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GERALD SCHNEIDER: OK. Now, we discussed motor system at spinal level, a few basic things dealing with spinal reflexes, that applies also to hindbrain. The first-- a first blush at the motor, looking at higher control is just to continue using the reflex model and speak of motor control in terms of a hierarchy of reflexes.

In other words, you have reflexes involving various length of pathways reaching finally the neocortex. The idea is that information from one of the somatic systems reaches a primary sensory area of neocortex. And from there it goes to association areas. And from there it finally will reach motor cortex and that way influence movement.

And first of all, information does follow such pathways. OK. Anatomical studies and physiological studies that demonstrate that. There are such pathways. So isn't that then the adequate way to think about it? And you'll see it written about it this way in textbooks and so forth.

But there's a number of problems with it. One is that it's an inadequate theory, as one is that neocortical areas have many outputs other than these transportable pathways that reach the motor cortex. They can control movements without any motor cortex. OK.

For example, visual cortex doesn't just reject the areas adjacent to it. And there are some very nice transcortical pathways and they are of major importance in our vision. But it also projects directly to subcortical systems. It projects to detect them, for example, as do other visual areas. OK. And they can affect movement directly through their pathway to the midbrain without going to motor cortex.

And also we have this issue of endogenous control. You can have movement that originates from activity generated within the nervous system, not involving specific inputs. Now, in clinical neurology, frequently, a chapter on the motor system will begin by defining the pyramidal system and extrapyramidal systems. And in fact, a view that you will still sometimes see taught is that the pyramidal system is our system for voluntary motor control. Extrapyramidal system for involuntary movement.

You will see in the film, that is very, very unlikely. But you don't have-- the film is about monkey work, even with human work you can have people that have had sections of pyramidal tract, they lack the pyramidal system for motor control. And yet, they certainly have voluntary movement. It may not be completely normal. They have motor defects. And we'll see that for the monkeys in the film.

But it's this initial consideration that it has to do with voluntary and involuntary is certainly not the case. But their anatomical considerations that also show that this is unlikely, at least some of the major extrapyramidal systems, the two major ones usually discussed in medical school textbooks are the cerebellar system and corpus striatum.

In fact, their major outputs in higher mammals is to the pyramidal system. I pointed out here how that works. Cerebellum projects to these more anterior parts of the ventral nucleus of the thalamus, the VL and the VA. Cerebellum goes mainly to VL, which then projects to motor cortex.

Sorry. Did I-- Not reading what I'm reading here. Cerebellum goes mainly to VL Corpus striatum to VA. OK But they both project to both those areas and they go to the motor cortex. OK. And which then is the major contributor, at least 40%, of the pyramidal tract comes from the motor cortex.

And these neocortical areas, even the motor cortex, have many other projections other than to the pyramidal tract. For example, almost the entire neocortex projects to the corpus striatum, which has outputs separate from those that go back to the thalamus and motor cortex.

So the way we're going to do this is we're going to follow Lawrence and Kuypers and their classic work which was begun with neuroanatomical studies of descending pathways and the organization of spinal cord motor neurons. So we'll look at the spinal cord at one of the enlargements and the organization of motor neurons. And then we'll talk about how the higher systems project to that.

So these are their two pictures. I have an enlargement of this one. So I want you to understand what this is showing. At the top there, you have-- these are all cross-sections of the spinal cord at the lumbar enlargement, controlling the lower limb muscles.

So first, look at the bottom here. They're showing motor neurons. They're located all across, from medial to lateral here. We'll call this dorsolateral here. We'll just call it lateral. This is ventromedial. We'll call it medial. Now, those motor neurons are arranged in an orderly way, so that the most distal muscles are represented laterally.

So if you wanted to find a neuron controlling the toe, you would look way out here. If you wanted to find a motor neuron controlling, say, the muscles along the back, you would look in the most medial area, OK here. And in between you would find motor neurons controlling the hip, similarly now for the cervical enlargement.

The lateral motor neurons would be controlling our fingers, and then the arms as you move medially, and then the girdle muscles, the shoulder. And then most, medially, the axial muscles, keeping us upright, controlling our balance and posture.

