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GERALD SCHNEIDER: OK, I'd like to introduce neuroscience to you by going through a bit of history that I use to describe three kinds of goals that recur in this field since the 19th century-- three different kinds of goals, and then what modern people are doing, sort of a synthesis, the subsystems approach we'll describe in the fourth lecture.

But these are the goals, and we're going to start today talking about this one, OK. Number one, coming up with specific narrow circuits which could explain behavior. And if we could do that adequately, we would be able to come up with a machine that would behave just like a person.

So I'll talk about how that goal originated with the discovery of the reflex arc, which was not in the 19th century. It was long before, at least the concept of reflexes, discovered a long time ago. That led to a philosophical view called reflexology. I'll explain that to you. I'll talk a little bit about the machines that have inspired neuroscientists' models of brain and behavior-- currently, of course, especially computers. And then we'll talk a little more philosophy before we go on to talk about neurons.

This first goal of reducing behavior to specific neural circuits, which could be used to build a machine, can be described very well by a story about Karl Lashley, who's considered one of the pioneers in behavioral neuroscience. He did his work largely in the 1920s and '30s, though he continued for some time after that. And we'll be encountering some of his work again a couple of times in the class.

When he was just a student, so roughly your age, he encountered histological sections of the frog brain. Now, do what "histological sections" means? "Histology" means the study of tissues, and you can study tissues by fixing them, slicing them into thin sections and mounting those sections on slides. And then if you stain them with certain stains, you can see cells. Depending on the stain you use, you will see different things.

And he had some slides like that of the frog brain where he could see nervous tissue and some of the elements of the neurons, at least the axon. He could tell axons from cells. And that's the idea he had that [INAUDIBLE] there. He said, I could explain the behavior of this frog if I could just figure out all the connections in that brain. It was actually a pretty naive view. You know why?

First of all, it'd be pretty difficult with that kind of slide even to see the connections. An enormous amount of effort has been made developing techniques where we can actually get evidence of connections in the brain. So we'll talk about some of those methods in this class, and then much more in the second-term class 914, which is more focused on anatomy, and development and evolution.

But let's say that the techniques were good enough, and you could see all the connections. And this has actually been done for the nematode C. elegans. They've been able to specify pretty much all the connections that allow you to explain behavior. You know the circuit diagram. What do you think?

In a sense, like a great idea. We have all the connections. We could draw the picture. Then we've got the model. And we should be able to simulate the behavior of the animal if we know how those things are, those elements are hooked up to the sensory apparatus and to the muscles. We ought to be able to explain behavior.

You will learn in this class why that in fact doesn't work so well, why it was naive. It turns out that those elements of the neurons are incredibly complex. And just knowing how they're connected doesn't give you enough information. Neurons can do a lot. They have a lot of activity even without connections. But we'll learn about that as we go along. OK.

And I listed here some of the ways that they're not like electrical circuits, these neurons. Knowing where a connection is, even where it is on the neuron, doesn't necessarily tell you how effective the connection is. It doesn't even distinguish between two basic types of activity at the connections between neurons, the synapses' excitation and inhibition. There are some differences which can be seen in electron microscopy, but in many places in the nervous system, it's not obvious at all.

It also doesn't tell you anything about the effect of the chemical background, the temperature. These affect the conditions, responsiveness of the neurons. And it tells you nothing about the time course, the dynamics of the nervous system, including endogenous activity. What does that mean? What does "endogenous" mean? Yeah, internally generated, activity generated from within the neuron and not from those connections from outside the neuron, OK. So we'll talk a little bit about that in class.

Now, I'm going to say that simplifications can be pretty useful. We use them in science all the time. So we want to consider how far reflex connections can go in explaining behavior in terms of neural circuits, because that was the first big attempt to explain behavior in neurological terms.

But before I go on, this kind of term, which you didn't all know, or I would say, probably a lot of you did, but you were just too shy to tell me, being MIT students not wanting to make fools of yourselves-- and that's a bad mistake, I can tell you. You've got to be willing to ask dumb questions, because they're a lot better than dumb mistakes later. And that's the way you learn. I love dumb questions because it shows me what I'm not getting across to you and what I need to get across to you. So you can help me teach you by asking me good questions.

