

The following content is provided under a Creative Commons license. Your support will help MIT OpenCourseWare continue to offer high quality educational resources for free. To make a donation or view additional materials from hundreds of MIT courses, visit MIT OpenCourseWare at ocw.mit.edu.

PROFESSOR: OK, I had told some of you that there would be a quiz today. I won't give the quiz because I didn't announce it online, but I would like you to take it anyway. Take for your own benefit. So it won't count. I just want you to see if you can write down the names of the 12 traditionally-named cranial nerves for humans.

I want you to see if what you remember-- just number them 1 through 12 and see if you remember their names, and see if you know which ones are mixed nerve, which ones are purely motor, which ones are purely sensory. Just try it. Just take a few minutes and try to do that.

And if you're not in class, you're at home listening to this, I would still like you to do it. And if you're home, you can let me know by email how many you have got.

Do you need the mnemonic? On old Olympus' towering top, a Finn and German viewed some hops. I don't know why, but I can remember that mnemonic better than I can rem-- at least when I was learning them, I used it. On old Olympus' towering top, a Finn and German viewed some hops. So use all the first letters.

Write it?

AUDIENCE: Yes.

PROFESSOR: Just write these first letters, on old Olympus', O-O-O, then towering top, so O-O-O-T-P, a Finn, so A and F. A Finn and German viewed some hops.

OK, so there is a table in the book which you can find, obviously that occurs in those earlier chapters, but I keep referring to cranial nerves throughout the book. How many of you think you could name all of them? Yeah? Olfactory, optic, oculomotor, trochlear, trigeminal, abducens, it's an oculomotor nerve.

AUDIENCE: Facial, [INAUDIBLE].

PROFESSOR: So you give 10, 11 and 12 again.

AUDIENCE: [INAUDIBLE]

PROFESSOR: First--

AUDIENCE: Oh, oh, vagus.

PROFESSOR: Vagus nerve. Spinal accessory, OK, excellent.

Now you need to know just whether there are a few purely motor ones, somatic motor, the oculomotor nerves, and the one controlling the tongue, glossopharyngeal nerve and the-- sorry, not the glossopharyngeal but the hypoglossal.

And of course there's several purely sensory nerves. The others are mixed. And the mixed nerves always have-- they're [? attached ?] where they come in and join the brain. Sort of in that middle region, whereas the purely sensory ones in the hind brain are like dorsal roots. They come in dorsally. Purely motor ones are like ventral roots.

Except the trochlear actually, doesn't actually leave the cranium ventrally. It comes around, comes up between the cerebellum and the inferior colliculus, and exits that way.

But it's very useful to know these in neuroanatomy. All right.

Throughout the book I've emphasized these two structures, the medial pallidum and the corpus striatum. The early striatum, mainly an olfactory structure, but the striatum provided the link to motor systems. And that's still true of the whole striatum, except it's not just olfactory anymore.

And the other system is the medial pallidum, which as you probably remember is the hippocampal formation. But what did I suggest was, even very early, was the role, the major role, of these. They both concern learning, but different types of learning.

And you could see the entire neocortex organized around these two systems, two types of learning. Because cortical areas, many cortical areas, have projections that go towards one or the other of these structures. So what is the striatum involved in? What kind of learning?

It's always sensory motor habits of various sorts. But now we think it's much more than sensory motor in higher primates. We think it's probably habits of thought, habits of even feeling. A habit of feeling is something like a prejudice, so your prejudices probably depend on connections that have been learned and the change that's occurred in that parts of the striatum.

And what about the medial pallidum or hippocampus? Originally a type of memory, though, because what we just talked about is all memory too. Habit memory is memory. Spatial memories, where we are in the environment, episodic memory, came out of this.

And yes, it's become important for navigating our cognitive space, our social space, our imaginary spaces. But that's not how it originated. It all evolved out of the system for navigating the world and remembering, being able to remember, good places and bad places. That required a somewhat different kind of learning, different kinds of algorithms had to evolve to underlie those two kinds of memory.

