GERALD SCHNEIDER: OK, what is the Betz cell, and where is it? A few of you were asking questions about that at the end of the last lecture, so I thought I would start with it today. What kind of a cell is it? That kind of question in neuroscience has several different types of answers.

First of all, it's a neuron, the main cell that communicates in the central nervous system or in the peripheral nervous system. But another answer would be it's a certain type of neuron. It's a pyramidal cell in the neocortex. Betz cells are in the major output layer that is output to non-cortical sources.

So now, I don't know how much you know even what neocortex is and what subcortical sources means, but you will be learning, OK? Don't worry about it if you don't understand something when I first mention it. Anything, especially in anything neuroanatomical, that I expect you to know I will repeat and add to the information a number of times, OK? It won't be something I just mentioned once.

So be patient with yourself. I'm going to do something else this year that's different from what I've done in the past. I realized that these two classes that I teach, undergraduates require you to basically acquire a language. You learn many, many new terms.

So we're going to make available to all of you a program, basically a flash card program. But it's probably the best of its type written here at MIT by a student of mine in course six, Jordan Gilliland. He will come to the class probably next time, either the next time or Friday, and describe the program. He can demonstrate it to you on my computer, and you can download it.

What I will do-- I will try to remember to do this today-- is I will put on the web some text files for the first lectures that will give you terms and definitions that will help you in your study. But those will be the files that are used in his program, very useful for learning definitions, learning languages. It's used in Mandarin and Japanese classes here.

I said a Betz cell is a cell in the neocortex in the layer that provides output to non-cortical structures. That means it must have a very long process, OK? Right there it says, A. This is a picture from Ramon y Cajal.

That's the axon. It shows two branches. The axon starts here, and then he has it going like that and then like that. That's because, on the section he was studying, it was cut off.

Now, one of those branches would probably go up into the cortex and terminate on adjacent cells. The other would go out, leave the neocortex. And the Betz cells are large because they support a very long axon. It goes all the way down to the spinal cord. The longest ones would end at the bottom of the spinal cord or near the bottom of the spinal cord, what we call the caudal enlargement that innervates the legs and feet. OK.

OK, we discussed Carl Wernicke last time in discussing localization of function. We mentioned the Kleist localization map. And if you look-- I don't if you can read it there on your printout, but these are basically psychological functions. And that raised many questions and led to a criticism and the pointing out of many contradictions in the neurological literature, so people started to simplify these maps, the Morgan and Stellar map. And the first text of *Physiological Psychology* took that to an extreme and only mentioned a few places, like motor cortex and visual cortex.

So what about this localization of function? There's been argument about it since very early on. Now, this should go back to your printout. I hope you have those. We have a few more today if you don't, but the early objections were of the sort that you see at the top there.

Isn't the human soul unitary? How can you carve it up like that? How can you say that one thing is here, another thing is there, as if people were a bunch of little people in the head?

A lot of it was because they would mix up arguments about mind and soul because many people assume they're the same. And to a psychologist, the mind is the organizer of behavior. A neuroscientist says behavior is organized by the brain. That would mean the soul is the mind. But in fact, you don't have to assume that, and it gets you into lots of problems if you do.

But let's talk about then another tradition that arose very early. It's sometimes referred to as anti-localization tradition, but, in fact, they did believe in a kind of general localization of function. And we can begin that with Pierre Flourens who studied pigeons and other animals, too, published first in 1824.

OK, so this was at the time when phrenology was becoming popular. It was before Broca, and then it continued with other people after Broca. Let's talk a little bit about Flourens.

I've sketched here a picture of a pigeon brain. And when Flourens studied this brain, he did it by making lesions. And he would make lesions in one of these four regions. The lowest we'll start with, the hindbrain, cerebellum, optic lobe, and the cerebral hemispheres, OK?

