PROFESSOR: So last time, we talked about the responses of auditory nerve fibers and we talked about tonotopic organization and frequency tuning and response areas of auditory nerve fibers. So any questions about that? OK.

So this time, today's lecture was going to go on. And the auditory nerve, of course, leads up into the brain. So we're going to talk about the auditory central nervous system, starting with the first nucleus in the CNS for the auditory pathway, which is the cochlear nucleus. And this nucleus gets its name because the auditory nerve is sometimes called the cochlear nerve. Right? It's coming from the cochlea. And so this is the cochlear nucleus.

So can anybody give me a definition of a nucleus in terms of a central pathway? Not a cell nucleus. This is a nucleus in the brain.

Just a collection of neurons. Right? So a nucleus is a collection of neurons in the central pathway. A ganglion is a collection of neurons out in the periphery. So you have the spiral ganglion in the cochlea, being where the cell bodies of the auditory nerve fibers-- it's called the ganglion there because it's in the periphery.

And that nerve goes into the central nervous system and it ends on neurons-- a collection of neurons in the cochlear nucleus. In the part of the brain called the cochlear nucleus.

We're going to talk in the cochlear nucleus about the various types of cells that are there. And instead of just having one or two types of auditory nerve fibers, as we had in the periphery, there's going to be a whole bunch of types of cells. And they have really fanciful names like octopus cells and pyramidal cells. So we'll talk about those.

When we go into the cochlear nucleus and record with microelectrodes, we get single units. And there's a way of classifying those single units, which was developed here in the 1960s at MIT, and it was one of the first applications of computers to the study of neuroscience.

Looking at the action potentials as a function of time, right after you turn the sound stimulus on. And by looking at those patterns, you can classify the units into various types. And now we know a good correspondence between the physiology and the anatomy, so we'll go over how we establish that correspondence.

And because these are these various types, we really have one type of auditory neurofiber coming in from the periphery, and now we have a bunch of types. We're now going to think of the system as having multiple parallel pathways for the sense of hearing in the central nervous system. And perhaps one pathway helps you with one aspect of hearing, and another pathway helps you with another aspect.

And maybe we'll end up at the end of today with a little bit of discussion-- advanced discussion-- of implants. So we're going to talk about cochlear implants next week. There is a kind of an implant called the auditory brainstem implant that's put in the cochlear nucleus.

But here, things are so complicated. You have a variety of cell and unit types, each doing a different function. You can imagine how hard it would be to wire up a prosthesis to stimulate each one of those correctly. So just let's keep in mind the challenge of putting a prosthesis into the cochlear nucleus, which is required of people who lack an auditory nerve. They can't get a prosthesis in the cochlea because the message wouldn't be sent to the brain. They need to get a prosthesis into the cochlear nucleus. But it's very complicated here.

And maybe it's as complicated processing as you have in the retina. Right? In the retina, you have the retinal ganglion cells being very complicated. Some have center surround fields. Right? There's not just turning on and turning off. There's turning on, there's inhibiting the on, and so on and so forth. So the cochlear nucleus

I think of a little bit as like the retina equivalent in the visual system.

OK, so let's look at the auditory central nervous system in terms of a block diagram on the top and in terms of what it looks like when you cut sections through the brain.

So here's the block diagram. And we've been talking about the cochlea here, and the spiral ganglion is where the cell bodies of the auditory nerve fibers are. This would be the arrow of the auditory nerve coming from the spiral ganglion into the CN, the cochlear nucleus. And of course you have one of those on the left side, and another on the right side. So this diagram is showing both sides of the central pathway.

From the cochlear nucleus, the neurons of the cochlear nucleus send axons to a variety of places. One of them is in the region of the brain called the pons. And in the pons there is a complex called the superior olivary complex. And it's abbreviated SOC here.

So what's a complex? Now, we've had a ganglion, a nucleus, and a complex. Well, as we'll see in a couple of weeks in the course, when we talk about the SOC, it has a whole bunch of nuclei very closely spaced within it. Maybe a dozen or so different nuclei. Each of which is a different collection of cells. So the whole thing is called a superior olivary complex.

And superior olive? What's that part of the name? So has anybody heard about the olive? Or the inferior olive? What's the olive? We should talk about it. Nothing? Anybody? Any ideas?

So it's involved in the motor system. And if you cut a section of the brain-- it's not illustrated here, but if you look at a section of the brain in transverse sections, which are the kind of sections that we have here-- you find a structure that's kind of gotten wrinkled edges and sort of has a central pit, and it looks like an olive. At least it did to the first neuro-anatomists, maybe who had their eye on the clock, and were waiting for the 5 o'clock dinner call. They said, hey, that looks like an olive. And they probably didn't have very good microscopes, so they were looking at things at very

low power.

And what happened later is somebody discovered another complex over here that was nearby but didn't look anything like an olive, but it was near the olive. And it was a little bit rostral in the brain, and things that are rostral are called superior. So they called this the superior olive, and this has become known as the inferior olive.

And after they got even higher power magnification, they could see this was really a complex of nuclei, so they called it the superior olivary complex.

OK, so this is motor. And this is auditory. And they just happen to be located near one another in the brainstem, in the area of the brainstem called the pons, down here. So these are sections of the human brain. So why do we cut sections? Anybody?

AUDIENCE: To look at the anatomy?

PROFESSOR: To look at the anatomy. Right. So a compound microscope that we usually use to look at the anatomy can't look at a big hunk of tissue. You have to cut sections. And the thinner section you cut, the better resolution you get. Because you can bring a very high-powered objective and look at very fine cellular detail.

So cutting sections is what neuro-anatomists love to do. An example thickness of a section might be 10 micrometers. 100 micrometers is a very thick section. So you can imagine how many sections you'd have to chunk through to go through the whole human brainstem. That's why it's nice to work with small animals like mice. They don't have as many sections. Right?