But one thing I'm going to do to help you that's different than what I've done in the past is that we have a computer program, this flashcard program, that's better than most such programs. It was written here at MIT by a student of mine and in course 6, Jordan Gilliland. So we will post that on the website. We'll give you a link to his website so you can download the program. And then I will provide text files that give words that teach you the vocabulary of neuroscience.

I think I will add audio files to it. So I will also pronounce the more difficult words for you, because that's also a difficulty. Learning neuroscience in my two classes is learning a language, OK. You'll be amazed how much at the end of these terms, how many more words you know. So it will help you with that program, and I will ask Jordan to come to the class, probably on Friday, to explain more about that program to you. And it's a program you can use in your other classes too. You can add your own files to it. You can add words and terms to the things I give you.

OK, back to the first goal. The existence of reflexes was first understood by René Descartes. And so we'll start with him, and then we'll talk about how we became aware of its anatomy and how it was studied by physiologists like Charles Scott Sherrington.

We think Descartes got the idea for reflexes when he was walking in the French Royal Gardens. The King had a sense of humor, and he installed these hydraulic dolls that when people [? were ?] caught trigger a thing in the path they were walking on. This big thing would jump out at them. A big doll would be triggered into somewhat lifelike action.

And that led Descartes to the idea, we think, of stimulus leading to a response through an intermediary of connections in the nervous system. Now he did dissections, and he knew something about anatomy. He wasn't totally-- he's known as a philosopher, but he did do some simple kind of science, scientific observations as well.

And in his dissections, he saw nerves, and they appeared to him to be fluid-filled tubes, which in fact they are, connected between the body surface and the spinal cord. And the spinal cord, of course, is connected to the brain. And he saw such nerves connect to the muscles as well. So this is what he postulated.

Sorry. Here's the picture. I might come back to the other one in a minute. Here's the picture. What it shows here is this boy sticking his foot into the fire. He was doing an experiment on himself. The idea was that the fire here stimulated the beginning of a nerve, and he shows the nerve here beginning at A and going up. He shows it as continuously going all the way up to the brain.

[INAUDIBLE] said it went up to the brain that way, and then to an area of the pineal gland, where it then interacted with consciousness. In this view, he couldn't think of this without consciousness, even though now we do that more readily. And then he said the impulses came back to the muscles. So it was a circuit triggered, and that caused contraction of the muscles of the leg, the withdrawal of the leg from the fire.

Now, he wasn't right about the details of the anatomy. He didn't understand that in fact, the connections don't go directly from the skin all the way up to the brain and the pineal gland. They in fact go to the spinal cord, and then there are many interconnections, many interruptions in the pathway. And in fact, the reflex he was talking about, the withdrawal reflex, doesn't depend on the brain at all. You can have what we call the spinal animal, an animal that is spinal, and with no brain connected. You can disconnect the brain from the spinal cord and you'll still get withdrawal reflexes.

When you pinch your hand or stick your hand on something sharp or something, you withdraw. And of course, you feel that you might feel pain. You'll become aware of it. But, in fact, the pain you feel and the awareness you have comes after the triggering of the withdrawal reflex. And we'll talk more about the withdrawal reflex when we get to studies of the motor system.

OK, so Descartes didn't understand completely how the details of how a reflex works, but the basic idea was a correct one. When the demonstrations of the existence of reflexes increased, certain lawful relationships were worked out. They knew that they could be varied with the strength of the stimulus, with the number of times the stimulus was applied and so forth

And that led to a simple S-R model of behavior. That is, behavior can be explained in terms of stimuli leading to responses through the intermediary of the nervous system. That didn't mean that the model could point to any specific neural circuit yet. It hadn't been discovered. We had the kind of dissections that Descartes did and many others did, but those dissections are not capable of really seeing connections.