So what connects to those? Well, first of all, the interneuronal pool of neurons that are not motor neurons, but they connect to motor neurons. They also connect in an orderly way. So the lateral or dorsal lateral part here connect the lateral motor neurons. The medial ones connect the medial.

There's one other point about that, the medial interneurons tend to have axons that go to both sides, but not the lateral ones. And that will see a consistent pattern here, that those medial ones tend to be more bilateral in their connections. And we'll see that's because they're controlling whole body movements, movements of large part of the body.

So then the next step for Lawrence and Kuypers was to say, OK, what projects to those interneurons? They knew that major contributors were coming from the brain, so they looked at the corticospinal tract, and they saw-- these were degeneration studies that are looking at the pattern of projections shown by degenerating axons after lesion of motor cortex or a section of the pyramidal tract.

And then they see that it goes to the whole thing here. It goes laterally. It goes medially, and a little bit to the other side. But when it goes to the other side, it goes only to that ventromedial area, almost entirely. OK.

So now, other than the pyramidal tract, where do the other descending connections that come from the brainstem go? They saw that they were nicely divided into two types of connections. The red nucleus, the rubrospinal tract connects to the more lateral, interneuronal pool, connecting them to the [? left, ?] which then would be influencing the lateral motor neurons. And that fits functional studies that show that the red nucleus is particularly important in limb control, limb and hand control.

Whereas, the pathways that come from the ventromedial hindbrain, and they tend to travel in the ventral and [? med ?] ventral columns of the cord, the ventral funiculus. They project to that ventromedial area, controlling axial muscles. And again, axons coming here down the left side will also tend to crossover and go to the other side.

Now what are those pathways? Vestibulospinal, tectospinal, cerebellospinal, the fastigospinal, sometimes we call it because it comes from the fastigial nucleus, the most medial nucleus in the cerebellum. And also from the medial, reticular formation, large neurons in the reticular formation which we know are concerned with various fixed action patterns and so forth, control off-- often concerned with whole body movements. OK. I just list them there for you.

So now, this just shows those same pathways, instead of on a cross section, there I put them on a picture of the monkey brain and I show here the motor cortex with the areas representing the distal muscles in the dark lines. And then I also show the other-- I show that both systems are going throughout the cord.

If you're just looking at motor neurons representing hands, they would go to the upper enlargement, the feet, the lower enlargement. But basically, the neocortex goes to all levels and to all parts of that system, medial and lateral. Now, if we go-- Here's the red nucleus and I show its cross projection here, you see where it travels laterally in the hindbrain. And here it's in the longitudinal view, it's crossing over. It projects to the lateral hindbrain. And then it projects mainly, laterally, in the cord at the enlargements.

The medial pathways travel medially in the cord and they tend to distribute bilaterally. Here they are going through the hindbrain. Here's the origin of the tectospinal tract, here I'm showing the way that the fastigospinal tract originates, descends to all levels of the cord, now not just the enlargements, but all levels and tends to terminate in that medial part of the cord.

This is just to show you that my pictures are a lot better than appears in the textbook. These are very difficult to understand. If you study it for a while, you might be able to make it out and relate it to what I've shown you, showing here the corticospinal tract, traveling laterally here, the lateral funigulus of the cord, and trying to depict various levels.

So now, we're going to look at this film. And this is what we're going to see. First, they did [? pyramidotomies. ?] They sectioned the pyramidal tract. Here's the first lesion on that anatomical diagram. They cut the pyramidal tract here in the hindbrain. So here in this picture, that's where they cut it. They cut it bilaterally.

So we'll see a monkey then with no pyramidal tract. And we'll see he has a lot of voluntary movement. We'll see what he lacks. He doesn't have single digit control. He loses some-- he loses some manual dexterity, also loses speed.

Then lesion two, they made a bilateral cut in the hindbrain sectioning all those medial pathways. And they're going right there through the pyramidal tract, but that's already degenerating. And we'll see the histological sections demonstrating that. And I'll explain that when we see it. So here on this view, there is where they're cutting it.

