GERALD SCHNEIDER: This is where we were at the end of the last lecture. I think I said a little bit about how the cerebellum can fit into this kind of scheme and the corpus striatum. Now, concerning the corpus striatum, in this book of readings, there are some very interesting chapters here at the end about pathologies of corpus striatum.

It starts out with the chapter called "Still Smiling." It's in the book *Newton's Madness, Further Tales of Clinical Neurology* by Harold Klawans, a neurologist. They're very interesting stories. It gives you a real feel.

It's very easy reading. I'd like you to read those chapters. And there will be some things about these dyskinesias, abnormal movements, and not just Huntington's chorea and Parkinson's disease, but some other pathologies of corpus striatum, also.

I want you to remember that the neocortex in mammals-- it's the defining structure of mammals in the brain. We have a neocortex, even if we're a tenrec or an insectivore. They have very little neocortex-- or a hedgehog. They still have probably more than 10% of their brains neocortex. In us, it's enormous.

And the neocortex affects all levels of the nervous system, including both of these major output systems of the endbrain, medial, and lateral forebrain bundles. And this is the scheme pretty similar to what I showed you before, with neocortex having not only a direct output to the brainstem and spinal cord, and that includes the upper brainstem, like the tectum, the hindbrain, and finally the spinal cord. But it also has-- just about every area of neocortex projects to the dorsal part of the corpus striatum, which has an output to the brainstem also, but it has a much larger output to the thalamus, the part of the thalamus that projects to the motor cortex. So the major output in higher mammals, especially, for striatum, the influence movement is through the cortex.

And it gets input from all over the cortex, too. And so it's doing something special that the neocortex needs in addition to what it can do with its direct outputs. And we think it has to do with implicit learning, reward learning, learning of skills. They're very highly developed in animals with large neocortex.

But now, in addition, neocortex talks to limbic system. And the connections are-- even though many more synapses are involved, they're parallel because limbic endbrain structures connect also to the thalami. I have another picture here to make it a little even more parallel, though it gets a little hairy in looking at it. It has a loopback through the ventral striatum, as well as the thalamus.

The thalamic connections go to neocortex, just like these did. But they are not as voluminous as for the dorsal striatum. But the ventral striatum is really part of-- it's right in front of the hypothalamus and basal forebrain, and highly connected with these structures that affect motivation and motion.

Now, what about other motor systems? First of all, remember that the neocortex controls movement independent of the pyramidal tract. Don't always just think of motor cortex when you think of cortical control of movement.

We have mentioned how the cortex projects to the midbrain tectum, and we'll talk more about that when we get to the visual system. The same is true of-- other major sensory regions of the posterior neocortex also project in the midbrain tectum, and deep in the midbrain, as well. In addition, besides the primary motor cortex, there are other motor cortical areas. And for those of you who did that reading in the textbook, you already know about that. They have slightly different functions.

But now what about the limbic system? It controls movement, too. And as we go into this hypothalamus, for example, and stimulate, we certainly get an animal change in its movements. In fact, we can get specific patterns of what looks like motivated behavior, fixed action patterns, and so forth, by stimulating there.

But we usually don't call that "motor system." We think we're affecting the urge to move, and not the movement control itself. But you see it's a little bit of-- it's just the way we choose to talk about it.

Now, in the files I put up on the web, I think it includes 23 to 25. I gave you the first half of that today. We're not going to make it clear through the handout you have today. So bring it back with you next time, and we'll probably have the second handout for you next time, also.

And last year, it took about three and a half classes to get through all of that, but we'll see if we can do it in three classes, discussing temporally patterned movements and rhythmic output. We'll describe some temporal patterns. We'll review some studies of locomotion a little bit.

And then we'll talk about circadian rhythms, and sleep, and dreaming, a little bit on rhythms today. We'll get to sleep and dreaming probably in the third class, but maybe next time we'll get started on that, also. One of the favorite topics of 9.01 students is that topic.

So first of all, we'll talk about the different types of explanations we have for explaining temporal patterning and movement, the straight-through processing concepts based on SR models, feedback circuitry, and spontaneous CNS activity. And then we'll go through a little model on control of the respiratory rhythm.