So let's say he made a lesion in the hindbrain. He found that, if he made a big enough lesion in the hindbrain, the animal just died. He was disturbing vital functions. We know that to be true now. But he claimed that, in fact, the amount of disturbance depended on the size of the lesion, but it didn't really seem to matter where in the hindbrain he made the lesion. So he claimed there wasn't any very specific localization, but there was-- vital functions were localized in the hindbrain. Because when he made lesions in these other areas, the animal didn't-- you didn't disturb vital functions, and the animal usually lived at least for a while.

OK, if he made lesions in the second area here-- I've abbreviated CB. That means cerebellum, a structure present in mammals as well, all the vertebrates. He claimed, if he made a lesion there, again, the disturbance depended on the size of the lesion and not the exact location. He said it disturbed motor coordination. So if he was doing it in his pigeons, they became more and more clumsy depending on how big a lesion he made in the cerebellum.

If he made a lesion in region three there, the optic lobe-- and it was called the optic lobe because, even with just gross anatomical dissection without doing any sectioning of the brain, you could see that it was connected to the eyes through the optic nerve and tract. And he, surprisingly actually, considering what we know about it today, he claimed that vision was disturbed, but it didn't make a difference where he put the lesion. But if you made a big lesion, it disturbed vision a lot.

I say it's surprising because we know that the left eye is connected to the right of the lobe in the pigeon and right eye to the left optic lobe. So he should have been able to tell the difference between the visual fields.

Finally, if he made lesions in the cerebral hemisphere, he claimed it disturbed functions like ability to initiate action. He didn't use those terms. He called it volition and will. And again, it just depended on how big the lesion.

So in other words, he didn't agree with the localization of function people, but remember he was using these small animals. He wasn't using animals very close to the human brain, but other scientists later on continued with that same kind of argument. Goltz published, in 1876, studies of dogs.

Now, dogs are a mammal. They have a pretty large brain, much closer to our brains. And yet, he came to conclusions pretty similar to Flourens. He studied mainly the cerebral hemispheres, and he was making lesions in the neocortex. And he claimed he was disturbing higher functions just like the sort of functions that Flourens had claimed for his small animals.

The problem was, as I see it with Goltz, is he was using very general terms to describe behavior. He didn't have any-- he didn't do experiments. He didn't analyze behavior in any very specific way. This was before the development of ethology, the study of natural behaviors in animals. It was before the development of experimental psychology. So his problem was really a lack of analysis. He wasn't look-- it just depends on how he was looking at the animals.

AUDIENCE: Higher function.

GERALD SCHNEIDER: Higher functions? He claimed things like volition, will, initiation of action. Now, there were other people around that same time that were discovering greater localization. It was around that time that people began to see that vision was disturbed with more posterior lesions in the hemispheres, OK?

And Lashley was one of those people later on who did localize the visual cortex. But in his early work, he did a large lesion study trying to locate the engram. So let's talk about Lashley's studies. Lashley is an important figure in brain behavior studies. Because unlike the clinical neurologists, he did experiments. He wasn't just informally making informal descriptions of single cases.

He was using quite a few animals in each experiment, so he was basically repeating the experiment many times in different animals. He was using quantitative methods applied to both behavior and anatomy. And he was the first one really to do that systematically. And that's why we consider him important even though, this particular study, his conclusions were probably wrong. So let's look at that.

First, I'll show you this picture taken by myself showing hamster brains because they're pretty similar to rat. I'm showing an adult and a newborn brain. And you'll note there that, in the adult brain-- and here's neocortex-- you'll note that it's a smooth brain animal. It doesn't seem to be divided up by the kinds of fissures that you see in larger brained animals.

But anatomical studies do indicate some subdivisions in that cortex. You can also see there subcortical regions. If you think of the neocortex as the highest part of the brain, all these other structures are below it in between the spinal cord, which you see beginning right here. And then here the hindbrain begins. The hindbrain is partly covered here by the cerebellum. And then you also see a little bit of the superior colliculus, which is the mammalian equivalent of the optic lobe in the pigeon.

Well, here's Lashley's way of depicting his lesions. Here was his approach. His idea was we will train the rats in problems. We'll give them to solve mazes.

