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PROFESSOR: We're going to spend most of the time on the corpus striatum today, but I want to finish the other major part of the basal ganglia, the amygdala, which is closely connected to the basal forebrain. So let's define the basal forebrain. In discussions of aging in human pathologies, you always hear about the basal forebrain, because of the degeneration of acetylcholine containing neurons in the basal nucleus, located there. And that'll be in the pictures.

So let's look at the medial view of the cerebral hemisphere in a rodent. And this is the hemisphere. This is the brain stem. And I just cut off the hypothalamus here and included it here. Because, remember, in the basal forebrain the hemispheres are joined at the bottom. So to get the hemispheres separated from the brain stem we have to cut through the basal forebrain. And I've cut it right along the midline here.

And I've indicated basal forebrain structures here. Includes a collection of structures, including the olfactory tubercle right at the base. You see it in the sections. See, here we're in the hypothalamus. There's the amygdala in the hemisphere. This is in front of the optic chiasm. And there you see all the major basal forebrain structures, plus the septum. We usually don't include the septum as part of the basal forebrain, but it could be. Functionally it's very closely allied to these structures we call basal forebrain.

The other, broader, term is ventral striatum, which, in recent research, is proved to be more ventral medial striatum. And I've indicated that the way I've drawn the color here, showing that the medial part of the more dorsal striatum is really part of the limbic striatum. Maybe limbic striatum is a better term than ventral striatum now. But it usually uses ventral striatum in the book, because that is-- most of the literature calls it that.

So what does it include, besides the olfactory tubercle here? Well, I indicated two major structures here. You see the largest one, little further forward here, the nucleus accumbens. It's major inputs from the hippocampal formation and from the amygdala. But the amygdala primarily projects to the more caudal one here. This is where they overlap. That's the bed nucleus of the stria terminalis, which we mentioned last time.

And I've indicated in blue there the acetylcholine containing neurons that you see in the medial septum. You see them in this diagonal band of cells. We call it the diagonal band of Broca, because he named them, that area. And then the basal nucleus at the bottom here. And you see the basal nucleus [? they're ?] forward as well. Those are the cells that have this very widespread projection to the neocortex. They project to most if not all of the neocortex. So it was mentioned in chapter 17 when we were talking about brain states.

OK, now one other topic here, the kind of abnormal brain connections that we know occur, at least many types of schizophrenia. And the types that don't include the abnormal connections appear to have abnormalities, though, in the receptors, affecting the same system we're talking about.

I came up with this hypothesis of an early lesion explanation of some forms of schizophrenia back in the '70s, based on work in the olfactory system and visual system that I and other people had done. It was inspired by a study of people with temporal lobe epilepsy that had been operated on in order to get the tissue generating seizures-- it's a tissue in the temporal lobe-- removed, to cause the seizures to stop.

And they found that the patients could be grouped into two types. After they took the tissue out it included amygdala and adjoining structures. They found the signs of early damage. But they found that they could be grouped into postnatal lesions that were due to high fever in infancy, and prenatal lesions, due to what we call hamartomas, a prenatal tumor. So that means one group had much earlier lesions. And I've summarized there at the bottom the real basis for this idea, other than the fact of early lesions. And that is that the earlier the lesion in these other systems, at least, the greater the plasticity, that is, more sprouting, more chances of regeneration, and so forth. But here we're talking about sprouting. So I just wanted to run through the hypotheses. These are the connections I'm talking about.

In green there I show the very widespread projections of the catecholamines, the monoamine, serotonin, and some acetylcholine axons as well. I was thinking mainly of the catecholamines, dopamine and norepinephrine. And I knew at the time I drew up this hypothesis that there were dopamine abnormalities in the prefrontal cortex in schizophrenics in many of them.

OK, so here I'm showing how the catecholamine axons have these very widely branching axons that go through the amygdala. They go into the basal forebrain and septal area. And they go to the prefrontal cortex. The cortical projections are much more [INAUDIBLE] these prefrontal areas than they are to other cortical areas. And according to that study I was just talking about, both of these groups had amygdala lesions, but one of them had much earlier lesions. And I would predict this kind of sprouting.