So how can you explain timing of movements and reflexes if you just have an SR model? Well, first of all, conduction time-- we can talk about the temporal pattern and the startle reflex just by talking about the time it takes for the input to conduct to various levels of the nervous system. But then we can also introduce this concept of chaining, that one reflex movement-- because the body moves, it will lead to another stimulus, and that stimulus then can lead to another reflex, and so forth.

So you could explain a temporal pattern as a chain of reflexes. And in fact, reflexologists were doing that for a long time. And in that context, we'll discuss a famous paper by Karl Lashley that he wrote in 1917, before he did the studies we talked about in the introductory lectures on memory in rats for mazes. He was thinking about this problem, and he wrote a paper called "The Problem of Serial Order in Behavior."

So the startle reflex, the temporal pattern-- when you get a startle--

[BANGING NOISE]

--a nice startle reflex from some of you-- the first thing that you did, and you might not have noted it, but it was an eye blink. That's the first thing that happens. Then you get other facial muscles contracting.

And then, it depends on how loud it is, but let's say it's really loud like a bomb, then you'll get neck flexion, arm flexion. And with very intense sound, actually the legs will flex. People go like that, and they might even fall.

Now, we can explain the timing of the movements in terms of conduction time, which is affected by the fiber size, synaptic delays, and temporal summation times. But for longer patterns of movement, we can't use such explanations. I am going to talk about the behavior of a fish, the stickleback, and its courtship pattern.

Tinbergen, 1951, did an analysis of these movements, analyzed them as a series, basically an SR series. He was really dealing with what we would probably call fixed action patterns, but it could be broken up into these series of movements, each with a specific stimulus and a response that led to the next stimulus. And then we'll talk about reflex swallowing, which I've mentioned before.

Now, in Tinbergen's study, he's dealing with movements by a pair of animals and not just one animal. The interesting thing about this movement, which is described in the next slide, is that if you interrupt one step, the sequence stops. So each step is a necessary stimulus for triggering the next step. Did I not have that here? Here it is.

So it starts when the female appears near the male and she's got a swollen belly. And that is the trigger for the male's zigzag dance. That dance makes the female approach the male, so that's her courtship response.

The male swims towards the nest. She responds by following. Her following him is necessary to get the next step, which is a special posture here he assumes at the entrance to the nest.

That posture causes her to enter the nest. And if she enters the nest, he makes this trembling movement with his snout or tail, which then makes him-- causes her to spawn, and then that causes him to fertilize the eggs. Now, if you interrupt that at any one point, the whole thing stops. So in that sense, we can think of it as an SR sequence, a chaining of SR movements.

Similar studies were done in the case of reflex deglutition, the swallowing reflex. It's a complicated movement. It involves about 20 muscles controlled by neurons from the midbrain to the spinal cord.

Now in this case, the pattern of contraction appears to be centrally programmed, the whole pattern. Actually, you can trigger-- if you have the right stimulus, you can have a steady stimulus, a continuous stimulus, and you will swallow repeatedly with a rhythm as long as you have that stimulus. Once I start talking about it, I'm suddenly aware that I'm swallowing.

That pattern isn't changed by eliminating proprioceptive feedback from the movements. You can literally cut out some of the muscles-- they don't do this in humans, of course-- to eliminate some of the feedback from the intervening movements. But the sequence will continue just without some of the elements if you do that.

So it's normally triggered by this stimulation in the back of the throat, back of the tongue. You have a little row of papillae there, the circumvallate papillae. And if you slide a little probe, a stick, or your finger, as soon as it gets back beyond that spot, you will start to gag. You'll try to swallow.

But I think it's closer to what we call a fixed action pattern because there is an endogenous input that builds up over time. So it's a motivated behavior. It's just that the motivation to swallow-- its major input is from the back of the tongue, but it also has a spontaneous contribution that builds up in the nervous system and that lowers the threshold. So finally, you will tend to swallow with the slightest stimulus, just moving your tongue during talking, for example, and you will swallow, which of course, has a function-- to keep the throat lubricated and so forth.