And then why did dorsal and ventral parts of the striatum segregate? What was the big event? I said it was olfactory originally, and that became ventral striatum.

So that should tell you what happened. Other senses projected mostly through the thalamus into the striatum also. And they took advantage of that ability to form-- to change connections that became habits. Obviously we don't just form olfactory habits, we form visual motor habits.

Think of the sports you learn, think of simpler things like riding a bicycle or various things you learn when you're growing up. Learning how to throw a baseball properly, learning how to hit a baseball, all these things in sports. But many things that we don't even think about, they're not sports, they're things that we learn, part of our lives. Those habits depend on the striatum.

And we call that kind of memory, implicit memory, they are not-- we don't remember individual events. If you're talking about your memory for an event, where you learned how to ride a bike, that's different, that's not a striatum, but actually learning.

We say, well, I know how to type, I remember in my fingers. Well, that's striatal. All right.

So I go through this, call it a likely scenario, for the origins of corpus striatum. And I'm just going to go to this picture here, this just summarises that whole scenario. If you go through this, I describe it in the book, that the beginnings is a link between olfactory input and motor control.

This is slide 37. And that became a ventral striatum, that early link, and then I said, well, the outputs went to the hypothalamus as you see them drawn here in a primitive brain.

And then the major point that I added was that these were modifiable links. And that was a big innovation, different from spinal cord. You have a little bit of learning in the spinal cord, but nothing like this. Types of learning you get in spinal cord are rather short term. This is long term. These are the formation of habits.

And then I talk about the non-olfact-- well, I talk about the feedback you need for learning. We know that it involves the dopamine pathways pretty heavily. We know that very early taste as well as olfaction were important sources of feedback that affected that system.

And then I talk about the non-olfactory inputs that resulted in a dorsal striatum as well as ventral striatum. And then I talk about the early expansions of the endbrain.

It wasn't just the striatum, but it was the pallium as well. Originally, the pallium was olfactory, the olfactory cortex. But very, very early the medial pallium began to evolve. We will look more at that, I'll show you pictures of the way that looks in non-mammals.

You'll see, for example, in the frog, the major pallial structure is the medial pallium. They have a little bit of structures adjacent to it, but they're just-- they provide input to that medial pallium. It's called the dorsal cortex, and yes, the neocortex did evolve out of that.

OK, and then you had the expansions of both the cortex and the striatum. But the major change that occurred in mammals was that a major output of the striatum went to the cortex, because it projected to the thalamus. So we'll see that.

All right. We get a good idea about origins and the relationship of different major segments of the endbrain and other brain regions by looking at gene expression. And this was one of the earliest studies that did that. It showed that genes expressed in neocortex as well as adjacent areas like hippocampal area and the olfactory cortex.

You can find closely related genes in the hyperpallium of birds, in the dorsal cortex of reptiles, including turtles, and in this dorsal cortex of the frog. And that thick part there is the medial pallium of the frog, that is the hippocampal formation.

And then you can see the other genes are expressed in the striatal regions and the adjoining septum. Notice that it goes all way down to the base of the brain where the olfactory inputs come in, even in mammals. And there is a corresponding striatal area in the birds, in the reptiles, and in the amphibians.

And then there are additional regions that aren't expressing the genes of those two major regions. And that includes this in the reptilian dorsal ventricular ridge area. In birds, there is also a dorsal ventricular ridge area. It isn't called that anymore in the adult bird, but its connections are pallial-like, and that's true in the reptiles too.

But if you look at mammals, you don't find that gene expressed in the neocortex. You find it mainly here in the amygdala. But we know now that the amygdala does get projections of various senses, somewhat like cortex. And we also know that from these subcortical regions there are cells migrating to the neocortex.

And this just shows, from more recent studies, the same picture holds. But it shows how come-- this is just to give you an idea of the complexity of these gene expression studies. And because the gene expression studies don't always-- they are sometimes hard to interpret because of the number of genes involved and the relative degree of expression. I still like the studies that depend more on connections, and the reason for that is that the connections are what underlies behavior, and the behavior is really critical in evolution.