For one thing, by removing this structure we've eliminated these projections to basic forebrain and prefrontal cortexes. But we've also pruned these axons, making it likely that they will show compensatory sprouting in other areas. So those two factors together indicate that this kind of sprouting would be expected in the basal forebrain and in the prefrontal cortex.

And the question is, OK, what about schizophrenics and early damage? The fact is, a number of schizophrenics, particularly the ones that are the hardest to treat-- they're the ones that often are in mental hospitals for most of their adult life-- have enlarged brain ventricles. Now, of course, with more drugs to treat them, more of them are not in the mental hospitals. Because you can alleviate their symptoms with some of the drugs.

But this just shows schizophrenian monozygotic twins, where you have one twin with schizophrenia. The other doesn't have it. And as they often find in these cases, the affected twin has larger ventricles. And we know that larger ventricles can result from early damage.

And this is from a study where they had a lot of patients and they looked at the relative size of the ventricles with respect to the rest of it, to the whole brain. And here that is in normals. And you can see it changes with age. The ventricles do tend to enlarge after age 40. This is for males here. The curves are a little bit different for females. But it's a very significant finding, that the schizophrenics have larger ventricles, an indication of early damage. Many of them do have this temporal lobe damage.

Now, different studies have indicated, well, the hippocampus is important, the amygdala's important. Sometimes they don't know. But the particular study I'm talking about was more of a natural experiment. Because the surgeons had actually removed the tissue to stop the seizures. And then they found one group with earlier lesions. So the question is, then, did any of these people have schizophrenia.

So they checked for hospital admissions for schizophrenic type symptomatology. And they found that the ones with the earlier lesions, the hamartomas, were much more frequently admitted for schizophrenia. It's a fairly high percentage. Of course, there's always a lot of variability in the studies like this. But-- yes?

AUDIENCE: [INAUDIBLE] in like epilepsy in schizophrenics?

PROFESSOR: That's a good question. You'd like to know if in studies of schizophrenics, how many of them have epilepsy. Usually they're kept separate, but I don't know of studies that have just looked broadly at schizophrenics. I actually have seen some of these studies, but I can't recall at the moment. It'd be worthwhile checking.

OK, and then just to remind you of the widespread nature of these projections. The dopaminergic projections are a little more widespread according to recent studies than they were in the earlier studies, where they were seen mainly in the cortex, which is seen mainly in the prefrontal areas. Now we know they are also in the more caudal areas, but just less dense. But also we know the basal nucleus projections are shown here. Very widespread. They could be affected too. And note that this is the way they depict the amygdala. And in every case these four systems of widespread projections all go to the amygdala as well as to other parts of the brain. All right?

And this is just to show you binding to receptors for these different transmitters of the various anti-psychotic drugs. The blue shows the D2 dopamine receptor binding drugs. And you can see very commonly that these drugs have a high affinity for those receptors.

But there's an affinity for the receptors for the other type of dopamine [? receptor. ?] So there's two kinds of dopamine receptors studied here. There's two kinds of adrenergic receptors. Some of them, the binding's higher, especially for this big group on the right. And I'm not saying that-- what it indicates is that we know if you bind the receptor you'll reduce the effects of the [? rejections. ?] If the prefrontal cortex is functioning abnormally because of sprouting of these axons, also the basal forebrain, then binding to the receptors will move it more towards the normal. And that could be a reason. Just saying that it does [INAUDIBLE].

Let's talk about the other part of the basal ganglia, the larger part, the corpus striatum. Going back to these earlier pictures where I talked about the evolution, remember very early there was no dorsal striatum. It was more of an olfactory structure. But it was a link between the olfactory, [INAUDIBLE], and motor control. And that's what evolved into the ventral striatum. And we also know the outputs of that region go to hypothalamus and subthalamus. They influence the endocrine system and motivational states by these projections. They also have some connections in the midbrain, where they can influence the stacking patterns, especially locomotion.