So, but these are sections of the human brainstem. And here, this word says spiral ganglion, so this is the auditory nerve coming in. And this is the cochlear nucleus. And I've heard it described that by the time the sense of hearing came along, the brain was formed. Primitive animals had the brain, and all the other functions like motor. So there wasn't any room in the middle. So it was stuck on the outside. The sense of hearing-- the cochlear nucleus, at least, was put on the outside of the brain because there wasn't any room for it in the inside. Cochlear nucleus structures tend

to be superficial in the brainstem. This is the cochlear nucleus. And these are the axons crossing. Because some of the cochlear nucleus axons cross from the left side to the right side. And the superior olivary complex is deep within the brainstem.

But some of the cochlear nucleus axons don't go to the superior olive. They bypass it and go all the way to the IC, the inferior colliculus. That's at the level of the mid-brain. So this is the inferior colliculus. So you've studied a collicular structure before. What was it? Right? In the first half of this course.

The superior colliculus, right? So why is it superior? Is it better? No. It's just a little rostral in the brain.

So if you cut sections from caudal-- so this is the spinal cord down, and your microtome's chunking through the medulla, and the pons, and you get to the midbrain. And then you cut through the inferior colliculus, which is right here, and then a little bit more rostral, you cut through the superior colliculi, which are right here. And they tend to be a little flatter. These inferior colliculi are more dome-like shaped.

So what does colliculus mean? Anybody know French? Who knows French? Come on, somebody knows. OK, who knows Latin? OK, well, that's the expected result. Colliculus means a little hill. And this lives up to its name. These are little hills right on the top of the brainstem. The Inferior colliculi are here, left and right, and the superior colliculi are here. So what is the superior colliculus-- what does the superior colliculi do?

What happens when you stimulate in the superior colliculus? Your eyeballs move, right? So the superior colliculus is intimately involved in saccadic eye movements. Right? You guys must have talked a lot about that in the first part of the course.

And the inferior colliculus, what does it do? Well, I've heard people who have spent their whole research career studying the inferior colliculus, and they say, well, I don't know what it does! That's not an uncommon statement in the sense of hearing.

So the inferior colliculus certainly is a meeting place for lots of axons coming up

from the cochlear nuclei, from the superior olivary complex. It's a midbrain meeting center. It's certainly involved with many parts of the sense of hearing, but we don't know exactly what role it plays. Certainly not as simple as it moves ears, OK? Whereas the superior colliculus moves eyes.

All right, coming up the pathway even further, the next level is the thalamus, where you have, for the auditory system, the medial geniculate. And what was the analog in the visual pathway? A lateral geniculate, right? OK, so in the brain, medial is toward the middle and lateral is a little bit toward the lateral part. You don't have the lateral geniculate in this section, but it would be a little bit lateral to the medial geniculate. And what does geniculate mean?

AUDIENCE: Knee.

PROFESSOR: Knee. Right. A genu is a knee. And the lateral geniculate-- if you use your imagination and if you were an early neuro-anatomists with a low-power lens on your microscope, it looked like a bent knee. It's sort of bent. The medial geniculate is not that at all. It doesn't look at all like a knee. But it's just medial to the lateral geniculate, so that's how it got its name. OK, very good answer. What is to genuflect?

AUDIENCE: To bend.

AUDIENCE: Kneel.

PROFESSOR: That's right. To kneel down, bend your knees. Ah, king! Ruler!

All right. And then finally we have the auditory cortex, the AC, in those boxes at the top. And the auditory cortical fields are in the temporal cortex on the sides of the head. So I'm pointing to my left temporal cortex if I could go through my skull. It's behind the temporal bone.

OK, where were the visual areas? Back here. This is called the occipital cortex, right? In a completely different part of the cortex. And in the primate-- of course, humans are primates-- you have a big temporal lobe of the brain. And that's this

lobe here. And the auditory cortical fields, for the most part, are on the dorsal surface of that. And you have to go down inside the temporal gyrus-- this big gyrus-- to look and see them, because they're not on the surface of the brain in the primate. They're down inside the temporal gyrus.

Well, how does this look compared to the visual pathway? Let's say this is the retina here. OK? Where does the retina project? That's a great exam question! Where does the retina project?

That's not a one answer question, right? In large parts of the LGM. That's right. Where else does it project?

AUDIENCE: [INAUDIBLE]

PROFESSOR: I don't know about that. Certainly projects to the superior colliculus, right? Aren't the x and y cells projecting to the superior colliculus? A few of the retinal ganglion cells project to the superior colliculus. You better ask Peter for sure. Obviously, I don't know much about the visual pathway.

But so how does that look here? We have the cochlea, and even the cochlear nucleus. Does it project to the geniculate? No, not at all. Between the periphery and the thalamic level for the auditory pathway, you have the cochlear nucleus. You have the superior olivary complex. And you have the inferior colliculus. And these structures are on the main highway up to the cortex. It's not as if the main pathway bypasses the inferior colliculus. This little side arrow is just a few axons. The main pathway is cochlear nucleus to superior olivary complex. And, to a certain extent, cochlear nucleus to IC. Superior olivary complex to IC. And then to medial geniculate. So it's a big difference

What about the somatosensory system? You have a dorsal root ganglia in the somatosensory system, and they project actually all the way to the somatosensory regions of the thalamus. So that's more like the visual system. There's something different going on here in the auditory system. There's a whole bunch of brainstem and midbrain nuclei in the auditory pathway that you don't have represented in

these other systems.

So we're going to learn, in about two weeks, about the superior olivary complex and the inferior colliculus. These extra brainstem nuclei are very involved in the process of sound localization. And that's because for the auditory system to figure out where a sound is coming from, in best case we use the two ears. And we use cues like the difference in time of arrival of a sound at the two ears, and the difference in sound level at the two ears, to figure out where a sound is coming from. Certainly in the azimuthal plane.

And in the visual system, and in the somatosensory system, the localization of where the stimulus is coming from is mapped right at the periphery. So you know that a spot of light is coming from over to your right because it hits your nasal retina in your right eye, and your temporal retina in your left eye. So that position information is already available in the periphery.