If they do that lesion unilaterally, they didn't get much effect, but remember that system tends to be bilateral in its connections, so you really have to cut it on both sides. The most impaired monkey you'll see in the film is one with that the pyramidal tract lesion first and then this, the medial hindbrain pathways section. Because he can't right himself, not for 40 days anyway. He finally recovers enough, the sensory control of righting that he can right himself again to relax those vestibular pathways.

And then finally, in some of the [? pyramidotomized ?] monkeys, they tried just doing the lateral pathways, but only on one side. And then we'll compare the two hands. OK. And you'll see how they affect, the hand movements now are mainly under control of that system.

So could you hit that button and see if we can get the video? Oh, good. OK. So first, just a normal animal, and you'll see how they're testing him. They have him strapped to the chair so he can't run around and they're presenting little pieces of apple here. You see the normal animal, very dexterous, moves very fast, can grab just about as well as we could the pieces of apple.

And on this little board, they make the hole smaller and smaller, so he has to be more dexterous to get the apple out of the tiny holes. And when he gets so excited, he has a little problem, but he can do it. Monkeys have hands similar to ours, they're very dexterous. They also have the opposing thumb, although not nearly as good as ours.

In order to prevent the animal from using both hands, they often have to hold or hold one hand down. The monkeys that just get their dry food will always want this fruit. So you don't have to deprive them much to do this. They're like hamsters with sunflower seeds.

So now in these little holes, he can't get it out unless he can use one digit. Yes, they have some independent control of the one digit. And that's what they're showing here, just like a person, just like a person, they're pretty good at that.

OK, so now they do the pyramidal tract lesion. And we're going to see him, this first monkey, five months later after that bilateral section at the hindbrain level of the pyramidal tract. And on these histological sections, if they're standing for myelin, see the one at the bottom, it's white at the bottom, because the pyramidal tract has lost its myelin.

This section, this section, there you see some torn tissue, but you also see these dark areas. That's an accumulation of glial cells. It's called gliosis. That happens with lesions. The glial cells are phagocytic. They eat up the dead tissue, and they accumulate and remain in these lesions, at least some of them remain.

OK, so now this is five months. He's recovered pretty well. And pay attention to how he's using the hands. He's not quite as fast, but you will see that he mostly [? bends ?] all his fingers together, like a baby grasping something. A baby, a newborn human in the first few months of life, doesn't have pyramidal tract connections yet. So he moves his hand like this. Or she's.

And you'll see that's pretty consistent here. They use the whole hand together. They have pretty good control. They tend to flex a little more than usual. They have a flexor bias, so they have to move the board a little closer. But he can definitely do it.

Now, if you look sooner after the lesion, you'll see a greater impairment because of the diaschisis effects of the removal of all those [? accents ?] to the cord. And later when they did the histology, you saw the demylinization of the pyramidal tract. It appeared to be a complete lesion. And here you see the gliosis and the pyramidal tract.

Here you see the torn tissue. So with enough sections you can reconstruct the pathway of the knife. Difficult surgery to do, because if you don't do it right in this part of the brain, the animal will lose vital functions. Well first of all, you see that he's actually able to climb. His reflexes are slowed a bit, but he is able to climb, grasp his cage bars and so forth. Shows a lot of voluntary movement.

Here's the slow placing reflexes. You touch his chin, this should be the most, this is the greatest impairment you'll see just after pyramidal tract section, now just corticospinal tract axons. Their lesions were pretty good. This animal died earlier, but you do see the course of the knife here. It has not had time to accumulate too many of the glia.

Now if they spare some of the pyramidal tract, you will get some sparing of the individual digit control. Many pathways in the brain, in order to get a complete deficit, you pretty much have to get the entire thing. So neurologists who have not seen this study and have not seen humans, of course, very rare will have a pyramidal tract section like this. They might be surprised that their textbooks are not correct about voluntary movement.

But notice here how he can climb. Sorry. Oh, yes, they can climb. Once they-- pretty much spinal mechanisms, but they do learn of course details of cages compared with trees. I think this animal, when they may feed him, because he has difficulty reaching, well, he tries to get the food like a dog, just directly with his mouth.