Brains change in order to change function, which of course includes behavior. This just gives you another view, one based on connections. This is Karten and one of his students publishing back in 1989. Karten was the guy who was at MIT with [? Nauda ?] and was the first to discover these pathways in birds from thalamus carrying visual and auditory information to that big subcortical region in the birds.

This was more like neocortex up here, the hyperpallium, but this region here also had connections just like neocortex. All right. So he related the specific kinds of connections in mammals to similar connections in birds and where they were located.

So then I discuss the medial pallium a little bit. We've already done that. But I wanted to point out this one rather interesting study, it's a highly cited study. This was a group of investigators who realized that in one genus of birds, there were some birds that formed food caches, they stored food when food was plentiful, and then they had to remember where they put it. They had to remember well above chance levels for it to be really adaptive. Whereas other members of the very same genus didn't do that.

So these people studied the brains of these two groups of birds and other songbirds as well that formed these food storage locations, the food caches, and those that didn't. And this is a plot of the size of the hippocampus versus the volume of the whole telencephalon, the whole endbrain.

And you can see here this is the dimension you want to pay attention to. OK? How far they are from that diagonal line, and you can see there's no overlap. The birds that formed the food caches had bigger hippocampus. So the correlations aren't just statistically reliable, they're dramatic. Animals need that structure for spatial memory.

AUDIENCE: [INAUDIBLE]

PROFESSOR: Sorry?

AUDIENCE: What's the difference in [INAUDIBLE]?

PROFESSOR: Difference in? Oh, the members of the one group, these are all the same genes. The triangles. The others are not members of that genus. I did reproduce this, I believe, in the book, so you can find the source. And I probably spelled some of that out in the legend. All right.

And then there was a parallel evolution of the pallial and subpallial structures, expansion of both, although we know that it was the pallial structures that expanded the most, especially in mammals with the evolution of neocortex. So I pretty much answered question eight, part of the primitive endbrain that the neocortex evolved from was that dorsal cortex. There's a parahippocampal region, and it's supported by gene expression data.

And you should know that some mammals have a very small neocortex. Although having a neocortex is fundamental to being a mammal, not just having mammary glands and some other characteristics, hair on the skin and so forth.

I redrew the gross views here of a couple of hedgehogs. European hedgehogs just have a really small neocortex, smaller than the hamster. A West African hedgehog, a possum, a prairie vole, they're all fairly similar to a hamster. And the relatively slightly larger are animals like the vole and mouse, other voles and mouse, rat.

And these are what cross sections look like. Here we have a tenrec. It's another animal that like the European hedgehog has, I think relatively speaking, the smallest neocortex of all the mammals. And that's shown in this section through the middle of the brain. This is the mid-frontal section through the middle of the hemisphere.

You see the neocortex is even smaller, or at least no bigger, than the whole hippocampus there. And this is all olfactory cortex. And then the opossums and the hedgehogs also have relatively small neocortexes.

OK, and then we went through these pictures, and now we want to do this. We want to get started with talking about the limbic system, and this will be the first session on that. Stressing the hypothalamus at the beginning, and then we'll talk about striatum and then the neocortex.

All right. So this is actually called class 28. When I put the slides up after the class I call them sessions, so they will start with the slides we just covered on the forebrain introduction.

OK, so what is that term? Where does it come from? Why do we call it limbic system?

AUDIENCE: [INAUDIBLE]

PROFESSOR: Sorry?

AUDIENCE: Doesn't "limbic" mean the edge of something?

PROFESSOR: Yeah, the fringe. The fringe or border or edge. It came-- I must have brought that up a little bit later. Let's come back to that in a minute, and talk about the structure that is central to any discussion of the limbic system, the hypothalamus, and why it became important to separate out an endbrain system that was closely connected with it.