In the sense of hearing, what does the periphery map? It maps sound frequency, right? So obviously, sound frequency is a very important characteristic. It allows you to identify the sound. But it doesn't help you to tell where the sound is coming from. And if you're a mouse running away from a cat, and it's night time, and you can't see the cat, you need to know where the cat sound is coming from. Is it coming from your right, or is it coming from your left? And it takes a lot of brainstem processing, comparing the inputs from the two sides, to reconstruct where the sound was coming from. Especially if you're doing it by intra-aural time and intra-aural level differences.

So all of this brain stem processing-- or much of it-- is devoted to figuring out where the sound is coming from. It's figuring out the location of the sound. So we'll spend a good week or more on that, in a couple weeks in our course. Because that's one of the things you can really sink your teeth in, in the auditory system. The thing it does is to figure out where the location of the sound source is.

OK, now we're going to spend the rest of the lecture today on the cochlear nucleus. The very first nucleus in the auditory pathway. And we're first going to talk about

basic things like the anatomy of the cochlear nucleus and its tonotopy.

So this is a drawing of the cochlear nucleus in the so-called sagittal plane. We should all know what the sagittal plane is. Can anybody explain it to me? Or can anybody explain? Yeah? Right like this. So I like to think of it as the zodiac character Sagittarius. Right? Who was Sagittarius?

AUDIENCE: [INAUDIBLE].

PROFESSOR: He was the what?

AUDIENCE: He was an archer.

PROFESSOR: Yes, he was an archer. Happened to have a horse behind him. Or for his behind. So he shot the arrow, and if he shot it effectively, he'd hit me right in the center of my head, and my two halves of my brain would fall apart. And if you picked one half up and looked at it, you would a sagittal section. OK? Of my brain.

And the cochlear nucleus, as we saw before, is hanging off the side of the brain. But if that archer shot-- instead of right at the midline, shot a little off-center, and the cochlear nucleus half fell away, you'd get this sagittal section of the cochlear nucleus.

And so the cochlea is down here and the auditory nerve is coming up into the cochlear nucleus. So what is up on this section? Well, it's going dorsal, going higher. So here's your compass.

The cochlear nucleus is ventral. The auditory nerve climbs up dorsally into the cochlear nucleus. And that compass gives you two clues about the two big divisions of the cochlear nucleus. This biggest part of the cochlear nucleus is called the ventral cochlear nucleus, because it's down ventral. The VCN is the ventral cochlear nucleus. And the other part is the DCN. That's the dorsal cochlear nucleus. This is the part that comes up dorsally.

And they look different. If you look at the VCN, it looks like sort of a homogeneous mass of cells without a huge amount of organization. But as you can see by these

dash lines here, the DCN has layers in it. And people have pushed the idea that the DCN is like a mini-cerebellum. | know, the cerebellum is at the back of your brain. Cerebellum means it's a part of your brain that deals with motor functions. And has these beautiful layers. Certain kinds of cells are in each layer.

And there is an analogy between the DCN and the cerebellum. It certainly works as far as the layers goes. Some of the cell types are the same. You have lots of little granule cells in the cerebellum and the dorsal cochlear nucleus. You have pyramidal cells in layer two. The ventral cochlear nucleus, by contrast, is very homogeneous.

Now this slide shows you, in sagittal view, not only the cochlear nucleus and the subdivisions, but it shows you some labeled auditory nerve fibers coming in, in the auditory nerve. So we talked about labeling before. We talked about how you can put a microelectrode filled with neural tracer in the auditory nerve and get the tuning curve and the characteristic frequency, or CF, way down at the tip of the tuning cure. And then you can inject a neural tracer.

And the last time, we talked about labeling and tracing the auditory nerve fibers in the cochlea to the inner hair cell that it contacted. But you can just as easily go the other direction. Neural tracers fill the entire neuron. So these fibers were labeled, and now we're looking at their central trajectory into the central part of the auditory nerve and into the cochlear nucleus.

And it's pretty hard to read, but if you could read them, these arrows and the numbers following them indicate the characteristic frequency of each of four different labeled auditory nerve fibers. This one way down here has a CF of 0.17 kilohertz. This one is a CF of 2.7. This is a CF of 10.3. And the top one, I think, is a CF of 36 kilohertz.

And you can easily see a progression from low CF's to mid CF's to high CF's. So 36 kilohertz is way beyond the upper limit of human hearing, but in this experimental animal, which was a cat-- cats hear up to 50 kilohertz, at least an octave above the upper limit of our hearing. And they have auditory trainer fibers that respond quite

well at 36 kilohertz.

So you can see that there is a organization, and this organization could be called a tonotopic organization-- for the projection of the auditory nerve onto the cochlear nucleus and you can bet, than, that if you were to explore around here-- in the DCN that we've been talking about-- if you were to record here with an electrode that's sampled not from the auditory nerve fibers but from the cell bodies of the cochlear nucleus. And you can design electrodes to record from either fibers and no neurons, or neurons and no fibers.

If you were to use the latter, and sample from the neurons here, you would expect them to respond to low frequencies. Whereas if you were to record from way up there, you'd expect the neurons to record and respond to high frequencies. And in fact, that's what happens. And these kinds of electrode mappings of the cochlear nucleus have been done for many years. These are data from the '50s from the University of Wisconsin.

So what's done here is an electrode is put through the cochlear nucleus and each 100 micrometers or so, it's stopped to record from, in this case, cochlear nucleus cells. And their CF's are indicated by the many numbers here above the recording track.

And the CF, it looks like, started at 0.5 and quickly went up to 4 and went higher and higher and higher. And then went through a region of the cochlear nucleus where they didn't sample any neurons. And then they went through high CF's and went back down to low CF's. OK? Because they went into a part of the ventral cochlear nucleus here, where the tonotopic mapping was a little bit different.

And you can see how an electrode might record from a different projection of frequencies, if you had the angle right, going from the dorsal cochlear nucleus into the ventral cochlear nucleus. Because, as you can see, the branches of the auditory nerve fibers are quite complicated here. They all come up and they do a bifurcation. One part goes into the VCN over here. Another part goes through the VCN over here. And then finally up into the DCN.

OK, so the tonotopy of the cochlear nucleus is quite complicated. There isn't just one tonotopic axis. DCN has one, and in the PVCN you can have at least one.