The ones to the midbrain are probably influencing all of these basic movement types. Although I'm not saying those were all there at the very beginning. And we also know that-- I'm postulating that very early this was a modifiable length. So it must've been modified because of feedback of some sort. And we know the feedback in modern animals is mostly dopamine systems, coming from, in most vertebrates, the hypothalamus, but in mammals and other amniotes, the birds and reptiles, also the skates and the rays-- sharks, skates, and rays comes from the ventral tegmental area.

And we know that, especially if you look in fish, where the dopamine feedback comes from the hypothalamus, that a major input to the hypothalamus in those animals is from the taste [? cyst. ?] In mammals it's never been emphasized, but we know taste can be very rewarding and influences the tegmental area cells. The studies of rats have indicated yes, there are some projections, even in mammals, from that system. That's why I include it when I talk about the outputs to that region in this book.

All right. Now we know that substantia nigra in the midbrain is a major recipient of outputs from the dorsal striatum. We also know that the nigra, the dorsal part of it, called the pars compacta because of the packing of the cells, is where the dopamine axons of the nigra are located. Because the dopamine cells in the midbrain are not just the ventral tegmental area. They're in the-- it's an essential projection to the normal function of the dorsal striatum. The ventral striatum gets its dopamine from the ventral tegmental area, not the dorsal striatal.

The other part of the nigra's called the pars reticulata. It's more ventral. It has projections to systems influencing movement. They go to the [INAUDIBLE] and influence orienting. They also go to the midbrain locomotor area. They also project at thalamic nuclei that project to motor [INAUDIBLE] centric cortex.

We pick those projections here. Now here, in this slide, I'm showing just the major dorsal striatal components, the caudate and the putamen. So what's in between the caudate and the putamen here? It filled a space. The internal capsule fibers coming from the cortex. So this picture is more for the larger mammals, that have an internal capsule that's separating the dorsal striatum into these two parts. If you're dealing with a rat or a mouse or a hamster, the internal capsule fibers sort of come in multiple bundles through the corpus striatum. So it doesn't make a whole lot of sense to talk about caudate putamen.

So how come they just call it the caudate putamen or caudoputamen in these little animals? That's so you don't get too confused when you read this literature. But in cats and dogs and primates, in general you have a clear corpus striatum. So that's what I'm picturing here.

And in the picture I'm showing the dopamine pathway in the pars compacta of the nigra, distributing throughout pretty densely to the whole dorsal striatum. And then I show the output from the caudate that goes to the nigra. It's a GABAergic projection. It acts by inhibiting the cells.

Now, I also show the projection from the nigra here to the colliculus, nigra [INAUDIBLE] track that's also GABAergic. And I show it going forward into the medial structures of the thalamus, VM and-- the ventral medial and ventral anterior nuclei, which project pretty widely to motor and some of the sensory areas.

So then the question is, if the nigra's signaling some kind of reward or punishment to the striatum, giving it some kind of feedback, well, where's that feedback originate? And there are some interactions between limbic system and somatic system in the nigra. There are connections from the amygdala. It's like I added here. This is the same picture, but I've added here the more caudally-located amygdala, and shown that it projects to the nigra. I've also shown here that lateral hypothalamus projects directly to the nigra also. So it does appear to be a place where the limbic system and somatic systems show some convergence. Which may be very important to how this whole structure functions.

In the evolution of this structure you start out with the ventral area getting olfactory input. But then we know that non-olfactory inputs came in. And that led to expansion of the striatum, this area here. I showed how that's beginning to bulge, with these nice non-olfactory inputs. And we noted that led to some segregation of the olfactory part and the non-olfactory part. What was olfactory became the ventral striatum. And some of it still gets direct olfactory projections. Whereas sensory inputs come into the striatum.

And I'm just showing you here for a rat or a hamster or a mouse. We know the intralaminar nuclei of the thalamus, that we call the paleothalamus, the older thalamus. They tend to get multi sensory inputs. A lot of them come from the superior colliculus, for example. They project here. And some of them come directly from this final thalamic tract. They project to these intralaminar nuclei. So I just lumped them together here. And we show that they have strong projections to the dorsal striatum.