They are just doing this to demonstrate that he has a lot of movement control left. And here you see him, he's a little reluctant to reach. He wants to just reach out with his mouth and grab it because after just such a short time after the lesion, he doesn't have good control of his hands. OK but we know that not, just give him a little time and that will come back

Now, before this study was done, I should point out that clinical neurologists where a little bit in the dark about what these lesions would do. And so it was a very important study for human clinic. OK, so now remember, these animals now you'll see all had the pyramidotomy first.

And there's the demylinization of the pyramidal tract, the gliosis of the pyramidal tract. But here they've shown you with, they've drawn onto the section here, the reconstructed path of the knife that so that in addition to the pyramidal tract section, now they move the knife through the brainstem so it cut all the pathways that traveled medially in the hindbrain.

All right. So this will be the most impaired animal you'll see. I know it's a little disturbing to some of you to see the animal that can't get up. But it didn't last forever. But he's now with no pyramidal tract and without the medial pathways. He does not have good axial control. So he doesn't have his righting responses. It was only with recovery from diaschisis that he was able then to recover some sensory control, spinal control of righting and he was able to get up after 40 days.

And you'll see in a minute here that these animals that can be so entirely, almost helpless in these situations, actually have quite a bit of control. For one thing, they have good head control. This is now a little later, five months after pyramidotomy, one month after the medial reticular formation lesion.

It's a different animal. They're showing the lesion here, showing the gliosis in the pyramidal tract, and there you can see where the knife passed the medial lesion. They're not showing the midbrain, so we can't see the red nucleus, but they did look at that and they know they spared the lateral brain stem pathways that come from the red nucleus. They'll show those sections when they, in the cases where they did that lesion.

They cut off a lot of the section, the cerebellum would be huge here in the monkey. These are at-- this one is at the cerebellar level. And there you see a little bit of cerebellum at the top there, that's cerebellar granule cells.

OK. Now, they're starting out with showing the animal in the reaching situation. Now he's strapped to the chair. They have to strap him to the chair because he doesn't have good balance, so they hold him like that. And now he's holding his arms, usually flexed, but in fact he can grasp the food.

As long as they allow him to be a little bit hyper flexed, he can grasp the food. He does it with whole hand movements. He's still pretty slow because he hasn't recovered enough from the lesion yet. But this is just a month later. And you see, he's recovered a little bit. He's now better at grasping the apple.

And we'll see later that movement is more dependent on that pathway from the midbrain, from the red nucleus. Again, they're holding one hand down so he can just use one at a time. They test the two hands separately.

When they offer him-- when he has to use one digit to get the apple out of the small holes, he can't do it. Shows that he's got pretty vigorous responses of his limbs in the tests of placing. Now, this is a different monkey, again with the pyramidal tract lesion, and then two months after the medial hindbrain reticular formation. So this is just a replication of that experiment.

You see the demyelination in the gliosis and the pyramidal tract and then the reconstruction of-- although you see a little bit of the lesion here, the [INAUDIBLE] areas, you need to see all the sections. OK. So this animal, when he walks, has very poor control of his direction.

They're just making him-- and there, he falls over and you see, he wasn't able to right himself very rapidly. Somatosensory righting responses haven't come back much. Of course, now, if this were a normal monkey, he would just pick it up. But without the pyramidal tract, he is a little more like a dog in the way he responds, very unsteady with the lack of a fastigospinal, and without the tectospinal he's also not very good at orienting his head and eyes.

His eye movements, by the way, are actually pretty normal, if you see him in the chair and study them. And that's because has has the connections to the oculomotor nuclei intact. They cut those pathways further down the hindbrain.

OK. So now this will be the first of the third type of animal where they have pyramidotomy first, and then this is just a short-- a few days, five days after the lesion of the lateral hindbrain. You see it right here. He's missing the pyramidal tract. This is working less and less. OK, there you see it. See the gliosis.

And the question is now, did they cut the rubrospinal tract. If you look up here, there's some big neurons in the red nucleus there. And we can't see any there in the red nucleus in the midbrain. This is midbrain level. That's the cerebral peduncle down there.