But this tonotopic organization means the cochlear nucleus neurons are also tonotopically organized. So we've transferred tonotopy from the periphery through the auditory nerve and entered the brain in the cochlear nucleus.

And if you go back to the block diagram we just had, cochlear nucleus projects onto the superior olivary complex nuclei in an organized fashion. So you have such tonotopic mappings in the SOC.

The SOC and cochlear nucleus project to the inferior colliculus, and it's tonotopically organized. Inferior colliculus projects to the thalamus and the medial geniculate, they have beautiful tonotopy. The thalamus projects to the auditory cortex. And you have at least a half a dozen cortical fields that have beautiful tonotopy organization.

So this tonotopic organization is a fundamental organizing pathway for the auditory central nervous system. And it means, basically, that you're going to process certain frequencies of sound over here and other frequencies of sound over here. Keep the processing of different frequencies separate.

And so why would we want to do that? Well, it's a matter of debate, actually. There's speculation on that. But as we'll talk about during sound localization, you have different frequency ranges for the cues that are involved in timing between the two ears and level differences between the two ears. Some work best at low frequencies, and others work best at high frequencies. So maybe that is the idea, that you want to process those cues for the location of sound in different places in the brain.

So tonotopic organization is typical of almost all nuclei in the auditory pathway. So you could ask the idea, are there other mappings in the other directions? And it's not clear, in general, whether there are. Along the cochlear nucleus in this dimension there are different types of cells that we'll talk to.

But we should remember that there's a third dimension coming in and out of the screen here. What dimension would that be? That would be medial- lateral. So lateral might be close to you, and medial would be far away.

So that actually brings up the idea that we're looking at two-dimensional pictures of three-dimensional structures. And so I just brought in this reconstruction, or this model, of the cochlear nucleus to remind us of that.

This is the cochlear nucleus on the left side. And I believe this is from a cat. This is many years old. And you can see, in black, some nice little cells here that are lined up in the layers of the dorsal cochlear nucleus. So right here are the layers of the dorsal cochlear nucleus. And much of this is up dorsally here, so I should explain to you what plane of section we're looking at here.

This is the left cochlear nucleus, so it would be on my left side. And now, these are horizontal sections. OK? So for the compass for horizontal sections, dorsal is up. Ventral is down. Rostral is this way, forward in the model. And caudal is back. Lateral is to the left. And medial, where the rest of the brain is, on the right side, would be over the right here. The cochlea is ventral to the cochlear nucleus. And this is the auditory nerve coming up. And the colors are meant to represent the different CF's of the auditory nerve. So down here ventrally, we have the orange, low CF's. In the middle we have green, which is the middle CF's right here. And very dorsally, which would be way up in the top of the screen in the DCN, you have yellow, so that's the high CF's.

And so that's the model. So that's the DCN right here. And down here would be the VCN.

And so this is a model where there's 20 or 25 sections or so, but many have been skipped. In a typical cochlear nucleus, if you were to cut it 50 micrometers you might have a couple hundred sections.

So I'll just pass this around. But there are two other colors besides the three that represented the auditory nerve fibers. I think-- what did I talk about? Red, green,

and yellow. Right? So there are two other colors. There's orange, and there's blue on there. OK, so what's that?

Well, the auditory nerve is not the only thing that's providing input to the cochlear nucleus. Now you say, oh, this guy made a mistake, because on the block diagram it showed the only arrow going into the cochlear nucleus is from the spiral ganglion, the auditory nerve. All these other arrows are coming out of the cochlear nucleus. So what are the three other colors that are not the auditory nerve?

Well, this is a diagram of the so-called "ascending" auditory system, from low to high. Right? The cochlea is the lowest. The cochlear nucleus is the next. And then we went up-- chung, chung, chung-- all way to the auditory cortex.

Well, it turns out, in all sensory systems and all pathways there are some direction and information processing that goes the opposite way. Sometimes that's called the descending auditory system. So there's, for example, information that starts in the cortex and goes down to the medial geniculate. And those other colors in the cochlear nucleus represent inputs coming into the cochlear nucleus that are coming from higher centers and going down to this lowest level of the auditory pathway. So those are so-called "descending" inputs. And those are not very well explored.

Obviously, we know what ascending input is doing. It's telling the brain there's a sound and it's processing that. But why would the brain want to send information down to the lower levels? Well, there are lots of theories. We'll talk about them toward the end of our course. But it has to do with the brain controlling inputs coming into it. And there even inputs from the brain going out as far as the cochlea out to the auditory periphery. So those are what those other colors are in the model.

Now we get to the part of the lecture where the cochlear nucleus becomes very, very complicated. The anatomical cell types. And this is where Dorothy might say to Toto, "I don't think we're in Kansas anymore." OK? Everything was really simple in Kansas. In the auditory nerve-- sorry if somebody's from Kansas, here-- but the auditory nerve is very simple and the cochlear nucleus becomes infinitely more complex.

And so here is an example of how complex it is. This is the auditory nerve coming in and making its bifurcation to go into the VCN and into the DCN. And those drawings we had before were just sort of stick figures. And they didn't show all these nice little endings onto this whole variety of cochlear nucleus neurons here. So how many cochlear nucleus types are there? There's about 10 of them.

So that brings me to today's reading. I guess I'm developing this tradition here of bringing a different book every lecture and reading from it. So this won't take long. This book is called *The Primary Acoustic Nuclei*. So that's another word for the cochlear nuclei. And it's by Raphael Lorente De No, who was a Spanish neuro-anatomist at first, and did a lot of work on the cochlear nucleus. And then during the Spanish Civil War, he said, well, I better get out of here. So he came to United States and did a lot of work on axonal conduction and physiological measures.

And it says in the introduction that he put away his anatomical drawings ever after maybe publishing one or two papers. And he had a whole big file of them in a manuscript, ready to go, and he stuck it away in a closet for about 30 years. He dug it out, and finally published this. So a lot of this stuff was done in the 1920s and '30s and later published. In fact, the copyright date for this book is 1981. And the inscription in the front of the book says December 20-something, 1980. So this is important, because this is a book owned by Nelson Yuan-Sheng Kiang, who started this course, 904, with Dr. Schiller back in the 1980s and '90s.

