GERALD SCHNEIDER: So we want to finish the auditory system today. And then we'll get into the topic of pain and the limbic system. I had gone through rather complicated connections of the subcortical auditory system, pointing out that there are two major streams of information flow, one concerning more with identity of the stimulus, and particularly concerned with temporal patterns.

And we'll see more about that today when we talk about the cortical regions, which is represented in this diagram here. Here, we have the primary sensory neurons connected to the receptor cells-- the hair cells in the cochlea-- going to the two cochlear nuclei, the dorsal and ventral, where you have a number of different neuron types, some of which project, particularly for this ventral stream concerned with spatial localization, project to the cell groups in the trapezoid body.

There's at least three cell groups there-- the nucleus of the trapezoid body, or medial nucleus the trapezoid body, and then the superior olivary nuclei, a lateral one and a medial one. And we talked about the medial one being equivalent to this nucleus, nucleus laminaris in the [? chick, ?] which gets input from the two ears with precise timing.

And the time difference will determine where you will get enough spatial summation to fire the neuron. So you end up with a place code for location of the sound. Different neurons are excited according to where the neuron is located along the azimuth.

Then the pathways go up, reach through the inferior colliculus here. Some of them reach the superior colliculus, also, ones concerned with spatial location. Then they reach the thalamus. The main nucleus and the thalamus we think of, for auditory information, as the medial geniculate body. It's called that, geniculate, because it's a knee-like bump on the side of the diencephalon in humans, but it's true, also, in many animals.

In the human, because of the growth of the lateral nucleus and the so-called part of the lateral nucleus we call the pulvinar, the lateral funiculus body gets pushed more laterally. So the medial one, then, it's the auditory nucleus, and it gets a very large bundle of fibers, represented only by the couple of them in the diagram here. But it's very large.

It's called the brachium of the inferior colliculus, the arm, or brachium with the inferior colliculus. In other words, you can see it in a dissection. When you do your sheep brain dissections, you'll be able to see that.

You can open up the surface of the membrane. You'll see the four colliculi. And you'll see that big bundle of axons, myelinated axons, going into the medial geniculate body. But there are other nuclei in the posterior thalamus that also get auditory information. But they get, probably, sensory information. They get more than just auditory-- posterior nuclear group and the lateral posterior nucleus, which also get input from the superior colliculus.

And then we reach the auditory cortex. So that's what we want to talk about now. I'll talk about how the areas have been defined in terms of tonotopic maps, as if there's a place code, also, for frequency representation. And there is, but that doesn't mean that that's the main function of the auditory cortex.

I'll give some examples of unit response properties from-- some of the best studies in this area were done a long time ago by Evans and Whitfield in England. And I'm going to use those studies and then talk a little bit about ablation effects.

If you plot the characteristic frequencies of neurons in the so-called primary auditory cortex-- A1, auditory 1-- you find the tonotopic map. As you go from posterior to anterior, the best frequencies change.

And there's at least three other such maps in the cat neocortex, so four tonotopic maps in the cortex. And there's at least four other areas, in addition. I'll show you that map. And then we'll talk about whether this really means that frequency discrimination is what the cortex is all about.

This figure indicated to me that that's unlikely that [INAUDIBLE] frequent discrimination is the main thing. What they've done here is they've plotted distance across the cortex in the posterior super Sylvian sulcus in the cat. And these are in millimeters. You can see it's a pretty big structure in the cat. And we go from 7 to 15.

And here, they've plotted the characteristic frequency, the best frequency, the frequency where the neuron is most sensitive. So you can see if you take one position here, say at 10 millimeters, look at all the different frequencies you can get those neurons to respond to.

But if you take the envelope of all the frequencies across the cortex, then you do get the tonotopic map. You get response to higher frequencies the further you are from the posterior end of that gyrus, defined by the posterior super Sylvian sulcus.

This is the posterior super Sylvian sulcus here. So you're into A1 not right at the zero point but when you're so many mil-- like, 7 millimeters-- forward. And then they're going this way across that cortex in the super Sylvian sulcus, which is the sulcus here-- sorry, this gyrus. This is the sulcus, the groove here.