We'll teach the rat the maze, and then we'll make a lesion to see if his memory for the maze that he's learned disappears. So then we'll train him in the maze, and we'll make a lesion. And now, after he recovers from the lesion, we'll retrain him and find out, now, does he have to learn all over again or does he still remember?

And he made a great variety of lesions. This is an example of his lesion reconstructions of a rat with a smaller lesion and a larger lesion. He tried to make these lesions symmetrically. And you can see this symmetry of the lesion is not perfect, but it's not easy neurosurgery to make completely symmetric lesions. But he attempted to do that, but then he didn't depend on his surgical notes. He did histology on the brain afterwards and reconstructed the lesion.

That's very important because you can do extra damage. You can damage blood vessels and produce damage you weren't intending, or you might have missed some structures that you were intending to remove. So it's very important to follow up any lesion study like this with, at least this kind of anatomy, reconstructing the tissue.

The only problem with it is sometimes the brain's become a little distorted after a lesion, and then you have difficulty putting the lesion in this kind of picture. This is a standard diagram. Yes.

AUDIENCE: [INAUDIBLE]?

GERALD SCHNEIDER: Good question. No, this is not showing the depth of the lesion. He tried to make-- to remove only cell layers of the neocortex and avoid going deep. But of course, that's a question that this picture isn't showing you.

Well, where did he go deeper? Because if he went deeper, he's going to disturb fibers. He might even disturb underlying non-neocortical structures. But for the most part, his lesions were done pretty well using aspiration of the superficial cells in the cortex, the upper, what we call the, bark of the brain, the neocortex and avoiding any fibers underneath.

OK, so here were the mazes he used. He had three different mazes. The one at the bottom there, very simple maze, it just requires the animal to turn left. The animal's put here, where it says, S. That's the start box.

And food is placed on one side and not the other. The F indicates food. And then he trains him for a number of trials until the rat now is always turning left. Maze two is a little more complex. And maze three is the most complex.

So his method, again, is to train on one of the mazes, only one of them, then make the lesion, bilateral lesion. Then he waited, so the animal is no longer affected by the anesthetic. And he recovers for a while from the lesion. I don't remember how long he recovered. He let the animals recover probably at least two weeks. And then he tests for retention. The question was, is the memory still there?

Now, this is a diagram of his findings. Basically, well, on the abscissa there, he's showing the percentage destruction of the neocortex. Now, notice there's nothing about localization there, just percentage of destruction. And on the ordinate, he's plotting the errors.

And at least for maze three, where it's very clear-- that's the most complex maze. It's very clear that, if he makes larger lesions, he's disturbing the learning a lot. They make many more errors.

He claimed that it didn't make any difference where the lesion was. The anterior lesions, if they were of a certain size, produced about the same disturbance of the memory of the animal as the posterior lesions and similarly for other localizations. He said that, in that respect, the neocortex was equipotential for maze learning. That's his principle of equipotentiality.

And he said, to learn the maze, what the rat needed was a certain quantity of cortex. And the more he had, the better. That was this principle of mass action. They mean almost the same thing.

So that was his conclusion, and he wrote a book about it published in the late '20s. And that remained-- and it was often cited, because of its beautiful methodology-- until these irreverent people at MIT in 1965 decided to reanalyze Lashley's experiment. Charlie Gross, the first author, is moved to Princeton after that and actually moved to Harvard first then Princeton. Steve Chorover is retired from our faculty not too long ago. And Cohen was one of their graduate students.

They thought that he was probably-- they looked at his lesions, and they said he was probably disturbing two distinct functions that were both needed for solving his mazes. One was visual abilities, which depend on this area back here. This is the visual cortex. And it's often called area 17 or striate cortex. And the other area they felt he was disturbing was this region anterior to the motor cortex, again, bilaterally, prefrontal cortex.

Now, why-- that was known in studies done shortly before this to be important for learning to alternate left turns and right turns. And if you look at this maze, you can see that these mazes depend on the rats being able to learn to turn one way and then the other. See, in the top maze there he has to turn right, then left, then right, then left, then right to get into the food box.