All the endbrain structures that we call limbic system, or limbic endbrain system, are all closely connected to the hypothalamus. Sherrington, remember, called it the head ganglion of the autonomic nervous system. It's much more than that, because it controls motivated behavior including eating, defending, attacking.

The structures there underlie motivational states, the drives. And of course they're associated with strong feelings, so we also associate it with emotion. And we call them, when we talked about motor system, we called them central pattern generators. This is the picture of-- what it shows is the locomotor hierarchy with the pattern generators in the spinal cord. Here's the motor neurons.

And then, in the midbrain and 'tweenbrain, Swanson called the structures that initiated locomotion the locomotor pattern initiator, the midbrain locomotor region, and the locomotor pattern controller, the hypothalamic locomotor region.

And when we're in the hypothalamus, we're concerned with structures that underlie what we call the biological drives. So why is there a locomotor pattern generator in the hypothalamus? It doesn't directly control locomotion. It controls the structures in the midbrain and hindbrain and spinal cord that underlie locomotor movements.

But with every drive, think of hunger drive. Locomotion is always involved. If an animal has a high level of hunger, he will move more. Unless he's so hungry, he's getting weak. But that comes rather late, we're talking about just in the normal state. When you're hungrier, you're more likely to locomote to the refrigerator or to the store.

But think of animals who are motivated to forage. Or if they're food storing animals, like a hungry hamster, will only forage at certain times of day when he's safest, when the sun is very low in the sky. But other times when he's hungry, he will generate locomotion to get to the places where he's stored food. And he has an elaborate tunnel, and will go to various places in his tunnel to do that.

So locomotion is associated with all the drives. So it is connected to the other neurons in the hypothalamus that underlie the various motivational states.

So now the cortical layers that we call limbic endbrain structures, they are closely connected to the hypothalamus. Where are they found? And that tells you the origin of the term limbic system. We already discussed the meaning. The term came from Paul Broca, Pierre Paul Broca, who used this phrase, "the great limbic lobe," in French in 1878, for the human brain.

But I have to point out that that doesn't mean that Broca understood the functions, OK, or the connections, because the methods simply weren't good enough for him to know that. It wasn't until the 20th century that we began to realize that.

But what Broca called the great limbic lobe, you have to look at a human hemisphere from the medial side. And this particular picture of the human brain on top and rodent brains down below, I've divided it according to major functions. And I say that these are all structures closely tied to motivational states because they're closely linked to the hypothalamus.

And notice that they're always around this edge of the hemisphere. So if you start just at the corpus callosum and go just above it, you're in limbic areas of singular cortex. These are the parolfactory regions. The orbital frontal region is closely connected to these.

Broca's area would not be included. This would be Broca's area here, and this would be the area controlling the movements of speaking, just behind Broca's area but in the motor areas of the cortex.

But that doesn't mean that Broca's area is not connected to these areas. It is. The various, multi-sensory association areas of cortex are the areas most closely tied to these limbic structures.

We often call them paralimbic, and reserve the term limbic structures to the subcortical structures that are closely tied to the brain stem. But the paralimbic structures are these structures that are near that.

But that's the great limbic lobe that forms this whole ring. The medial edge of the brain, and here you see them in a rodent brain. Some of this would be connected to the [? MD, ?] which means it's prefrontal neocortex, but in the rodent those areas get connections from the anterior nuclei too, which cannot be the [? singular. ?] We'll be going over that.

So I've shown that ring of cortical areas, there, indicated by the arrow here, just on the medial view. But we include with it the olfactory areas. So here you see it in the rodent. I've used that same designation because the olfactory areas are paralimbic too in that sense. They are closely linked to the hypothalamus.

And then I continue that designation here on the brain stem, and I show the hypothalamus and epithalamus marked that way, and I show it continuing into the midbrain, as [? Nauda ?] described in his work on the cats and monkeys primarily.

OK, now there are various types of studies that separate limbic system areas from what we've been calling somatic areas, the non-limbic areas. And when it was done a number of years ago in describing systems in the brain that cause arousal, in electrical stimulation studies and in behavioral studies, aroused animals are very different from unaroused animals.