We also have some of these [? exons ?] extend right up into the hemisphere. So we'll see that here. And then of course I'm showing the cortical striatal connection there. And I'm showing the dopamine pathway as well.

This shows you the same thing from the Brodal textbook, where he shows one part of the intralaminar nuclei. It's called the centromedian. It's because in primates that part, which is a caudal part of the intralaminar nuclei, has become particularly enlarged. So in humans it's very large also, and other large primates. But this is just to say this isn't just something that happened early in evolution. It actually enlarged in more recent evolution. As this one nucleus gets mixed non-olfactory inputs, projects strongly to the dorsal striatum.

OK, and this shows you pictures of what that looks like. I have this one picture in the book. I have three here. This shows in a rat the parafascicular nucleus, which was like the centromedian of primates. And you can see the widely branching axons terminating in the striatum. And here there's a branch going on into the cortex. It projects a little bit to other structures too. And here's one in the centralis lateralis. Little further forward in the intralaminar nuclei. It's also projecting to both the caudate or putamen-- here they're just calling it one structure, the caudoputamen-- and to the frontal motor cortex, in this case.

And here's one that's not in the intralaminar. But it's in another ancient part of the thalamus. We call it the posterior group of nuclei. They're outside the areas of the thalamus that project to the primary sensory areas in the neocortex. They project the multimodal areas. They get multimodal input, and it shows them projecting again to the dorsal striatum and into the cortex.

Now, I'm showing you pictures of axons that terminate in both places. Many of the neurons in those structures project to one or the other, either cortex or striatum. But because a number of them project this way, it emphasizes the point I want to make, that they're going to both structures. So in many cases they are separate neurons.

OK, so then with the non-olfactory input, you had expansions of both the pallidum and the striatum. Here's the pallidum. Here's the striatum. Here I'm showing olfactory input going to both. The non-olfactory input into the pallidum we know went through the thalamus, most of it. And then it also did the same for the dorsal striatum, but not the ventral striatum. The olfactory were [? displaced ?] separate.

And then, of course, in more recent evolution of mammals we had this huge expansion when the pallidum became an-- a part of it developed into neocortex, and that part is expanded so much. And those earlier outputs and inputs remain, even in modern mammals, when all that expands from the [INAUDIBLE].

But let's look now at-- this is a rodent. And this is the earlier picture. I put this one in the book. If you look at the hemisphere from the medial side, you can picture where the ventral striatum, dorsal striatum, and also the hippocampus are located. So here in the middle section you see the amygdala area, here.

Further forward, the ventral striatum, down here. Dorsal striatum there. And very [INAUDIBLE], you see a structure related to the ventral striatum. It's really a caudal-- it's called the caudal amygdaloid area, sometimes hippocampal amygdaloid area. It's very [? part ?] caudal. It's right next to the hippocampus, which is in here. So that just gives you the picture of these subcortical structures of the hindbrain.

So now we want to answer these kinds of questions. What are the two major outputs of the corpus striatum? Most of them are by way of the globus pallidus. You just deal with those, coming from the globus pallidus. One of them is much larger in mammals, which is why we sometimes talk about the extrapyramidal system projecting directly to the pyramidal. Because the extrapyramidal systems are the striatum, the cerebellum, and many other structures that aren't part of the corticospinal system. It's basically the pyramidal tract. So let's look at that.

This one you can guess that the answer contrasts the major sorts of sensory input to the striatum in amphibians and in mammals. And just of the striatum. What is the big change that happened in mammals? In general, in the forebrain, what was the big change in mammals? Expansion of? The neocortex, right. The evolution of the neocortex that expanded. That happened in mammals. It didn't happen in the amphibians at all. Amphibians have this little dorsal cortex that's equivalent to a parahippocampal area. And they have a medial pallium.