So maybe-- and they did separate tests of that themselves. And they showed that, if they made lesions of that anterior area and compared it with lesions of the posterior area, it disturbed only the ability to alternate. It didn't disturb visual discrimination abilities. They had separate tests for visual discrimination, discrimination of patterns. That depends on the visual cortex, but not on that anterior area.

And they demonstrated this, also, with-- they had a series of mazes that they found to be quite dependent on the visual cortex. And they had a separate test of alternation that didn't involve mazes at all, but involved pressing a bar, the left bar, then the right bar, then the left bar, and the right bar, and so forth. So they showed that these two functions were disturbed separately. And they, these two functions, can be dissociated by these lesions.

So they concluded that Lashley's interpretation was incorrect. And in fact, after Lashley's work, a man named Hunter argued in a fairly similar way. He said that maze learning is such a complex function. The rat is using many different senses.

He's probably using olfaction, somatic sensation, and so forth. He didn't know about this dependence of alternation on the frontal cortex. He probably did know about the visual cortex and vision.

And Hunter argued that Lashley was probably, with his lesions, just disturbing to varying degrees different senses, all which were used in maze learning. But together, the Hunter arguments who-- and Hunter always lost the debates to Lashley. Lashley was a very good debater. So that's why this study was needed. So now, we still recognize Lashley for his methodology, but not for his analysis of that particular experiment.

The keys to that kind of problem are these. You need both neuroanatomical knowledge and behavioral knowledge. Lashley didn't have adequate behavioral knowledge about the functions the rat might be using to solve those mazes. He did, later, do more neuroanatomy. And he came to-- he actually studied the localization of the visual cortex in the rat. And so he did come to understand that posterior localization of the area that is most closely connected to the retina through a pathway that's become well-known was only becoming well-known at the time of Lashley's experiments.

You need both kinds of knowledge to do that. And even when I was in graduate school, which is a long time ago, 1960s, many people were still doing this kind of lesion study with very little neuroanatomy. And they didn't worry much about connections in the brain. They weren't interpreting. They were thinking of localization of function without thinking about the connections involved. And that was a major problem.

I'll give you one other example there. I'll show you this kind of problem, especially with knowing the behavior. Because neuroscientists studying brain and behavior, I would say that, with all the advances in anatomy and physiology, behavioral knowledge still often lags behind a little bit. And let me give you one example.

A claim developed by findings that were done on experiments at Rutgers, mainly, where the claim was made that sexual ability is located in the neocortex in the male rat, but not the female. Now, how did they come to that conclusion? Well, very simple, they did lesions like Lashley, lesions of varying size in the neocortex. And they did it in both male rats and female rats.

And then they had a very simple test of sexual behavior. They simply observed whether their animals would copulate or not. And they found that the females would still go into the lordosis posture and accept the male rat. And the rat, the male rats, if they had much more neocortex missing, failed to copulate.

So very simple, they said neocortex is needed for sexual behavior in the male and not the female. Of course, everybody thought, well, let's see. It's a higher function in the male, not the female. What was wrong with that?

Well, you've got to think about the behavior. They didn't understand sexual behavior in the female at all. All they understood was this posture that the animal entered. The equivalent in the male would be, say, the ejaculation reflex. That wasn't disturbed after the neocortical lesions.

What they were disturbing was the ability of the rat, the male rat, to orient to the female to find her to position himself properly and so forth. That involves a lot of sensory motor control. They were disturbing the senses and motor control by making those lesions.

But what about the female? Well, if they only look at the end point, they're missing solicitation behavior, mate choice, a lot of things we know about sexual behavior of female rodents and many other animals, almost all animals.

They weren't good ecologists. They didn't look at the behavior in any comprehensive way, so they made the same kind of mistake-- well, a somewhat different kind of mistake-- than what Lashley made. I just want to point out that, when you read these kinds of claims in the literature, you've got to think about whether they adequately dealt with both anatomical knowledge and behavioral knowledge before you just believe it.