Nelson was very good friends with the author, here, and when the author published the book he promised Nelson to give him the very first copy that came off the printing press. So this is the first copy in the original run. It's not only a first edition, it's the first of the first edition. And the inscription here-- Nelson put December 1980-- is actually a year before-- a month before the copyright date. So this really, really a special book.

So these pictures here, as you can see-- you can judge this book by its cover. These pictures are the beautifully complex incoming auditory nerve fibers-- which are drawn in orange here-- bifurcating and showing the many, many types of

endings on the cochlear nucleus cells. And that's summarized by the reading here. This is the very first sentence of the book.

"Each neuron in the ganglion of Corti"-- that's the spiral ganglion-- "gives rise to two nerve fibers, which, according to their destination, are either called peripheral"-- those are the ones that are contacting the hair cells we talked about last time-- "or central"-- which we were talking about right here.

"The peripheral fibers, at times called dendrites, penetrate the organ of Corti. They form sensory or afferent endings in contact with the hair cells. The central fibers, after a relatively long trajectory in the cochlear nerve, enter the primary cochlear nuclei, where they form elaborate sets of endings."

OK, that's the reading for today, and we pass it around. You can enjoy the pretty pictures.

So these are the elaborate sets of endings on the elaborate variety of cochlear nucleus cells. And one of this type of elaborate endings is called a large end bulb. That's the very top one there. And the other name for an end bulb-- so, it's large end bulb-- it is the end ball of Held. Because Held was the early German neuro-anatomist who first noticed this huge ending.

So this ending is so big that you can hardly see the cochlear nucleus cell that it envelops. Here's another drawing of the large end bulb, and there's a scale bar. The cochlear nucleus cell is 20 micrometers in diameter. OK? So you could say that's the largest ending in the cochlear nucleus. Or you could say that's the largest ending in the auditory pathway. Or you could say that's the largest ending in the brain. And you'd be right with all those claims.

So this is a huge ending from the auditory nerve fiber onto the cochlear nucleus cell, way at the tip. And we can just go back to the previous drawing. These are stick figures where most of the endings are dropped off for the purposes of clarity. But way out of the tip of the auditory nerve fiber these end bolts of Held are so big that you can see them even with this really low-magnification picture of the auditory

nerve fibers.

OK And they go onto a particular type of cochlear nucleus cell, called a spherical cell. And in parentheses, that type of cell is called a bushy cell.

Why are there two names? Well, this is kind of a long story, but there are two main techniques to look at-- or there were, in the 1950s and '60s-- to look at cells in the brain. And one of them was to use a Nissl stain. You can cut your section of the brain, cut your section of cochlear nucleus, put your Nissl stain on it, and you can see very beautiful staining of all the neurons in the cochlear nucleus. Some of them look round. The central nucleus. And they were called spherical cells because they're so nice and round.

And this work was done by a pioneering neuroscientist who everybody before-- didn't draw this very well-- everybody before thought all the cochlear nucleus cells just look like one type. They look about the same. This neuroscientist, whose name is Kirsten Osen, was the first person in the 1950s to look at sections of the cochlear nucleus and say, oh, those actually don't look exactly the same! Some are spherical. Some look like octopus. Here's a cell Kirsten called the octopus cell, because it was sort of eccentric, and these little appendages coming off of it-- which were the dendrites-- all came off from one side, like the tentacles of the octopus come off from one side of the octopus. And this big nucleus, right in the center, to her looked like the eye of the octopus. Right?

Some of the cochlear nucleus cells were multipolar. Here's one called the giant multipolar cell of the DCN. And a pole just means that something came off the cell, and those are the dendrites. OK? The Nissl stain doesn't stay in the dendrites very well. If it did, the whole cochlear nucleus would be black because there are dendrites everywhere. But it stains the cell body very nicely.

So what does the Nissl stain stain? It stains DNA, RNA, and some protein. Which are, of course, found mostly in the cell body of the cell. So it gives you a good look at the cell body of the cell. Not a good look at the dendrites, because they don't have as much DNA and RNA. And hardly any look at the axon. The axons are

invisible. But for classifying cells, it's really great, because you have every single cell stained, and you can look at them.

Here's a cell called the globular cell. And that is a little bit like a spherical cell, but it's more oblong. Here are some other multipolar cells. Here's a cell called the pyramidal cell.

So I should have said that the Nissl designation of these cells is given non-parenthetically. OK? So you have, by Nissl, spherical cells, multipolar cells-- here's another kind of multipolar cell-- globular cell, octopus cell, and pyramidal cells. So those are the cells I would like you to know. Those of the important types of cells.

Let me write that down. The view graph is a little bit more-- it makes more distinctions than I care to make for this class.

So you have spherical. These are cells in the cochlear nucleus. Spherical cells. You have multipolar cells. You have globular. You have octopus. And you have pyramidal.

Right? I mean, since scientists are classifiers, you have sub-types of each of these. OK, you could just keep sub-typing as much as you want to. But these are the main types that we want to pay attention to for our course. And these are Nissl stained.

Now along comes another person and wants to make his mark on science, and says, I'm going to use a different type of stain and look at the cochlear nucleus in a different way. And his name was-- his name is-- Kent Morest. And he worked at Harvard for quite a while, and then went to the University of Connecticut.

And so his stain that he used was called the Golgi stain. And many of the pictures in the book I passed around were Golgi stains of fibers. He wanted to look at Golgi stains of cochlear nucleus cells and compare them to the Nissl stain. So what does the Golgi stain do? Does anybody know? Or who was Golgi? Yes.

AUDIENCE: Golgi stains the whole cell, but it doesn't stain all cells.

PROFESSOR: That's correct. In fact, in the ultimate case, you can put your brain in the Golgi

solution and come back a couple months later and you could just have one neuron in the entire brain stained. But the good thing about that is that the neuron cell body, it's dendrites, and a good portion of its axon pick up the stain and they stain it jet black.

So the Golgi stain takes a spherical cell and transforms it into something that's really beautiful. The cell body is completely filled. It's black. I should be using black. This is a black stain.