So let's just go through that a little bit and talk about the two arousal systems in the midbrain. One of them we associate with the midbrain reticular formation. It's somatic. The other is associated with the limbic areas.

So we've already seen this picture when we talked about midbrain and diencephalon and those chapters where I was introducing all the various levels of brain. So there are the limbic midbrain areas [INAUDIBLE] central gray area and the ventral tegmental area. And the rest are all somatic.

And the part with the horizontal black lines, here in the midbrain picture, is called the midbrain reticular formation. OK. And that's the area, you can get arousal from stimulating anywhere in the midbrain, but it's that region where you primarily get arousal. And you get it from stimulating those limbic areas too.

But then I'm asking this question. I want you to compare the two arousal systems. What structures are involved? Well, we just mentioned that. What are the major types of connections of these structures? What are the effects of electrical stimulation? Is there habituation when you use electrical stimulation?

If you just keep the stimulation on one point and stimulate again and again, do you keep getting the same effect? Or do you get habituation? It's very different for the two systems. Just like they give different inputs, the effects of electrical stimulation are different. What are the differences?

It's a complex question. OK. Does anybody want to say anything?

AUDIENCE: So the non-limbic system is more physical responses to, with physical manifestations of, arousal whereas--

PROFESSOR: What do you mean? Physical manifestations of arousal? In non-limbic?

AUDIENCE: And then limbic would be more associated with pleasure.

PROFESSOR: OK, so you're saying limbic is associated with [? affect ?] feelings, positive or negative feelings, pleasurable or not pleasurable. The opposite-- unpleasant or very pleasant. And that's all correct.

What kind of inputs did they get? They get different kinds of inputs. Those limbic areas-- what kind of inputs are they getting from below? They're the inputs that come in mainly through the vagus nerve. From the viscera. They're visceral inputs, OK, visceral sensory inputs.

From above, they come from hypothalamus and limbic endbrain structures. OK. Now the non-limbic areas get all the various inputs from the various sensory systems and also from the cerebellum, that is the motor system and sensory systems.

So there are these big differences. We've shown how they're located in different places, the types of inputs, and the types of outputs are different too. OK. Now, electrical stimulation, both systems cause the arousal patterns in the electroencephalogram. That is, you're recording with large electrodes, recording from the scalp of a human.

You get this fast, high frequency pattern. Very different from the pattern of a drowsy person or a sleeping person. OK. And if you stimulate repeatedly in the same place in the midbrain, the effects decrease, you get habituation.

If you move the site where you're stimulating a little bit, the arousal comes back. So just like behavioral effects of novel stimulation that habituate as the stimulus becomes more familiar.

Now if you do the same thing in the limbic structures, you get the EEG arousal, all right, but it doesn't go away with repeated stimulation. It's a little bit more like someone calling your name repeatedly, thus stimulating the limbic system a lot more. We tend to be pretty attached to our name, and we don't habituate readily at all.

Just like we don't habituate readily to good taste in food if we're hungry. If we're not hungry, sure, but that's something else. We just keep everything else constant. Hunger is constant. You keep responding, you don't habituate, at least not very much. OK.

Now you said pleasant and unpleasant. If you're in the non-limbic areas, there is a very mild rewarding effect of being stimulated. But if someone's very sleepy, it's probably non-rewarding. But if you're in those limbic areas, and you're up and around the central gray, it's generally negatively rewarding.

If you stimulate an animal there, they generally will work in order to be able to-- they'll do something, take some action, if they've learned how to turn it off. And they will work to be able to turn it off. They don't like to be stimulated there.

Whereas if you're in those ventral regions, the ventral tegmental area, we say you get high levels of self stimulation. That is, they will turn the stimulus on by themselves. They very quickly learn. It's a very effective way to train animals to do things if you have the electrodes placed in those areas and they can stimulate.

And then I just talk a little bit about ascending and descending connections. I do the same thing here for the second type of arousal, you can call it limbic arousal. And notice here I mention, besides the hypothalamus, connections to the limbic midbrain area. These are the other major forebrain systems besides hypothalamus.