But none of it's like neocortex, really. Even though it does get some non-olfactory input. And then I'm asking a question that we've pretty much been answering, what's the limbic striatum? How does it differ from non-limbic striatum? And what are several structures that it includes? Well, I'm really asking what are the components of that ventral striatum? So we've shown it in some pictures, and we'll look at some more. They're just major parts of it which reoccur in the literature and the discussions, including discussions of human pathologies. So you should be learning a few of those.

All right. This is a simplified diagram of major outputs of the neocortex. And here I show the striatum as one of the major outputs of the neocortex. So if you compare now amphibians and mammals, we said amphibians don't even have a neocortex. So how is their dorsal striatum getting input coming from the thalamus, the older parts of the thalamus? It's the major part of the thalamus in those animals. Whereas in mammals the major input to the striatum, even though the striatum is still getting thalamic projections, as we've pointed out, now the neocortex is by far the larger structure. And it dominates the dorsal striatum, as it dominates a lot of the systems, because of its size.

So this shows the cortical striatal connection. I show it connecting to the limbic hindbrain as well. And here I just included as part of the limbic hindbrain the ventral striatum. We'll separate that in a minute. But note that besides the striatum, the neocortex bypasses even the brain stem for its long connections. Because it has corticospinal connections. So I have it here going to the brain stem and spinal cord directly.

Whereas the striatum has a connection to the brain stem, relatively smaller, none to the spinal cord. But in mammals it does have a major connection back to the thalamus, which then goes to the motor and premotor areas of cortex. So that's how the striatum is influencing movement, primarily. Some by its connections to the midbrain, but then also much more through the thalamocortical connection, which affects the neocortical output.

So it leaves out the ventral striatum. So those early stages of chordate evolution are just left out. So I made a more complex diagram that will drive you a little crazy. But what I've simply done is separate the somatic and limbic systems. If we just want to say, well what's most unique on the somatic side? What's most unique on the limbic side? What's the most unique thing about this somatic diagram here? It would be this long connection, directly to spinal cord. You don't see anything like that from the limbic system. The longest connections of the limbic system go into the midbrains. It's now-- they [? show ?] it in there much weaker. I didn't even show it here. It's a relatively weak projection. It just shows where the limbic midbrain is. Most of the connections are shorter for limbic system. So that's a major difference in the two sides.

Another difference is in the [INAUDIBLE] length. Somatic system, the connections are to and from the thalamus. The limbic system, connections to and from the hypothalamus. And then in the striatum, dorsal striatum for somatic system, ventral striatum for the limbic system.

The older picture of this was when we talked about the lateral and medial forebrain bundle. And you can see where the dorsal striatum is in those [? dissolved ?] pictures-- right there. And then these more ventral and ventromedial structures are ventral striatum. And they connect through the medial forebrain bundle. Whereas the dorsal striatum and neocortex, they connect to more caudal structures through the lateral forebrain bundle, which, remember, the most [INAUDIBLE] component of the lateral forebrain bundle is the internal capsule and the white matter at the hemisphere, shown on that side. And this is just is from another slide.

So we can take these pictures, like this one, and make it much simpler to talk about the striatum. This is one based on a simplification of one of [INAUDIBLE] pictures. Shows cerebral cortex getting input from the thalamus and projecting to the striatum. They don't show the corticospinal projections [INAUDIBLE]. I'm just showing the striatum here. And then we see its major outputs. And here, by including the pallidum, we show the major connection going to pallidum, but some connections directly to the substantia nigra. Those are the two main connections of the dorsal striata.

So the pallidum, its biggest projection is to the thalamus. That information is going to neocortex. But it also has projections to the caudal midbrain. And here we're talking mainly about that midbrain locomotor region. The literature names it pedunculo pontine nucleus, and not always called it by its full name, nucleus tegmenti pedunculo pontinus [? paruscompacta. ?] Because it was one part, compact cell part of that region where the striatum had its main connection. But I use often the functional terms in the locomotor area, because it's the major part of that area which, when stimulated, leads to locomotion. Here I just call it the caudal midbrain.