And you can see, coming from the spherical cell, one major dendrite. It's a big one. And it, very close to the cell body, ramifies into thousands of little bitty dendrites. Like this. Where this scale might be 20 micrometers. And so the dendrite is sticking very close to the cell body.

To Kent Morest, this looked like-- he must've been planting stuff in his yard, because this looked like a bush. You go to the nursery, and you pick up a bush. Here's the top of the bush. This is the trunk. And this is the root ball the nursery people bundle up for you, or this is in a pot. So this looked like a bush. So he called it a bushy cell.

And so in parentheses on the view graph there are the designations that are given to these cells in the Golgi stain, which is all in parentheses there. It looks completely different, because you're staining different parts of the cell.

So let's make our little chart. Spherical cells in the Golgi stain are called bush. We'll put these in parentheses. Bushy cells. Multipolar cells are usually called stellate because now, instead of just the beginning of the dendrite coming off, you have long expanses of dendrites that go for 500 micrometers from the cell. They can go across the cochlear nucleus. And they look like beautiful, twinkling stars. At least they did to Kent Morest. Globular cells look exactly like spherical cells in the Golgi stain, and they were given the same name. Bushy cells. Octopus cells are so clear, what they are, they're given the same name. Pyramidal cells are sometimes called fusiform. Fusiform means sort of spindle-shaped. They just look different in the Golgi stain.

Now, this is sort of old stuff. And so now, when somebody talks about a certain type of cell in the cochlear nucleus, they use a hybrid terminology. They'll say, "I was recording from spherical bushy cells." So they use both names. Or, "I think I was recording from globular bushy cells." Or, "My study is on multipolar stellate cells." OK? Or, "These cells in the DCN are pyramidal fusiform cells." So they use a hybrid terminology and they concatenate, if you will, the two.

OK, so these are the cell types, if you will.

Now let's go into the cochlear nucleus and record, with recording electrodes, a sample not from fibers but from cell bodies. And see what we get.

I think that's what's next here. Yes. OK.

Where are these data from? From Pfeiffer. So Pfeiffer worked with Nelson Kiang, who owns that book. And they worked at MIT during the 19-late-50s and 1960s. And these were, again, some of the first applications of computers to neuroscience.

They said, well, what we want to do from these cells to classify them-- well, maybe they used a whole bunch of different schemes and all of them didn't work out very well, except this one. They said, for this one, what we're going to look at for these units in the cochlear nucleus, is not the tuning curves, not their responses to this or that. We're going to look, very shortly after we turn the tone burst on-- the tone burst is the stimulation-- we're going to look at the timing of spikes.

And so these are in the order of millisecond intervals. In fact, some of the bins have width less than a millisecond. OK? They want to look very precisely at the time pattern of spikes after you turn a sound on.

So tone burst. What is a tone burst? I've used that term. So it's just-- I think we had, earlier in the course, a tone pip. So a tone burst is just sounds that to do this. So it's a burst of tone. Burst of a pure tone. And it looks like the duration here is 25 milliseconds.

OK. And all these neurons are tuned, so you want to use your sound frequency at the CF. So within the tone, versus the CF. You want to get spikes coming from the neurons. So you want to be at CF. You want to above threshold. You turn your tone burst on, and then you have your computer look at the spikes and say when they occur in time.

OK, so this is pretty important. So I have a pointer here.

So how did this experiment work? Well, here's data from one, two, three, four different cochlear nucleus neurons. And from each neuron there are two types of displays. This display on the top is called a dot raster display. And each little dot signifies the time of occurrence of a spike, an impulse, from the recorded neuron. And on the Y-- down the X-axis is the time axis. So starting at zero is when the tone burst went on. Tone burst goes off at, looks like, 40 milliseconds here. And then there's an off time when there's just silence for the last 40 milliseconds.

And the important thing about this is that this column here shows you that there wasn't just one tone burst presented, but there were many. And these experiments can use 600 or even 1,000 tone bursts. Each time the stimulus is turned on, you give it a stimulus number. So the very first tone burst is stimulus number one. And that's the first dot raster here. And the neuron fired a dozen or so action potentials at those times. And then it stopped firing, except for a little bit of spontaneous activity.

Then tone burst number two was presented. And the neuron's dot raster for number two is the next line down. Then you go through your silent period, and go back to the beginning.

Tone burst number three was presented. And you get this pattern of spikes. It's a little bit different. Each one looks like it's a little bit different.

Down here is tone verse number 15. OK? And you get that dot raster of spikes. And then you go through your hundreds of tone bursts. And this might be tone burst number 999 down at the bottom, and you get that raster.

And you keep track of all those dots. And you have the computer put them into bins here. And this histogram shows you the bins where the number of action potentials is along the Y-axis now. And the X-axis is still displaying time. And this horizontal line shows you when the tone burst was on.

So this type of histogram, which is compiled from many stimulus presentations and many dot rasters, are sometimes called the PST histograms. And that stands for post- or peristimulus time.

Obviously, it's a time histogram. Obviously, there's a stimulus. Why is this a post? Well, the terminology started up when you, instead of having a long tone burst, have a click. So that when the click goes on, it goes off real quickly and everything is post- stimulus. So it's really, in this case, a peri-- around the stimulus-- time histogram.

Does everybody explain-- Does everybody know what I'm talking about here? About what this display is? OK.

So you can think of this PST, then, as reflecting the average firing rate as a function of time for the neuron. And quickly, you're not turning the tone on for many seconds. It's within a few milliseconds. Within the first 40 milliseconds of when the tone burst is turned on. And it's an average response.

And here's data from one unit. Here's data from another unit. Now, even in the dot raster you don't need to worry about averaging here. This type of firing is fundamentally different from the type of firing we just talked about. It looked like on every single tone burst there was a kind of a different firing pattern. Sort of random. As if you took your pepper shaker and just spread out some salt and pepper here. There wasn't a real organization to it. Sure, there's a higher firing during the tone burst, after a little latency. But over here, there's a real nice pattern to it.