Just mentioned now Lashley's argument in 1917 in "The Problem of Serial Order in Behavior." He was very interested in hand movements and how do we do that. How do we control that sequence or any sequence of the fingers?

And he realized, by filming a musician and noting how fast his fingers move, that he can be doing six movements in a second with a specific order of successive finger movements that he's learned. And he realized, Lashley realized, that the succession of movements is too quick even for reaction time. There could not be a chain of reflexes explaining that because that would take too long. So there has to be a central generator, central program generator.

And when Lashley wrote this, he didn't have the concepts from ethology yet and he didn't have the concepts from CNS physiology that would help him explain it, but he knew just from the behavioral observations that we would have to have what he knew about reflex timing and reflexes from Sherrington's work and others, that there would have to be some kind of central generation. So how could you do that? What's the CNS doing?

Well, you could have self re-exciting loops of activity within little circuits of neurons, which could lead to regular bursts of action potentials. And I have that here in my little picture. This has to make some pretty big assumptions, simplifying assumptions, about how neurons are working.

But let's say this neuron-- this one in the center there, the darkened neuron-- requires summation to fire. So if you have a steady input, the neuron won't fire, but the membrane will be depolarized. And if a pulse of input arrives in another pathway, then an action potential will be fired.

And let's say it fires a burst of action potentials when that happens. And that's enough to trigger an action potential in this interneuron, which has an axon that goes back through another neuron, or directly, to this neuron. Now, if that's also excitatory, the result will be if the neuron, the synapses, are sensitive enough, this will be the result.

If you have a steady input, one pulse of activity here will lead to a self re-exciting circuit, and you'll have a series of pulses coming out. And the timing will depend on the time delay in the feedback. So that's one way to do it-- positive feedback.

You can also have a negative feedback like a homeostatic mechanism, where as you probably know, the response will oscillate around some set point. The homeostatic mechanism is a governor of some sort, or it's like a thermostat that controls your furnace. And of course, the furnace comes on, heat goes up, the thing goes off because it gets negative feedback, and so forth.

We have the problem of how you get more complex patterns other than such just a rhythmic pattern, but we know that could combine more than one such circuit and you could get a pattern of any arbitrary complexity, depending on how you combine them. Then, of course, we have the problem of how you stop the rhythm. You're going to have to inhibit those cells at some point in order to stop the thing because it's a self re-exciting circuit.

Now again, these are not the only two methods-- the straight-through processing feedback circuitry. You also have spontaneous CNS activity, and this means cells that are generating their own rhythmic changes in potential. The first really good studies of this that I've seen were by Felix Strumwasser who was studying the sea slug, the Aplysia, also became famous later for studies of learning, simple conditioning procedures, in Eric Kandel's lab.

But before that, Strumwasser was studying large abdominal ganglion neurons in the Aplysia. And there was a secretory neuron that he could identify from animal to animal. He could keep finding the same neuron, which is why he liked it.

And he found one neuron that generated a rhythmic potential change with a period of about 40 seconds. So that means if you look at the upper curve, this is the membrane potential. And as the membrane potential, it becomes-- depolarization is up, and we see it's generating action potentials as the membrane becomes more depolarized.

Then it becomes less polarized. It stops generating the action potentials, and that keeps happening. And the period means the time from one peak to the next here, and that was about 40 seconds.

Now, if he blocked the action potentials by applying the poison tetrodotoxin, he could block the action potentials, but he found that the membrane potential kept cycling, as you see there in the bottom curve. If he blocked the sodium pump, however, with a different chemical, Ouabain here, then he didn't get the potential changes any more. The cell-- I guess he must have been pretty excited about these studies because to stay there more than 24 hours is-- well, I guess some of the physiologists in this building might do that occasionally, but they work in teams.

Well, maybe Strumwasser had a team, too, but he found that, in fact, these cells could change with a 24-hour rhythm, too, or something close to it. If it's a rhythm in the vicinity of 24 hours, if the period is within that vicinity, we call it a "circadian rhythm," "circa," approximately, about, "dian," day, about a day in length. And that rhythm he could entrain, he could synchronize with the light cycle, he could affect by exposing the animal to light.