And the visual areas would be in this, the lateral sulcus up here. These would be so-called association areas in between primary visual and the auditory regions. Everything in the pink color there is responsive to auditory input in the cats.

You can see that these carnivorous animals that prey on other animals, they need-- sound plays a very important role in this behavior. And they have an expansion of auditory representation in the cortex. So it doesn't mean they don't also use other senses very well. There are also a lot of somatosensory representation here and visual representation back here.

This is an attempt to sort of pry open the cell side and show these auditory areas. So A1, then, is here. And they're showing that high frequencies are represented more anteriorly and low frequencies more posteriorly. The orange color is just where the cortex is normally completely buried in the sulci.

There's another representation in the anterior region here, this region, the cortex, the anterior, next to the Sylvian gyrus. And it goes from high here to low, so there's a reversal of the map. And then there's two more maps, one in this posterior area and in the ventral posterior area.

So just by using frequency representation, they know that these can be separated. But they also get auditory responses where they cannot find such a tonotopic map. The second auditory area is this one-- it's ventral to A1-- and also the ventral area here, the dorsal posterior area, and temporal cortex way down here.

These would be equivalent to areas that were originally called visual association areas. But then we know they have maps of the visual field, or at least partial maps, and respond to more complicated aspects of the stimuli. And there's some evidence that that's happening in the auditory cortex, too. But the analysis of the auditory system has not been as extensive as the visual system.

So let me just tell you a little bit about the early studies of Whitfield and Evans in England, looking at some of their recordings. First, look at this one. The graph is a plot of the characteristic frequency of a particular neuron. So they varied the frequency here. They plot it in kilocycles per second, or kilohertz.

And here, they've shown the sound pressure level in decibels. And they're showing there, with the weakest sounds, they can get the neuron to respond at about 13.6 kilohertz. But it still does respond to the other frequencies if you're a little louder.

Now, up here, they've shown stimulation at this frequency and for frequency-modulated tones that vary these frequencies. So it's wavering--

[OSCILLATING WHISTLE]

--in this one. So first of all, with a steady tone in that frequency range, you can see that the neuron fires after the onset, and then it stops firing. And then, again, it fires at the onset of the tone and then stops firing. If they give the frequency modulation, notice what it's doing. It's responding only with the upward sweep of frequencies. So it's got some temporal specificity to it.

You see that again here, where they use ramp stimuli. Here, they have a lower tone. And then it jumps up. And the neuron just responds to the ramp when it jumps up in frequency. It doesn't respond when the same frequencies are traversed, but it's going down, indicating the specificity of this neuron. The neuron is tuned to upward frequency sweeps right in this range, even though it will respond to weaker sounds and slightly higher frequencies.

A little more about these temporal pattern specificities using these very simple tone stimuli. Here, for example, they give a repeated tone. And notice that it habituates. It responds best at the beginning and then less and less.

There are many neurons like that. But they have neurons that do just the opposite. You can call this an augmenting response. Here, it doesn't respond at all to a brief tone. Again, it doesn't respond at all. And then it starts responding at the offset of the tone. So it doesn't respond at the beginning. It needs some kind of summation. It's taking time to build up to that pulsed tone.

Here's another example of an off response where, here, the neuron is responding all the time. But it increases its firing at the offset of the tone. And it does so a little bit with the short tones. With a longer tone, it does so much more. So there's an off type neuron in the primary auditory cortex.

Here's an example of a neuron that will not respond to prolonged tones but will respond if the offset are very short tones. So it just gives you an idea of the variety of pattern specificity that's going on in the auditory cortex.

When people were just plotting the frequency specificity, they missed all this. And then Evans and Whitfield started looking at varying the temporal pattern and finding these interesting properties. And just like people had done in the retina, it's a much bigger topic in the retina. It's not been studied as much in the auditory system.

