INAUDIBLE]. So there's much more that amacrine which that find. They intensify the receptive field and the center surround organization and they also add those temporal properties. Well, this doesn't make sense. We're smarter than pigeons. We have better eyesight than pigeons. It's true. We have better eyesight. What's up with this. Who's got a hypothesis?

That is the right answer. Speak up. What is that? Speak up. I don't know if everybody heard you.

AUDIENCE: [INAUDIBLE].

NEVILLE SANJANA: Totally right. So I mean, pigeons don't have this complex layering of V1, V2, V3 and 4. And Jerry is going to go more into cortical vision later, but we're going to see that we don't need to do that much in the retina. We've got lots of other stuff. So let's try and do some of this maybe. Yeah, I can go a few more minutes, right? OK.

So let's talk about these ganglion cell types. And this is just a picture showing a few different types of ganglion cells. All I want you to take away from this is that there are many different types, there are many different dendritic arborizations. Normally the bigger ones have bigger receptive fields. Smaller ones, smaller receptive fields. And that these cell types, we find electrophysiological differences between the different ganglion cell types. Say like the membrane resistant, membrane capacitance, the way that they fire in response to different kinds of moving stimuli. Those are electrophysiological differences.

And the neat thing is that those correspond to the morphological differences. Morphology being this kind of stuff, how big the cell is, what is its arbor look like. So I think Jerry will explain probably a bit more about that. But what I want to focus, I guess, here on is that these Y cells we're going to talk about for a second more. And that the distribution seems very optimized in the retina.

This is a particular type of retinal ganglion cell. And that they seem to perfectly cover the retina and get kind of respect of these boundaries without leaving holes, which is kind of an interesting thing. I'll show this in more detail in a second. And this appears to rise because of these competitive interactions between the dendrites, as in the developing animal.

So we're going to focus just on these Y type retinal ganglion cells. Here's on cells, off cells. You guys know about that, right? Here are just pictures of them. So here's a neat experiment that was done. It's kind of like theoretical and experimental neuroscience combined. So they looked at the fields here, they looked at the dendritic fields here, and they just drew lines that would just link up all the dendrites.

Here are the lines drawn, and you can see there's this little overlap. Good coverage of the space by these dendritic arbors. Now, what if they just took some kind of-- I don't know why they chose a particular radius, but they say they put a dot where every cell body center was. And then they took some radius out from that and just drew circles around. Well, you get these gaps in here.

Now, say you took this right here and you just took the mirror image. Let's just say, so we can keep-- this way is to keep the area the same. I don't know. This experiment, actually, I don't know if I would quite done it this way but I think that this is kind of an older experiment so I'll respect it on those terms. So here they just flipped along an axis, like an axis like this. They just went flipped around the denditric field, and you get these huge gaps.

So they take this to be evidence for competition between the dendrites, that they had to-- that there are these actual interactions where they were going out and then they met some neighbor from dendrites [INAUDIBLE]. Oh, it's your space. OK. And then they just backed off and they each kind of agreed to only take up a certain amount of area. So that there's actual cell to cell communication during the development process, which is really interesting. Showing that random receptive fields placed around the cell body do not work. These dendrites, as crazy as this looks, this is very, very intentionally made for high coverage and no spots, no gaps in the coverage.

Let's do it. Let's do it. OK. So in the monkey and in us, there are these two types of retinal ganglion cells, parasol cells and midget cells. Love that. Parasol cells are like an umbrella. They have a big arbor, they're huge. And midget cells are like midgets. So the midget cells make up most of the retinal ganglion cells. Does this sound familiar? I think we talked about this before. From the retina, the optic nerve goes back to the lateral geniculate body in the thalamus. I guess they're right. OK. And then goes to visual cortex, occipital visual cortex.

So when I say LGN, it's the lateral geniculate nucleus of the thalamus. That's the next way station. That's where those synapse-- the retinal ganglion cells synapse there and then those guys go back to V1, primary visual cortex. And 80% of the cells are these midget cells. Why? Because they're small and they have fine receptive fields, fine color acuity.

Here, the parasol cells can convey information on movement because they've got huge receptive fields. So when I go like this and the whole world is spinning here, the parasol cells, which have huge arbors, can track movement over larger distances than the midget cells. But of course, this fine acute vision seems to be dominant 80% of ganglion cells and LGN.

This is to show you some differences. Midget cells are small, parasol cells are big. I think that's the takeaway point right here on midget thing. What is this thing? Oh, this is just showing from the fovea to the periphery, the diameter of the dendritic field. And this shows that consistently the parasol cells are bigger. They're about three times bigger as what this caption, I think, says.

So you can see that in the periphery, everybody gets bigger because fovea is where we want to be small, we want to have high visual acuity. Because why? Well, because the photoreceptors in that area are more tightly concentrated. Just cones really tightly packed. Many more cones in the fovea than in the periphery. And the fovea is a much smaller area too. This is just showing you, again, parasol system, huge. Lots of photoreceptors, midget system. Each ganglion cell has a small number of inputs, basically. That's it. I'm going to stop there.