Well, we know that many animals have what we call the biological clock, that we know depends on neurons like this, with firing with a periodic change of about 24 hours. You can record their activity rhythms, and we'll review some of that later. If you're recording an activity continuously with mice, so you get the actual period, and then you give them heavy water-- D2O-- this must have been done at MIT-- you give them heavy water, and their free-running circadian rhythm slows down.

And how much it slows down depends on the proportion of the heavy water in their drinking water, D2O instead of H2O. So we'll come back to that topic a little later. Since that time now, they've discovered specific genes that must be causing proteins, membrane proteins, that in fact generate these rhythms. We know less about genes controlling shorter-term rhythmic changes in membrane.

So let's go through this little model of the respiratory cycle. Here's the initial facts we need to start talking about this, and we're certainly not going to go through to the most complicated recent studies of respiratory rhythm. I just want to give you some basic things that'll help you understand how this has been studied.

First of all, we know that we have stretch receptors in the lungs. So if you expand the lungs, you're causing input to go into the nervous system by way of the vagus nerve. The vagus nerve carries sensory fibers as well as motor.

Second of all, we know if you electrically stimulate the hindbrain, you find some areas where you make the animal breathe in. It'll just breathe in and stop. You have other areas if you stimulate electrically, he will breathe out, he will expire. So he will inspire and he will expire, using "expire" in its literal meaning here.

And if you make lesions, you find that there is a dominance of the inspiratory center. Most lesions will interrupt breathing. Well, the animal will die in a state of inspiration. So let's go through the model.

To start with, very simple model-- we have stretch-- reset the lungs here, when they inflate due to movement of the diaphragm here, give rise to input. This comes through the vagus nerve. That stimulates neurons in the hindbrain, then, that stimulate what we'll call the expiratory center.

We should really start with this group of neurons, the inspiratory center. It's dominant and tonically active. That means that without any inputs at all, it's firing, it's activating cells at the C4 level, and leading to contraction through the phrenic nerve here of the diaphragm. So those are active all the time.

So that's all that's happening-- the animal inspires. When he inspires, the lungs inflate. These stretch receptors are activated. These neurons then are turned on, and through neurons here in the area we'll call the "expiratory center" because of its result, it inhibits the neurons of the inspiratory center, and turns these neurons off, then, and the diaphragm will relax.

So with a very simple feedback control from the lungs, we can get a respiratory rhythm. That doesn't deal with any of the other effects that we know about breathing, but with that model, it's capable of generating respiratory rhythm. So how do we test it?

Well, cut the vagus branch that goes to the lungs, and we find the rhythm is altered, but it persists. So we know that model doesn't completely explain it. We're just doing this, and we still get a rhythm, but it's not quite the same. It looks different.

Well, here's another model that doesn't depend on the input. This is a model to explain what might be happening without any input from the lungs. So here, with a little feedback circuit within the brain, here's our inspiratory center, tonically active same as before, causing contraction of the diaphragm, but now we have collaterals of these neurons that are exciting neurons in this center in the hindbrain, which then provides the inhibitory feedback here.

So depending on the timing of that loop, the activity of these neurons will cycle. So these are what we now know from lesion effects. We know that inspiration seems to be the dominant response. So we think those neurons are always active.

But the lesions also indicate that there's a more rostral center in addition to the one that's in the hindbrain which promotes expiring, breathing out. And that's been called the pneumotaxic center. It's in the midbrain. You can breathe without it, but you drastically affect breathing when you make lesions.

So this and other information they've gathered led to a little more complex model, still, of course, much simpler, probably, what we actually have. You can be sure that anything controlling something so vital is going to have some redundant representation. This is still at the simple level.

So let's start here. Here's the tonically active inspiratory center neurons, affecting, through the phrenic nerve, the diaphragm. Notice that those go out at C4.

That means if a person has a spinal transection below C4, he will keep breathing. If he has a high break and he interrupts this pathway, he won't be able to breathe. So they call that "high break," "the hangman's break," because when someone is hung, their neck usually breaks very high, and he doesn't breathe.

Sorry to be so morbid, but it's important in clinical neurology to know that these neurons controlling the diaphragm go up very high at C4. We think of the diaphragm being way down here. That's actually controlled from much higher up in the cervical cord.