Concerning the memory problem, I like to tell the story about my first visit to a telephone switching station in the middle of the-- well, it was probably about 40 years ago. My brother was running one of these stations for a large telephone company. It was the only one at that time, Bell Telephone. And inside the station, you saw this enormous amount of machinery. They were basically relays connected with wires coming from these large cables from outside, enormous numbers of wires.

And I wasn't an electrical engineer, but I understood something about circuits and I was learning about the brain. So I asked him, well, where's the input? And he showed me the input cables coming in. Where's the output? He showed me that, enormous amounts of machinery involved in this.

I said, but there's another problem. How do you remember who's calling who so you can bill them? And he said, oh, that's over there. And it was this little device, you know, obviously using a different kind of circuitry, a little tiny thing in one part of the room that he said did all the memory functions.

And it made me realize that probably in the brain it's something similar. In the neocortex, a lot of the cortical apparatus that's involved in sensory analysis and motor coordination memory could be distributed, or it could be localized, but it could be much more difficult to deal with. And of course, that proved to be true over the ensuing years. But now, we're beginning to get a much better handle on that as well.

When we deal with this problem of localization of function, you have to think about the question what is localized. What are we trying to localize? Is that a conscious entity? Is it a psychological ability? Is it memory?

My answer is that, no, those are not brain words. You have to be very wary when you read about sensors for pleasure, the pleasure center, the sex sensor, the hunger center, the center for mental arithmetic or whatever because those are psychological functions. That's not what's localized.

What's localized is physical or physiological processes in a structural substrate. We're never going to find the ghost in the machine. It's not there. You're going to find input pathways. You're going to find output pathways. You're going to find processing connections in the intermediate network.

Luria, the Russian, neuropsychologist, the great neuropsychologist in the last century, has this statement in one of his books on neuropsychology. He said, that mental functions, as complex functional systems, cannot be localized in narrow zones of cortex or in isolated cell groups. You see, they involve a lot of apparatus.

You might disturb a function more with lesions in one place than another, but the function as a whole would depend on a greater complexity of connections. And that certainly remains true. But if we go to the extreme, we can say, well, don't brains think? Can't we say that thinking is localized in the brain?

MacKay, who we met before, said that this is a poor question because it mixes different conceptual levels. And this is a statement from his paper, "A Mind's Eye View Of The Brain." He says, if we want to use language consistently, we cannot say that brains think or decide. Brains do those physical things appropriate in their own logical dimensions as correlates of what people do, you could say or animals, when deciding, thinking, feeling, hoping, fearing, believing, so forth.

Let's just talk briefly about the third type of goal of people that weren't necessarily concerned with reducing behavior to a specific circuit. And they weren't necessarily concerned with localizing function, but they're interested in correlating events in the brain with behavioral events. And I find these attempts to correlate brain and behavior to just be a never-ending fascination for people. In fact, they often forget that finding the correlation doesn't really prove causation at all.

Let's just give a few examples. If we record, with little electrodes placed on the scalp, we can record very small potentials there that are changing because they're picking up-- currents are being induced by electrical changes in the underlying brain, at least the part just below the skull. And we call those recordings the electroncephalograph. It's usually put on a graph showing the amplitude of these waves picked up by different leads attached to the cortex.

The recording is pretty much the same as with an electrocardiogram. You're looking at electrical activity of the heart. And we find that the pattern of what we call those brainwaves, the pattern of those currents changes, it's correlated with states of arousal or of sleep and that they're not localized functions, but they appear to be-- they might be a little different in different leads. But basically, we're looking at states of the brain not at localized functions.

And that's fascinated people. Because when that was discovered, now they had a way of looking in different stages of sleep and exploring what are the differences in different stages of sleep or in different states of arousal in the waking state. So these attempts to correlate brain and behavior have led to some very different kinds of information about brain and behavior. They've led to the idea of states of the brain on the whole, where the brain, over large areas of tissue, can change its state, behave differently.