But it's very easy to come up with a model involving asymmetric inhibitory connections that could account for that. These would have to be, if these are the inputs to neurons in the cortex, and these are the outputs, these could be the fibers coming from the medial geniculate, where we know we have tonotopic maps, orderly maps.

And if you connected them at low frequencies, then high frequencies, but you also had inhibitory interneurons that had an asymmetric distribution, then you could get a neuron at the output here. These neurons would respond to upward frequency and not to descending frequency.

Is that right? Yeah, because if you go this way, then the neurons at slightly lower frequency are already inhibited by the time the frequency gets there. So you'd get a preferential excitation with low to high frequencies. And we don't have direct evidence for that kind of connection in the auditory cortex.

But we do have some evidence, as I pointed out before in the retina for movement specificity direction specificity in the retina. Now, if you ablate the auditory cortex in the cat, you, in fact, don't abolish discrimination frequencies.

They've learned to discriminate one tone versus another tone. They can still do it. They can still discriminate different loudnesses. You will disrupt those things for a while, but they return. But what you really disturb is discrimination of temporal patterns.

If you've trained the cat to respond, normally, cats can do very well at learning to respond to these various kinds of temporal patterns. We've mentioned you can't get them to do that after these lesions.

If you just test habituation, the novelty, you get the same kind of thing. It reminds the thing in human neurology that this is reminiscent of is word deafness you can get with auditory cortex lesions. People can hear, and they can discriminate tones, tell when tones are loud or soft. But they can't discriminate the temporal patterns involved in hearing words. So something similar may be going on.

There have been many other studies in this, though not nearly as many as in the visual system. I remember some of the earlier ones, where they used squirrel monkeys in Germany and found in the more ventral parts equivalent to second and more ventral auditory areas-- what they were doing in the monkey but equivalent to areas below A1 in the cat-- they were able to find some neurons that they could only get to fire when another monkey was screaming. And monkeys have a particular set of vocalizations with different meanings to other squirrel monkeys. And they found neurons that would respond specifically to some of those sounds.

It reminded me of some early studies at Cornell University on bullfrog, where they found neurons tuned to things relevant in the life of the bullfrog. And one thing that's very relevant is to detect the splash of another bullfrog, so you know when a bullfrog's entering the water.

And they found neurons that respond specifically to the temporal pattern of that splash-- obviously, a pretty complex sound. Yet the neuron could do it. They didn't respond as well to other kinds of splashes.

We think this kind of specificity that's been seen in the auditory system of animals probably means that humans have units selectively tuned to phonemes involved in speech. And the evidence is that we can respond to all different phonemes when we're babies. And then we lose some of that.

So we end up responding mainly to phonemes in our own language. So there are probably experience effects involved in the tuning of the auditory cortex. Again, there have been fewer studies of that. Most of the studies have been in the visual system.

I just want to mention before we deal with a couple other topics about the work on birdsong. It's been important in recent years after the discovery of very specific pathways involved in control of birdsong, beginning in the auditory system and on the output side, as well.

These are in male songbirds-- male canaries, male zebra finches. They involve structures in the so-called neostriatum and hyperstriatum in the forebrain of these animals. They have a much more developed striatum and less development of anything that looks like cortex. It has to do with the developmental dynamics of forebrain development. You have more subcortical structures.

They do have structures, especially advanced birds, especially the crows and also parrots, have a part of the striatum that is layered. It looks sort of like a cortex, but it doesn't have a ventricle below it. So it doesn't have the same configuration as mammals.

But these birds have these subcortical structures that have marked differences in the sexes. They're much more pronounced in the singing birds. Not only that, but they're asymmetric. There's a left-right difference.

And it's similar to in human speech. We usually have left-side dominance. And that dominance is preserved in the output pathways all the way down to the innervation of the syrinx in the throat. So that's made it an interesting model that may be relevant to human speech representation.

We know it's a very plastic system. Birds have to learn many it differs among different species. But there's a lot of learning of song. And the most interesting thing in recent years that's been discovered-- it was discovered at Rockefeller University, where a lot of these discoveries have been made.