So now we have the feedback going to the midbrain here, just like in the little model we had before, inhibiting then through this group of neurons, these neurons. That gives us a lot of timing delay for that pathway to the membrane. And now, we have modulation from inputs coming from the periphery.

This is the one we talked about before-- stretch receptors in the lungs coming through the vagus nerve, the 10th cranial nerve to interneurons, then, that are exciting these neurons and the expiratory center. But we know another influence on breathing. This is the carotid body here at the branch of the carotid artery. It's responding to CO_2 levels in the blood.

So with more CO_2 in the blood, these neurons respond, fire action potentials. That nerve is the ninth cranial nerve, glossopharyngeal nerve, which comes in then through the ninth cranial nerve, and excites neurons that excite neurons in the inspiratory center. So that model then can explain more of the effects of breathing.

We call that expiratory center here-- it's sometimes called an accumulator of inspiratory activity because the longer this goes on, the more input it gets. And because of temporal summation, it will build up its level of excitation. And then it will finally turn off the neurons of the inspiratory center.

We know that the CO_2 effects speed up the inspiratory rhythm. And we have that happening. That's what would happen in a model like this. If we have this connection that excites these neurons, it would basically speed up that cycling.

It explains more of the effects of lesions than we could with the simpler models. For example, if you oblate that pneumotaxic center in the midbrain, the breathing cycle becomes dependent on the input from the lungs via the vagus nerve. So that's this lesion. You eliminate that pathway, you can still breathe, but now you have to have the input coming from the lungs.

Let's talk a little bit about locomotion studies. These are the terms I want to try to get across-- the notion of a command neuron. And these are neurons generally in invertebrate animals, single neurons which, when stimulated, lead to a movement sequence, a fixed action pattern of some sort.

And we'll talk about pattern generation of various sorts. We've already talked about that a little bit. These are terms used in studies of locomotion, interlimb phase and sensory modulation of the movement. And these four short articles on locomotor patterns-- have you ever seen such articles? Maybe they're not in your readers, and I will have to-- I can explain a little bit now, and we'll see if we can get those out.

First of all, the notion of a command neuron-- you can find specific neurons in the crayfish, for example, that when stimulated lead to this tail flip response and escape response. There are similar neurons in the goldfish, actually. There aren't many vertebrates that have single neurons that will lead to a whole fixed action path, but there are the large Mauthner cells in goldfish, which when stimulated will lead to the tail movement that occurs in escape responses. So that's the notion of the command neuron.

Pattern generation's been studied in a number of animals. This is a summary of some data on the medicinal leech, which has been used in a few labs because of the very nice rhythmic output generating the movements of locomotion. And they've worked out for specific neurons in an anterior and a posterior ganglion and other parts of the nervous system, that if they're connected in the specific way, they can explain the whole pattern, explain the firing of muscles.

And this has been done for the flight behavior of the locust, for example, as well as some locomotor patterns in other animals. And the models have been tested extensively by single-unit recording. So when they draw these diagrams of specific neurons hooked up in a certain way, it's not just theory. They do have the data. There are some anatomical studies and mostly physiological work that shows these connections.

Other studies have been done on the turtle. And they find, for example, that without the brain connected at all-- so with spinal transection-- you will get specific locomotor movements, which if they occur at different rates, will change the relative coordination in the circuit. So here, they're plotting that period of the movement against the latency between the movement of one limb and another, the interlimb phase.

And there, they're just showing some of the recordings for these quantitative studies. They're recording the output. And those require specific connections within the pattern generators.

There are some interesting studies of modulation during movement-- studies of dogfish that have been spinalized, for example. This particular study is a spinal dogfish which is also curarized, so he's not actually moving at all. He's paralyzed, but even in such a paralyzed animal, you still get the motor neurons firing.

It's just that because his muscles can't move, you can't get any feedback by any reflex pathway. So there's no feedback. Nothing's changing in the periphery. That's-- way they know this is-- but what they're interested in is what the sensory input does.

And so they impose a movement. For example, here's the movement, and you see the rhythmic changes in the movement. If they just slow it down by holding on with the tail and moving it more slowly, they changed the firing of the motor neurons.