Now, we're going to do some dissection for the class, and we can arrange to get some sheep brains and schedule. It's difficult with a class this size to do it, but we will do it. We'll get the room next door and we'll have to have multiple sessions, so all of you get a chance to do it. How many of you have dissected a sheep brain before? So maybe a quarter of you. OK. Even if you've done it, you can benefit from doing it again. And those of you who have not done it will-- I don't know. Some of the things I talk about in class will take on more reality.

Now, there were people that were critical of the S-R model of behavior, saying that, hey, behavior is too complex to explain this way. But it got a big boost by certain discoveries about these connections, and the main one that I want to talk about first here was the discovery of the law of [? roots. ?]

So let's talk about that. Some of you know about this also from your introductory classes. It was discovered twice independently in the early 1800s. Sir Charles Bell in England did simple experiments on spinal nerve roots of living animals. It's pretty gruesome to read about what they did because they didn't have anesthetics, and they had to do these on live animals with exposed spinal nerves.

And what he said was very, very simple. Because the only kind of stimulation he used was mechanical, he said that if he would tweak the roots that were on the ventral side of the cord, he got contractions of the muscles. He didn't get them from stimulating the dorsal, the nerves coming on the other side of the spinal cord. He could see that there was a separation between the nerve roots coming on the dorsal and the ventral side [? much ?] better.

Then he published that in the paper. Well, not really published, but he circulated an article to his friends, and we'll count that as a publication, in 1811. And then in France, the Frenchman Francois Magendie did a series of more convincing experimental experiments that converged on the same idea.

He, for example, also dissected, saw the distinction between dorsal and ventral roots. He used not only the mechanical stimulation that Bell had used. He used electrical stimulation called, at that time, galvanism. And he noted that he could get contractions of the muscles from stimulating ventral roots or dorsal roots, but the contractions were much more vigorous and strong from stimulating the ventral roots.

He also tried cutting the ventral roots or the dorsal roots. He found that cutting the dorsal roots did not produce any paralysis, but cutting the ventral roots did. IT produced a flaccid paralysis of the muscles, OK. He tried the same kinds of experiments after giving the animal convulsive drug, OK. And again, the convulsions would still occur with dorsal roots cut, but with ventral roots cut, even with the convulsions going on, the muscles that were affected by this lesion of the ventral roots remained completely flaccid, relaxed, OK.

So putting that all together, they came to the same conclusion, namely that-- when you look at the spinal cord, we're looking here at the dorsal view of the spinal cord, and you see here connections of the roots. You see little rootlets. Here is a nerve, OK, a spinal nerve with its branches coming into the cord. And it's actually dividing here outside the cord. One branch is going in dorsally after dividing into multiple rootlets, OK. But it's being joined by a root coming out more ventrally, OK.

And here, you can see-- well, it's not too obvious. You see the spinal cord inside one of the spinal vertebrae. You see the cord surrounded by a kind of canvas-like structure here, the meninges, the dura. This is dorsal here, ventral here. And here you see the roots attached. It's not very clear, but when you do the-- OK, you see here a dissection of an aborted fetus, a human fetus, where you see the 32 spinal nerves.

Every one of them, before they enter the cord, divides into a dorsal and a ventral root. Where's my picture here? So if you made a cross section like this, you see this is the spinal nerve here. And here, you see it dividing into a dorsal and ventral root.

And what both of my friends were saying was that the dorsal root is sensory, providing input. The ventral root is motor, OK, leading out of the cord and going towards the muscles. So then the spinal nerves here must be mixed, sensory and motor, input and output. And that was the correct conclusion. It didn't say anything about how the connections between input and output were made.

And there were a number of people that worked on that problem in the 19th century. But the most comprehensive work was done by a man in Spain who we often called the father of neuroanatomy, even though there were many neuroanatomists around his time, and even before him. But Cajal's work, Santiago Ramón y Cajal's work with the so-called Golgi method was the one that established the neuron doctrine, the neuron as the basic elements of the nervous system. So we'll look at some of his pictures of neurons.