Initially, the sex differences in the canary brain just discovered by people doing histology in the labs on these birds. And they found these structures that stood out so well. And they found that they were connected to the auditory system in specific waves. And then lesion studies and then, later, recording studies showed their relevance to song.

The sex differences actually vary with the season. Now, that was the most interesting thing. Because we were thinking when that discovery was made, most people still thought of the brain as pretty static once in adults, that the plasticity was early. And so the emphasis on birdsong was the early development of birdsong.

And then they found out that the brain actually varies from one season to the other and that you actually get genesis of new neurons seasonally in adult songbirds. I mean, it's dependent on, among other things, on testosterone changes. But there are other factors affecting it, also. And it's an important topic in developmental neurobiology in recent years.

OK, just a few other topics now that are relevant to mammals. We've talked about the middle ear. This is an enlargement of the middle ear with the eardrum, or tympanic membrane, shown here. It's cut here so you can see the bones inside the middle ear.

And it's also showing that there are-- so here's the malleus, the incus, the stapes, these little bones sometimes called the hammer, anvil, and stirrup. And here's the little muscles attached to it. We didn't talk about those before. But they're little muscles that, when one of them is innervated, the tensor tympani muscle here is indicated by a branch, the mandibular branch of the trigeminal nerve.

And there's another little muscle here, the stapedius muscle. When those muscles tense, they're dampening the vibration of these bones. So you'd expect, perhaps, that would happen when sounds are particularly loud-- and it does-- to protect the inner ear from being overstimulated by the oscillations caused by very loud sounds vibrating the eardrum. But they also contract whenever we're talking. That is, the little muscles in my middle ear are contracting whenever I'm speaking and decreasing the vibration of the middle ear.

So this is just attenuation up to 25 decibels with low frequencies, less than 1 kilohertz, when loud sounds occur. But we the innervation is very dense. It's indicating a high degree of control, about one motor neuron for every muscle fiber. We also, as I pointed out, know that we can track during vocalization. So this indicates to me that we probably don't understand fully the function of those pathways.

I want to talk about another centrifugal pathway, not just the one that dampens transmission through the middle ear. There is also innervation of the hair cells by fibers that come from the hindbrain. That's the so-called olivocochlear bundle.

The topic is of pretty general relevance because centrifugal pathways like that occur in all the sensory systems. They don't always go all the way out to the periphery. But ascending sensory pathways have connections coming from higher regions, representing the same senses that feed back onto the lower levels of the system.

And many people have related that to the phenomena that attention, we-- in this case of the olivocochlear bundle, the input goes right to the receptors. I pointed that out in the figures we saw and that are in your textbook, figures of the organ of Corti, where you see the-- I have that again here, a different kind of picture. This is from the Zigmond textbook, a graduate textbook, where they're showing here a little cartoon of the organ of Corti showing the inner hair cells and the outer hair cells. Let's just go through this a little bit.

Here's a part of the superior olive, where they show the lateral part and the medial part of the superior olive with some neurons surrounding these main nuclei. This is in their axons back to the cochlea. Here's what they're showing now. Here's the receptor cells, the so-called hair cells, outer hair cells and the inner hair cells.

These are the primary sensory neurons of two type, bipolar cells and pseudo-unipolar cells-- they're calling them type 1 and type 2 here-- going into the auditory nerve. They're contacting the hair cells.

So the dendritic-- this would be equivalent to the dendritic part of the neuron. It's stimulated by [? membrane, ?] potential changes in the hair cells. And those potential changes are generated by the shearing forces when you get vibration of the basilar membrane, which is down here.

But now, look at the centrifugal fibers. One of them here innervates by [INAUDIBLE] axon connections directly to the primary sensory neuron endings. Others here, the ones with the outer hair cells, connect to the receptor cells. But the input, the influence, is now in the opposite direction to the primary sensory neuron.

So those are the kinds of axons that make up the olivocochlear bundle. And the problem has been, what are they for? It's been difficult to figure that out. One study I like, it was the first one really to show or discover a mechanism.