OK. So it looks like a good lesion even though it was small, it seemed to have severed the rubrospinal tract in the hindbrain. Now they're going to test the two hands separately. You see the left hand, he's pretty good. And he can reach. He's got some control of his shoulders. But very, very poor control, almost no control now left of his most distal muscles, there with the left hand.

If he learns later to engage his whole body in doing it, and then sometimes he can get spinal mechanisms of whole body control activated and he gets a little bit better control of that. OK, so we'll see him one and then two months after the right lateral pontine lesion, so the same lesion.

The hand that's not affected by the section of the descending lateral pathway, then here's the side that is affected. And again, if they let him engage his whole arm, he can sometimes do it. He's learned a little bit about that. But if he doesn't get his whole body doing it, he can't. He doesn't have good individual control of the hand at all. So much worse than just the medial pathway, sorry, just the pyramidal tract. It's added a considerable amount of deficiency to the control of the hand.

And then you'll see that something quite remarkable here in a minute. Poor individual control when they're getting to use that limb by itself, here they're just showing that it doesn't depend on his posture. There are some neurological deficits where you change the posture, they might do a lot better. But you'll see he is about the same in this posture.

He can control the arm a little bit from the shoulder, but that's about it unless he can make his scooping movement with his whole body. And they tried very hard to get them to recover. And they did get a little bit. It was important for the human studies to know just how far can that recovery go, you know, and if there's anything they could do to promote it.

And now you will see some other responses where he's now able to use whole body movements more. And you'll see, it's much harder now to tell which is the limb affected by that lesion. Especially here, he's using both hands. He's grasping the cage. The same hand that could not grasp the apple pieces is grasping the cage. Why?

Because when we think of the word paralysis, it's sometimes very specific to the type of movement. OK. He cannot use the hand in one situation, but in climbing, fixed action patterns governed by hindbrain and spinal cord, he can do quite well. OK. So that's an important point. This is the very same animal. Very hard to tell which is the defective hand. So this is now a similar, a replication of that experiment.

In this case though, the lesion of the hindbrain, it looks larger here, but in fact, they missed some of the rubrospinal tract because you see some large neurons here in the red nucleus. So if I'm right, I think this animal shows more sparing. That was why it's always important when you do such studies to do careful histology and do your best to reconstruct exactly what you did in the surgery. It's not always possible to control it perfectly. And also there's a little bit of variation from animal to animal and exactly how those pathways travel.

You see the central gray there, several peduncles down here. And this would-- it's certainly deficient but more control than the other animals, just that the sparing of a small part of that pathway. And that's why in human cases, a tumor or something that's gradually destroying more and more of a pathway, sometimes you will not see the defect until it's almost completely destroyed, a pathway.

OK. Now, here they're making the lesion further down, so now they're getting the lateral pathway. In the medullary region, it's a little easier to get all of it. Here You see in-- this is medulla oblongata, the [? qual- ?] part of the hindbrain. And you see the lesion there, an animal that already had the pyramidal tract.

And here's the red nucleus with neurons on this side and not on this side. These are oculomotor nuclei here. There's the central gray. There's the aqueduct of Sylvius going through the midbrain. Here's the larger ventricle and the fourth ventricle and the hindbrain. The [? qual ?] hindbrain is looking more like spinal cord, but you can still see the widened ventricle there. Here you're almost at the beginning of the spinal cord.

I think we'll look at this one, and then we won't look it anymore because of the time. They do some controlled experiments where they look to just make sure they're not getting some of these effects because of somatosensory effects, they could be. It was important to figure that out, that these were really motor control effects and not due to a sensation.

So again, with a pretty complete lesion of the rubrospinal tract, he's almost completely unable to move his limbs. We'll have to try to see if we can get that working again. It's still on video. Could you hit that-- There we are.

So the result is that we they were able to separate two systems, one for control of axial muscles and whole body movements. The other for control of distal muscles and fractionated movements, not just control of the distal muscles but the ability to move individual digits, something that we don't see in humans until they've developed. And we see the same in monkeys, until there's a maturation of the connections between neocortex and motor neurons in the spinal enlargements.