And it looks like in this unit, which was called the Chopper unit, even from the very first stimulus number, it went "pop, pop, pop, pop, pop, pop, pop" if you slowed way down. Same for the second. Same for the 15th. Same for the 999th. This Chopper

unit has a very organized and precise temporal pattern of firing. When you do the averaging and get the PST, you can see this very nice so-called chopping peaks in the PST histogram for this Chopper unit as compared to this other unit.

Here is a unit where you can also see, from the dot raster display, that this unit fired a spike and took a substantial pause-- which gives it a name, the Pauser unit-- before it started firing again. And here is the PST histogram from a so-called Pauser unit, where the pause is a substantial pause. It's 10 milliseconds or so.

And finally, here's a unit called an Onset unit, which fires only one spike at the onset of each and every sound stimulus. Each and every tone burst. And obviously gets its name, Onset unit.

Now, let's go back to this first unit. Why? I glossed over the name. Why is it called the Primarylike unit? Well, if you go and record from primary auditory nerve fibers-- and where does that terminology come from? Well, in the auditory system you have the hair cell, you have the nerve fiber-- so the nerve fiber is the very first, or primary neuron. Then you go into the cochlear nucleus and you have the secondary neuron. So really, this is a secondary neuron.

But the pattern, the PST pattern, that you get in some of these cochlear nucleus neurons looks just like primary auditory nerve fibers. Except they have a little bit longer in latency. So this one is called Primarylike unit. It's not a primary. It's a secondary neuron, but it's like. Primarylike pattern.

OK. So in the cochlear nucleus, you have these different types of firing patterns. And let's make a list of them. Maybe I'll make the list over here.

So these are the unit types. Primarylike. Chopper. Pauser. And Onset. Those are the four basic types.

Now, again, scientists are classifiers, so you-- if you read the literature-- you will find some units called Primarylike with notch. So those are Primarylike units, but right after the first peak they have a little notch. Don't worry about that. It's basically a Primarylike unit.

Now, we have two interesting classification schemes here. One is how the unit responds to sound. One is how the neuron looks in the microscope. Can we make a correspondence between the two?

Now, one possible outcome could be, "There is no correspondence." Right? Could be that spherical cells can produce any of those kind of responses to sound. Well, obviously, I wouldn't be devoting a whole lecture to this if that were the outcome. And in fact, the cochlear nucleus is a place where we can really correlate anatomy of the cells with their physiological unit types.

And how is that done? Well, there are several different ways. And this graph shows you one way. That is by going to different parts of the cochlear nucleus. Where the cell types are not equally distributed, you find that the unit types are not equally distributed.

And this works very well for certain areas of the cochlear nucleus. For example, this area right here called OC. That's the area called the octopus cell area. What's found there? That's basically where you have all the octopus cells. They're found in a particular part of the ventral cochlear nucleus.

OK, let's go record there with our electrodes. And what kind of PST pattern do you get there? Well these are numbered types. Where number one is Primarylike. Number two is Chopper. And these are sub-types of Onset-- three, four, and five. And number six is Pauser. In the octopus cell area you get Onset responses.

OK, so let's start drawing some lines. Octopus cells then produce Onset patterns. Now, that's true. You can really sink your hat on it. How about going the other way? Do you always get Onset response from just octopus cells? Or how about some of these other types? Well, going the other way, you do have a few multipolar cells that can produce the Onset type.

And how is that shown? Well, octopus cells are just there, but you can get some Onset responses in various places in the cochlear nucleus. And I'll tell you how this dashed arrow was drawn in a minute.

So Onset units are not only octopus cells. Octopus cells are only producing the Onset pattern. That's the correct way to say it. Right here.

OK. Now, elsewhere in the cochlear nucleus, the cells tend to be mixed up. And you can't make very good regional distinctions-- in spite of what's said here-- with one other exception. In the dorsal cochlear nucleus there is a layer called the fusiform cell layer. And so it has the pyramidal fusiform cells. And there you get Pausers. And that's pretty much the only place-- well, not completely the only place-- you get some deeper in the DCN. But that's very good evidence that the pyramidal cells produce a Pauser type of response. You get no Pauser responses anywhere in the ventral cochlear nucleus.

Now, why am I messing around with these messy data when, to a certain extent, most of the cochlear nucleus cells are all mixed up together? Well, you can build up these data from thousands of recordings, and you can look at hundreds of cochlear nuclei. You can assure yourself this is the only place that octopus cells are found. You can record from thousands of units and not find too many Onset responses elsewhere in the cochlear nucleus. So you have the strength of numbers behind you if you use this type of approach.

We talked last time about single unit labeling. Why not apply that to the cochlear nucleus neurons? OK. The way you do that is you fill your electrode with neural tracer. You go in. You record the CF from the tuning curve. Then you turn a tone on and you get the unit type. Is it a Primarylike or is it a Chopper?

That's a very elegant way to answer this question, and it's been done, but it's also extremely difficult. For some reason, recording from the cochlear nucleus neurons with the type of pipette [? electrode ?] that's necessary to have your neural tracer in it, it's very difficult. You get the recording and then you go inside the cell to inject it, and it tears a big hole in the membrane. And so the neuron stops responding. Have you lost the neuron? Are you still in it? You don't know.

OK, so that's very difficult to do, but it has been done on this certain select number

of neurons. And here's some data from single unit labeling. So here is from a study-- this is from a study by Bill Rhode et al at the University of Wisconsin, in which he recorded from cochlear nucleus, Primarylike neurons. That's clearly a Primarylike PST. He injected and labeled the neuron and recovered in the ventral cochlear nucleus. And there's what the labeled neuron looks like. There's a big cell with one primary dendrite, with lots of ramifications close by the cell. It's not as clear as the bushy cell I drew on the board, but clearly this is a bushy cell, because all the dendrites are close by.

Now, I'm using the nomenclature from the Golgi stain because, clearly, that cell is stained in its entirety. The cell body is black. The dendrites, every little type of dendrite ramification is filled black. That big thread-like thing going right underneath the title labeled neuron is the axon. You can trace the axon wherever you want to. This is Golgi-like labeling that you get from filling these cells with neural tracer. Clearly, that's a bushy cell. And it had a Primarylike pattern.