But the other kind of correlation that you see much more often is to correlate the activity of neurons in specific areas of the brain with behavior. So for example, if you're looking at the movement of the wrist and you report you've, say, trained the monkey to make simple wrist flexion and extension, you can find neurons, for example, in the motor cortex that specifically fire in a precise temporal correlation with that movement. Certain neurons will fire when the animal is flexing. Certain neurons will fire when he's extending.

And in fact, they find neurons that will start to fire before the movement that always seemed to precede the movement by a rather precise time interval. There are other neurons, especially in the somatosensory cortex, which will follow the movement, that will fire after the movement occurs. So that kind of correlation has also been fascinating to people.

Looking at the limitations here, it never tells you exactly what causes what without other experiments that do that. Modern imaging techniques are a similar thing. They're looking at correlations of what's happening, not telling us about cause and effect. But we do find consistent areas of the brain where the tissue oxygenation is greater, the blood flow is greater when the person is doing a certain thing or sensing a certain thing or making certain movements.

So it's that third goal that we see pursued in modern imaging techniques. But it does make, of course, many suggestions about behavior. If you can localize consistently areas that have this kind of activation in a certain behavior, then we know we can go from there in thinking about how different regions are dividing up the task of controlling a certain function.

So what we're going-- I'm going to go through a little bit about the modern subsystems approach. I think that was the last-- OK. First of all, the modern synthesis has to take into account a number of things. But one thing, we know that central nervous system ingredients, the neurons, and the other cells involved in nervous system are a lot more complex than reflex motions would indicate. So our circuits the way we draw circuits are pretty limited in what they mean, because they don't take into account some of the complexity of neurons.

We know that we can localize subsystems, and we saw that with Karl Wernicke, localizing areas that were consistently involved in understanding speech and speaking. So we can draw information flow diagrams making use of neuroanatomical knowledge, localization of function knowledge, and what we know about neurons. We also have to realize that the connections aren't always the way the reflexologists had depicted them from sensation to response.

You get feedback from motor to the sensory side, also. In fact, one of the major connections of the sensory cortex responding to somatic sensation is to the sensory side of the spinal cord. That's a connection that, in fact, physiologists haven't, even now, paid a whole lot of attention to, but it's one that Professor Bizzi in our department is becoming much more interested in.

We also have to remember that our connections can be excitatory and inhibitory. And there are different types of connections, which we'll be talking about the next lectures. We also know there are modulating influence that are more system-wide. There are diffuse connections of certain systems in the brain. There's also changes in the chemical environment that we know less about, but the anatomists have told us quite a bit about some of these diffuse connections.

And finally, we have to remember that nerve cells can generate their own activity, but that varies a lot depending on the type of neuron. They can be spontaneously active. So what I'm going to do-- and I'll only do it with the case of reflexes. And we'll stop this lecture and we'll go back. We'll do this next time, and then we'll start talking about single neurons.

We'll talk about information flow in the case of reflexes, and then I'll use simple gating mechanisms to explain motivation and intention and talk a little bit about evolution of higher control. This would be an information flow diagram of the reflex. You draw the input, the sensory side. It comes into a box, which corresponds to the central nervous system and then goes out. That would correspond to the connections that go out through motor neurons to the muscles.

We can draw such diagrams without referring to the anatomy. We can base it simply on the behavioral studies. And in fact, Skinner at Harvard, a very well-known behaviorist, said, we don't ever really have to open that box because we can study the laws that relate the input and the output. We can study the sensory conditions. We can study the behavior of the animal. And we can find the lawful relationships between these. So we don't need the nervous system.

There's some famous debates where people argued with him. And some of those people were here at MIT, where the belief was, no, you can't get far enough just with behavioral studies. You need to open the box. And we know that that approach is the approach that we saw first in reflexology and ending with Cajal, who finally was able to specify the circuit, an entire reflex, and helped us understand more what's going on and its complexity. So we'll go from there next time.