And this just summarizes for you what you saw in the film, the effects are [? pyramidotomy, ?] the medial pathway lesion and the lateral hindbrain. Now, just a few more things on motor control. If you look at a human who's lost control of his movements because of severance of descending pathways, he might have spinal reflexes.

In fact, the brain areas in the motor cortex will still be active if he's wanting to move. So if you ask him, try to move your hand. Nothing. His hand doesn't move. But in the imaging, you'll see a hand area become active. And these are functional imaging studies showing that. This was a study just a couple of years ago.

Now does this help us understand other systems? Well, if you look at the cerebellum, you do see a related organization. There's many aspects of cerebellum here we're not talking about, but they're definitely medial and lateral systems. And the hemispheres, which are huge in humans, are definitely more concerned with distal muscle control. They're concerned with other things too, but it's only the most medial part of the cerebellum, which is also the most ancient part.

Remember, the cerebellum developed, seems to have evolved out of the vestibular system. OK. And the part, the medial and [INAUDIBLE] cerebellum that's connected to vestibular system, it affects spinal cord through the vestibulospinal tract and also connections to the reticular formation.

And it correspondingly to what we just saw, it coordinates axial muscles, whole body movements. The lateral cerebellum, and I mention here, its outputs. It has an odd name. I don't require you to learn it here, but it projects forward to the opposite hemisphere. And also that pathway connects to the red nucleus. Then it goes to primarily the [INAUDIBLE] the thalamus, which projects the motor cortex, and very important for coordinating the timing of neocortical control movements.

If we get a lesion, we can affect those things. For example, a lesion of the hemispheres that affect hand control or hand and arm control. If a person has a cerebellar lesion, when he tries to reach, he'll say, he reaches out here for the stylus. As he nears the stylus, he starts-- he gets a bad tremor. That's called intention tremor. It happens when he's trying to do something. He's trying to make a movement. And he will shake. He has poor control of the timing, timing and gain.

Now, you do get recovery from cerebellar lesions, but they take a long time. And the coordinate, it's not a complete recovery. OK, because other parts of the brain, particularly parietal cortex can take over some of those functions.

Now what about corpus striatum? This has been much more complex and difficult to study. But the main evidence we have of it's important movement, importance and movement control where the dyskinesias of basal ganglia pathologies. So for example, in Huntington's disease, the patient makes as the disease gets worse, he makes involuntary writhing movements that sometimes they're called choreiform because they look like they're dance movements. Chorea means dancing.

And another pathology of the output circuitry of the corpus striatum, when part of that degenerates, you can get people that when they tried to move their arm, move it in a ballistic way, so they're flinging movements of the arm instead of smooth, coordinated movements. That's called ballismus and hemiballism. If they have the problem and the degeneration on one side of the output pathways in corpus striatum, they'll develop that problem on only one side of the body.

The best known basal ganglia disease is Parkinson's disease where they have a different kind of tremor when they're just sitting at rest. They will shake. Many of you have seen this, many older people get at least some of this. But it's a specific disease.

And when it strikes younger people, it's particularly tragic. They develop the resting tremor. They become increasingly rigid. Their movements slow down. And then they get a loss of emotional displays. It begins to affect the control of these higher functions.

And it's correlated with loss of neurons in the substantia nigra, which is part of the midbrain that contain dopamine. And they project forward to the corpus striatum. And as dopamine becomes depleted, you begin to get these symptoms.

And this is what it shows in here, and dopamine receptors increase with the loss of axons in compensation for the loss. But then, with more and more neurons loss, and here you see the loss of pigmented neurons in the nigra, finally, the receptors go down too and the Parkinson's symptoms appear late after there's been a lot of loss. As I mentioned before, these slow pathologies, slow or slowly developing lesions, often the behavioral change is seen late. And they've developed ways of trying to replace the dopamine in the striatum.

And then I've mentioned that implicit learning, especially the work of [? Pam ?] [? Graybill ?] and other people working on this, they find that somehow there's an interaction in the corpus striatum when we learn habits, reward and reinforcement for movements seems to act in the corpus striatum and alter the connections.

And we know of course, that over time, things, movements that were initially voluntary become habitual and that always seems to involve the corpus striatum. And that's all we have time for. I will--