And similarly, here the other area that the striatum projects to, substantia nigra with its dopamine projections, and here, its connections to the other major midbrain structure of motor control, the superior colliculus for orienting the [INAUDIBLE] movements. So the nigra can modulate those kinds of movements through this connection.

This term occurs in discussions of human neuroanatomy. So you should know what it means. It's one of these connections. It's this slide. That's the ansa. Let's find out why it's called that. It means the handle at the lenticular nucleus. We've not used the lenticular nucleus before in the class. We've not used ansa before. But it's the handle of the lentiform nucleus.

Here is a picture of the human brain. And here's, of course, all cortex. This is the neocortex that's hidden in the depth of the Sylvian fissure. There's the Sylvian fissure. And there's the corpus striatum. There's the caudate up there. Here's the internal capsule. And on the lateral side we have the lentiform nucleus, which is the putamen plus the two segments of the [INAUDIBLE]. Thalamus on the other side there. This is where the internal capsules already going along the side of it.

OK, the output of the globus pallidus here, that goes to the ventral anterior nucleus thalamus, follows this sort of a hook or a handle, just like the handle of a cup. And that's why it was called the ansa lenticularis. Because this group of nuclei, the corpus striata, dorsal striata structures is often referred to as the lentiform nucleus.

And what they're doing is going around the edge of the [INAUDIBLE] here and then going back, forward, and in to the ventral anterior nucleus, primarily. You go to VL as well. The VL is dominated more by cerebellar input. The VA is dominated more by the [INAUDIBLE] injections. This shows you, if you want to see one of [INAUDIBLE] pictures. His are more complex than the ones like this that I've used. But he does show the projection from the motor areas of cortex to the caudoputamen, which then projects the globus pallidus. And here are the two projections, caudal midbrain and thalamus. And there's the curving pathway of the ansa lenticularis.

So when you hear the term "satellites of the striatum," we always mean two structures that are essential for the way the corpus striatum functions in mammals-- the substantia nigra and one other structure that so far I've not named. But it's part of the subthalamus. It's the subthalamic nucleus. I want to show those structures in a network diagram. But first, look at-- these would make good homework problems. But I think you can figure them out. Contrast the pathway to motor cortex and the pathway to the superior colliculus from the dorsal striatum. Well, the ones of the motor cortex we've described here. So from dorsal striatum through that ansa lenticularis, so dorsal striatum to globus pallidus and then directly to the VA of the thalamus, which then projects to motor cortex.

The one with the colliculus goes directly from the dorsal striatum to the nigra. And the nigra projects the superior colliculus. Those are the two different paths. And then you need to know what we mean by doubled inhibition. Here we're just looking at one of those satellites, the nigra.

And notice excitatory input from cortex. The output is inhibitory. Inhibits the globus pallidus and inhibits the nigra. But then know that the projections of the globus pallidus and the nigra both are inhibitory. So you're inhibiting an inhibitory pathway. That's what we mean by double inhibition. Important for understanding the pathologies when something goes wrong with these structures, as in Parkinson's disease, as in Huntington's chorea, and other basal ganglia disorders.

Because you can get not just a reduced function. You can get enhanced, too much excitation. So then to control it you need some way to reduce-- either replace the misconnections or reduce the overexcitation.

So this is where we'll come back next time. Just to point out a couple things about this, this is the worst diagram in the book, probably. But it's been important for people to see how knowing these connections explains some of the disorders. So we'll leave it here.

But just note, if there's just a subthalamic nucleus-- here's the nigra down here. So these are the two main satellites of the corpus striatum, [? caught ?] it in putamen here. And note, I put excitatory connections in blue, inhibitory connections in red. I didn't color the dopamine pathway here, in the nigra.

But note, the subthalamic nucleus is getting inhibitory connections from the globus pallidus. But it excites both segments of the globus pallidus and the nigra. OK? So it's unique in that way. And it's critical for the balance of this system. So anything that goes wrong with the subthalamic nucleus can cause major problems with movement. OK, so let's stop there today.