I would like to get you those articles so you can read this yourself. There's a number of studies of locomotion like that. It's easiest to do it in these lower animals, though there's a number of interesting studies of vertebrates, also.

So the command neuron-- in higher animals, we usually talk about a command tract because it's always more than one neuron involved, even in the goldfish where there's Mauthner cells, there's a few of them. But they come closest to being command neurons. We talk about the central pattern generator, which is usually an internal network, though it could be a single neuron. Usually the ones that have been studied are a small network of neurons.

We talked about interlimb phasing. We had that one study where you change the relation of one limb to another, but in fact, the forelimbs have to be coordinated with the hind limbs, as well as the right hind limb with the left hind limb, and so forth. And they're coordinated in different ways to get different gaits, like walking, trotting, galloping.

Where is that done? It's done at the spinal level. So when the rate changes, the animal will change the coordination between different parts of the spinal cord. And that does not depend on brain.

They talk about coordinating neurons, which are really intersegmental neurons going from one level of the spinal cord to another that interconnect these central pattern generators. Now, a lot of that is postulated based on the behavioral studies, but there are some studies where they actually make cuts between different levels, and so they can disrupt that to show that it depends on connections within the cord and not just peripheral feedback.

And then you have these changes in reflex during the movement. So in different stages of a cyclic movement, the animal can respond differently to sensory input. Obviously, that's very important to coordinate your movement when you're walking. I only gave a very simple example, the dogfish, but there are also many studies of the cat that have been done

We only have a few more minutes. I'll just mentioned here the deafferentation studies of locomotion. What is deafferentation? If you deafferent the arm, you would cut all the sensory input from the arm. Then you can study the movement of the arm.

There have been studies of fish where they cut all the dorsal roots-- very difficult to do that. But if you cause such a drastic deafferentation in a fish, you still get locomotor patterns, and even in spinalized fish. If you do it in the frog and cut all the dorsal roots so there's no sensory input, he doesn't move. But if you give just a little bit, like if you leave one dorsal root so the spinal cord is getting some input, then you will get the locomotor movements. So it's unlikely that very specific patterns of inputs are needed in order to get the movements.

In spinal cats-- I mentioned before in class the rhythmic stepping you can get in a cat. He's had the spinal cord transected and he's had time to recover his reflexes. So if you put the animal on a treadmill, and provide some stimulation-- they usually do it with perianal stimulation-- it just happens to be particularly effective-- they can get rhythmic stepping even though he's a spinal animal.

And I think I also mentioned the scratch reflex in a spinal cat when you put, say, a large paper clip on his back. A cat, a normal cat, will reach up with his hind limb and scratch that off. Well, so will a spinal animal if he's recovered for a while from the [? diathesis ?] effects.

There are also studies of monkeys where they deafferent an arm. And basically, he'll let that arm hang limp and he'll use his other arm unless you tie down the good arm. Then he will start using it.

There are a number of studies like that that have been done in monkeys. They were rather controversial, about whether monkeys should be used for such things. But they did provide clinicians with some data that was important for development of rehabilitation procedures of people that have had damage to the inputs.

There's also some interesting studies of grooming in mice. If you have mice, they show very specific patterns of grooming movements. And slightly different species of these mice, different strains of mice will show slightly different patterns. It's under genetic control.

And we know that it mostly depends on central pattern generation and not-- they don't need the feedback. For example, in a mouse, if you generate a specific grooming sequence that involves, for example, scratching at certain areas, movement over his nose, licking of his foot, and then scratching his face as part of their grooming, you can get the same thing if you remove the limb. Well, how would you get that?

Well, he will just move his shoulder, and he will lick an absent limb. He'll show the movement pattern. It's a fixed action pattern, and even without the sensory feedback, he will go through that movement, even if part of his body is missing.

So we know it's a fixed action pattern with central pattern generators in the brain controlling it. So in general, we know that reflexes aren't critical to much pattern generation and motor control, but they're very important modulators of the movements. So just take a look at these basic organizing concepts for thinking about circuits in the nervous system. And we'll start out there next time.