Well, first of all, I mentioned in a previous class the idea was it just dampens the input. And it has something to do with attention, that when we pay attention visually, we pay less attention to sounds. But that was all based on evoked potentials. It was found to be wrong. Because the reduction wasn't due to reduced attention at all. It was just due to activation of the cortex.

Other studies, though, have shown that when the olivocochlear bundle is active, it inhibits fibers that respond to the lower intensities preferentially. So it could play a role in reducing distractions and noise.

And that led to a study in the monkey where they cut selectively-- they were able to cut the olivocochlear fibers in some of the monkeys-- that had been trained to do a difficult discrimination of human phoneme differences. And they varied the noise level. So the monkey was required to do the discrimination. It was an overlearn. He could do it very well. So now they could just vary the noise level to see how well he can do it, how well he can hear it.

So you have this highly performing monkey performing at a very high level. You vary the background noise to see how well his performance continues. And you find out that if you cut the olivocochlear bundle, they don't do as well in the presence of the noise. They seem to benefit by-- you haven't damaged the primary sensory fibers of the eighth nerve at all.

How much of that's really due to olivocochlear innervation and how much of it's just due to the muscle contractions isn't too clear. Because we know that stapedius muscle contractions also attenuates low frequency more than the higher frequency. But we think because their main effect was on the olivocochlear bundle, the innervation of that we saw in this slide, they should have been affecting mostly these axons.

I want to cover just one more topic. And I'm not saying that's the end of it for olivocochlear bundle. There's been some recent work in the [? Keating ?] Lab that we've heard about here in Colloquia. It's been very interesting work that's done beyond those early studies.

I wanted to use one more study to introduce what we're coming to soon, studies of the limbic system. And this is a study of simple intensity thresholds. We know that they're very difficult to affect by lesions.

You can take out the auditory cortex. Animals can still discriminate different intensities. You can ablate the inferior colliculus, and they'll still discriminate different intensities, if you don't damage the cochlea itself. Now, if you damaged that, they can't do it. They're not using the trigeminal nerve for this. They're using auditory input.

So a study was done of rats that were trained to press a lever when they wanted to turn off the noise. So when the noise got too loud, they were uncomfortable with it, they could turn it off. And rats can do that. They can learn to do that. And they'll leave it on as long as the song is not too loud. If it gets too loud, then the rat will press the lever and turn it off to get rid of it.

You can ablate the entire inferior colliculus, as I said. You don't lose it at all. They keep doing it. You can add the superior colliculus, which also gets auditory input in its deeper layers. And you don't get any further loss-- any loss, still.

You can show that it's not just aversive noise. You can do such lesions, and they can discriminate different intensities where they're bar pressing for food. But they won't turn off the intense sound if your lesion goes down further in the midbrain, into the ventral part of the central gray area than the adjacent. They usually got adjacent reticular formation, too. And then they still had normal auditory thresholds, but they didn't turn off the aversive noise.

I just want to show you that anatomy because we'll be talking about the limbic system here soon. This is the midbrain tectum. We're right at this-- sorry, this level through the middle of the midbrain. You see the superior colliculus there, several peduncle fibers here.

And remember we said that these regions and the stipple there are related to our limbic system structures. Because they're closely connected with hypothalamus and limbic forebrain structures. And we call this area around the ventricle the central gray area. And it's been implicated in various studies in pain perception.

So these lesions that they were making ablated the inferior colliculus behind this. They ablated the superior colliculus. And then if they invaded the ventral part of the central gray, then the rat didn't find noise to be aversive anymore. It was part of the limbic areas.

This just shows that in an actual picture from a hamster midbrain. I've just blocked off the side because I took it from an animal here that had early damage. You can see the central grades. This is called cytoarchitecture. You can make out the difference in cell packing density and cell size.

Here's the aqueduct of Sylvius, which is the narrow ventricle in the midbrain. And so it's when the lesions reach just about below where the arrow is-- the got into this region-- that the animals didn't find noise to be aversive anymore.