Now, if you look in all the literature, maybe you get about eight or 10 filled bushy cells. And people have spent many years trying to do this. You see papers published with just a half a dozen labeled neurons. It's very difficult to do. But clearly, that Primarylike pattern came from that bushy cell.

This Chopper pattern-- this is a subtype of Chopper-- came from the stellate cell. Clearly, rather than one primary dendrite, it had a half a dozen. And the dendrites went forever. Here's a neuron that sent its dendrites all across the cochlear nucleus. Clearly a different type of cell-- a stellate cell.

OK, so let's draw an arrow there for those two neurons. Bushy cells. Spherical bushy cells. We actually don't know that it's spherical-- can produce Primarylike. Stellates can produce Chopping patterns. And these other correlations-- octopus cells correlated with Onset, we already established. And Pauser types correlated with pyramidal fusiform cells, we already established.

So we here have a nice chart of correlations between the anatomy and the physiology. And probably, this can be done much better in cochlear nucleus than

any other center in the brain. Auditory system or non-auditory. OK?

Now, you should be a little bit skeptical of me, as scientists, when I give you these really nice classification schemes. So what is really the difference between a globular bushy cell and a spherical bushy cell? You should be thinking, "Can that guy really make that distinction?" OK, sure, some things are spheres, and some things are oblong. But what about something in between? Are there intermediates in this classification scheme?

So let me give you just an arbitrary-- we classify people by the color of their hair, right? There are blondes. There black-haired people. There are brown-haired people. There are red-head. But then you have a lot of intermediates, right? You have dirty blondes. You have people who have darkish brown hair, not quite black, but not quite brown. What are you going to do with all those intermediates? What are you going to do with people who are losing their hair?

Problems with classification schemes are if you have a lot of intermediates. And then these things break down. Instead of being a nice, firm category they become really squishy, with a lot of intermediates between the two.

It turns out, here, that that's not a huge problem, although it is sometimes a problem. The aficionados who do this for a living have metrics where you can measure the sphericity of a cell or the oblateness of a cell.

You can measure things in the physiological response. Like if it's a pause longer than two milliseconds, it's a Pauser unit. But if the pause is less than two milliseconds, then it's a notch, or something else.

OK. So it turns out that there aren't very many intermediates or things that are hard to classify in these two kinds of classification scheme, which is very important.

Another important thing is what do these classifications then predict? If you're recording from a Primarylike unit, and you say it's one of these kinds of bushy cells, what does it predict? Well, one thing it predicts is where the cells project to.

Now, that's given to you a little bit on this diagram here, by this category. That says acoustic stria for the efferent axon. And so now we're using terminology that is centric to the cochlear nucleus. Efferent means going out of the cochlear nucleus. And there are three major pathways going out of the cochlear nucleus. The ventral, intermediate, and dorsal. And different types of cells project in one or another, but not all three of these output pathways.

So knowing the type of cell, knowing its response pattern, I can predict where the axon is going. So the predictability of the classification scheme, if it predicts things very well, means that it's a good classification scheme. But when somebody gives you a classification scheme, you should always be thinking, "Now, is it a good classification scheme? Or it is just something cooked up?" Meaning, are there lots of intermediates?

So speaking of projections of the axons. This is what I want to end up with today. Especially in terms of the parallel pathways that we talked about at the beginning of today's lecture.

So here's another even different type of diagram of the cochlear nucleus. This is the cochlear nucleus on the left side. This is a little bit of the cochlear nucleus on the right side. And so we have a whole bunch of the auditory pathway, the superior olivary complex, and the inferior colliculus more in the center of the brain.

And now you can get a sense of why the superior olive is really a complex. Here are parts of it. Lateral superior olive. Medial superior olive. Medial nucleus of the trapezoid body. Lateral nucleus of the trapezoid body. And that's just part of the superior olivary complex. It's really a whole bunch of different nuclei all glommed together.

The point of this slide, though, is the projections of the cochlear nucleus neurons, in terms of where they send axons to. So here are the spherical bushy cells, right here. That's its diagram here. And this little lending is supposed to be the giant end bulb of Held that they receive.

The spherical bushy cell on the left cochlear nucleus projects up here into the left superior olivary complex. And one of its most important places to end up is in the medial superior olive. Part of the superior olivary complex. And it continues on and goes across the midline and also projects into the right medial superior olive.

It's not diagrammed here, but analogous spherical bushy cells on the right side come in and do the same thing.

The medial superior olive is the place-- that we'll study in about a week-- that receives input from the two sides from the spherical bushy cells. And it compares the timing of the inputs from the two sides. It says, oh, if I heard the sound on the left side a little bit earlier, then that sound source was located to the left side of my body.

But if the MSO gets input from the right side first, it's almost certainly the case that the sound source was located on the right side of the body. And it'd activate the right ear and the right cochlear nucleus and its axons first. And by the time the sound leaked around to the left ear-- it a longer time to travel, here-- and started to activate the left pathway, it was a lagging signal and came into the MSO a little bit later.

So the MSO, then, receiving input from these two spherical bushy cells from the two cochlear nuclei, does an interesting comparison and helps us localize the sound using timing differences. There's probably a pathway in here that begins with the globular bushy cells, where you use the differences in level at the two ears to localize sounds.

That's two out of maybe 10 different types of cells that we really know what they do. So the other eight or so-- the pyramidal cells, the small cells, the octopus cells, the stellate cells-- we have no idea what they do. OK? So all the rest of these other parallel pathways, the function are unknown. We think they do something in the sense of hearing, but we're not sure what they do. So there's a lot of interesting information left to be gleaned from these parallel pathways coming out of the cochlear nucleus.

OK? So that's what I want to end up with. If there are any questions, I'll take them now. I also want to remind you guys that next week, Monday is a holiday, so there won't be any class. So the next time we meet is a week from today, on Wednesday. And in that lecture, we're going to talk about deafness and hearing loss, and toward the end we'll have our demonstrator come in to demonstrate her cochlear implants. So that's an important class, not to be missed. OK, have a good mini-vacation.