And Charles Scott Sherrington did physiological studies around that same time, electrophysiological studies, mainly using cats with their brains disconnected from the cord. So he was studying spinal cats. And he worked out many of the properties of various kinds of reflexes. And it was Sherrington, the physiologist, that actually gave the name we use for the connections between neurons, OK, the name "synapses" or "synapse."

And it's only with Cajal that we were finally able to reduce a reflex to a specific neural pathway. So let's look at some of those pictures. With the Golgi method, you see individual neurons that are more or less completely filled. So they appear like silhouettes. You see all their processes that look like tree branches. You can see connections, although it is not obvious to a naive person using the Golgi method the nature of those connections. But you can see, for example, it's in green here. This is a piece of a neuron.

The whole neuron would be like this, OK, with its branches. The nucleus would be here, OK. And here, I'm showing one dendrite and then an axon coming in here, which we'll show in red, and ending and these little swellings. And some of those swellings ended on the surface of this neuron. Others would end on other neurons. It might appear like they're just ending in space because the Golgi method is only staining the small percentage of neurons, OK. But it stains enough of them that you can see some of these connections.

Golgi, who invented the method, came to the wrong conclusion about those connections. He thought that there was continuity between these fibers and the cells they were attaching to. He thought there was cytoplasmic continuity. Cajal correctly concluded that that was wrong, that these were distinct. There was a membrane separation.

We didn't actually have the proof of Cajal's idea until around 1950, when the electron microscope was applied with good fixation methods. The EM method was applied to the nervous system here at Harvard by several people, Sandy [? Paley ?] among them. And they were able to see the synapse and see the gap. We call it the "synaptic cleft," OK, the separation between the two cells.

Here are some pictures from Ramón y Cajal. This is a picture of axons in the spinal cord. Now, the method works best with young animals, so he was using young mice or cats, kittens. And depending on details of how the method was applied and depending somewhat on chance, or at least some factors we don't understand very well even now, he would get different elements staining in different preparations.

In this particular one, he was mainly seeing axons. Some of them you see at the top up here were coming in from the dorsal roots. And you can see some of their end arbors. We call those the end arborization of the axon, the bushlike arbors ending often in these little swellings, terminating on cells in the nervous system.

Some of the axons there could be coming from descending pathways. And they're going also into the ventral part of the spinal cord. Here's another one where in this picture, he's separated dendrites and axons. Now, the dendrites are the receiving part of the cell, and they conduct differently from the axons. And we'll be talking about that in some detail, and you'll be reading about it.

Now, in the actual picture when he's looking through the microscope, what is shown in red here looks black just like everything else. But he saw structural details that allowed him to separate the axon and the dendrite. The dendrite tends to taper more from the cell body. The axon tends to start more abruptly. And also, the structure of the axon along its length looks different from the dendrite.

That's not always very true, but it's often true. And so he was often able to separate axons and dendrites. And he was helped in that conclusion by noting that we knew that it was axons that came out of the nervous system in the ventral roots and going to the muscles, connecting to the muscles. So when he saw them going out like this one here, he knew it must be an axon. So it wasn't more neurons in the spinal cord.

And here is his diagram summarizing a lot of his observations on the spinal cord, which was the first picture based on real anatomical evidence of a reflex arc, showing the connection between the stimulus on this side and the response on this side. That is, where I've shown the S, he's looking at the sensory apparatus. He shows endings of normal processes in the skin. And then he shows the direction of nervous conduction with the arrow here, going in through a dorsal loop.

In this case, the cell body of the dorsal root ganglia is sitting off to the side there. That's a peculiar kind of neuron. Of them are not like that. And then he shows that axon branching many times, but ending at various places in the spinal cord, contacting other cells. And in some cases, that initial, what we call a "primary sensory neuron--" and we'll define all these terms for you as we go along. I don't expect you to pick them all up the first time I say them. It's contacting what he defined as a motor neuron. A motor neuron is defined as the neuron whose axon goes out of the central nervous system and contacts an effector organ like a muscle. And so he shows that here.

So here, he would be showing a complete diagram of what we would call a monosynaptic reflex arc, which we now know to be a muscle-to-muscle reflex, OK. And we'll be talking about that when we talk about reflexes. So that certainly put the S-R model on a much firmer basis. In fact, S-R thinking became very popular in psychology, and the work of Cajal was important in that, but not just the work of Cajal.

Let's talk about some of the changes in thinking about reflexes. Initially, it was done largely through philosophers, or natural philosophers, you could call them, thinking about nature, but not doing real experiments the way modern scientists do. I like the way the thinking culminated in the work of La Mettrie, a philosopher who dealt with the question of, if everything can be explained as reflexes, then how are humans unique.

Descartes said animals are reflex machines, but humans have all those reflexes. But they have something more. They have a rational soul that interacts with these physical processes. That was Descarte's dualistic thinking. It's often called metaphysical dualism because it requires thinking of a physical realm and [INAUDIBLE] consciousness that's separate.

La Mettrie said something different. He said, no, humans are different just because of the complexity of the reflexes. They're just more complex. And certainly, looking, doing dissections of the human brain and spinal cord, it was easy to support that. It was incredibly complex, and it seemed like a nightmarish impossibility ever to explain details of behavior in terms of connections because of that complexity.

But there is another thing that was missing. We know that reflex connections, the way they were being described, would be fixed. But wait a minute. Humans, at least, are not fixed. We learn. We change. Such an [INAUDIBLE], his student Pavlov changed that picture and allowed reflexes to be continued as a major model to explain behavior, because through Pavlov, we discovered conditional reflexes, or "conditioned reflexes," it's more often called.

Next time, I will bring with bring to class a quotation from Sechenov and his book,*Reflexes of the Brain.* The original title was "An Attempt to Establish the Physiological *Basis* of Psychical Processes," but he couldn't use that title because the censors objected, OK. And so he presents an argument for why, in fact, it was a perfectly good title. But he doesn't mind *The Reflexes of the Brain* either.

He was accused of immorality, of supporting immorality, because he said that things were inevitable just due to connections in the brain. In other words, people said that we are physiologically determined by the anatomy of our nervous systems. So think about that. And I'll read you what he said next time.

Pavlov showed that reflexes can change. He demonstrated reflexes mostly in dogs that were fixed, but that they can be modified through learning. Many of you have encountered that already if you've had introductory psychology or done another readings about the Pavlovian reflexes. We often call it "classical conditioning."

You can classically condition a professor and alter his behavior just by giving him reward for maybe grunting or something like that. And by the end of the class, he's grunting a lot more and quite unaware of it, because you've conditioned him through subtle rewards that he's responding to, which just shows that some of this kind of learning is unconscious. It can happen to us even without much awareness. Of course, you and me are immune to that, right. OK.

It was in the last century, the middle of the last century, that Donald [? McKaye ?] in England reconsidered these ideas that Sechenov had dealt with a century almost a century before about determinism and freedom and responsibility. And he presents a very interesting argument, saying that even if we accept a determinism, if we apply it strictly to human behavior, we can't use it to argue that a person is not responsible for his actions.

Why do you think that could be? It has to do with the way we define what's true and what isn't. Let's say I know the whole state of your nervous system will be-- put this into a thought experiment. My science is so advanced that I can make out all the connections in your nervous system and their activity. Then I should be able to predict your next action, right. After all, what else is determining your behavior? It's just all in your brain. But the thing is, if I told you about it, which I would have to deal if it's generally true-- it has to be true for everyone-- you of course could confound that. You could choose to follow it or not.

It's a logical conundrum that he was pointing out that takes the strength of the argument away from using this argument to say, support a person who's arguing that he couldn't help doing something. He couldn't help murdering somebody. He had no choice. It was determined by his structure of his brain. You can't argue that way in any logical sense. And I will post a paper on the web by [? McKaye ?] because I think it's interesting enough. You should be familiar with it.