I didn't mention epithalamus, but it should be included. But in the endbrain septal area in front of the thalamus right between the hemispheres there's a structure right on the midline. It's called the septal area. And then below it, the basal forebrain in front of the hypothalamus, between the hypothalamus and the olfactory bulbs.

We'll see that picture a number of times in the next five classes. Then the hippocampal formation.

We talked about the medial pallium being important to spatial memory, that it is part of the limbic system. And there's a good reason why it evolved that way.

And then the amygdala which you probably know very well by now. It's associated with pleasant and unpleasant feelings towards things that we perceive. All right.

So let's talk about the hypothalamus here, and what it does besides controlling the autonomic nervous system. It controls the endocrine system by way of the pituitary.

The pituitary is attached to the hypothalamus. So how does the hypothalamus-- how do hypothalamic neurons control secretions from the two major parts of the pituitary? One that's directly [? between ?] part of the CNS, and one that's a gland that's right next to the CNS.

Those two parts of the pituitary, they're called anterior and posterior, because of how they're placed in humans. In the rodent, the posterior pituitary is above the glandular pituitary.

I've drawn it here from studies, fairly recent studies, of the rodent, and these are pictures that [? Nauda ?] did of these structures in the human. OK, let's look at the rodent here. You see the posterior pituitary or neurohypophysis, that is the neural part of the pituitary, receiving axons from these two cell groups in the hypothalamus, the ventricular nucleus, supraoptic nucleus.

See the axon coming in. And those axons that are ending in the neural pituitary, the neurohypophysis, aren't ending on neurons. They're ending on blood vessels.

So yes, they secrete a transmitter, but the neurotransmitter now enters blood vessels. It doesn't do that to distribute throughout the body, though. I'm sorry, it does that because it's a hormone distributed throughout the body, and [INAUDIBLE] pituitary here.

They come from these neurons, both of them. They give rise to two hormones. Do you remember what they are? Oxytocin and ADH, which means antidiuretic hormone. And what's the other name for antidiuretic hormone? Vasopressin. OK, because it causes vascular constriction and can affect blood pressure.

An antidiuretic hormone, of course, is involved in food retention. So if someone suffers a tumor that's in this region, it affects the stalk of the pituitary, and blocks these hormones so they're no longer secreted into the bloodstream, a person has a pathology called diabetes insipidus.

It's called diabetes because the symptoms are actually the same as the acute onset of diabetes mellitus, and the person lacks the ability to secrete insulin. Because when the person can't secrete insulin, he uses different metabolic pathways to get energy and get glucose into the cells of the body because you need insulin for that.

So he uses other metabolic pathways and starts metabolising his muscle tissue. That produces ketone bodies in the blood which raise blood acidity and that can kill, of course, if it goes on too long. Sorry?

AUDIENCE: [INAUDIBLE]

PROFESSOR: The ketone bodies are what cause the thirst to get so high in acute onset diabetes. I experienced that for a while, and I got diabetes. And I felt very thirsty and was drinking a lot of fluid to basically get rid of the acid.

So you have the symptoms of polyuria polydipsia. Polydipsia means drinking all the time, thirsty all the time. Polyuria causes a lot of urination, and, of course, you're getting rid of the acid. You're also getting rid of a lot of sugar because the blood sugar levels get high.

Normally, ketoacidosis, that effect, does not occur if I just get high blood sugar today. It would take a long time and a lot of insulin deficiency for me to develop enough ketone bodies to cause that kind of problem. But that's what actually kills in diabetes. Unfortunately, the high blood sugar has a lot of other bad effects too.

All right, so we call it diabetes insipidus because you get the same symptoms, polyuria, polydipsia. But now it's because of the lack of ADH, OK. They don't have normal regulation of fluid levels. So people with that, just like insulin diabetics need to be treated with insulin, people with diabetes insipidus need to be treated with these hormones.

And, of course, more importantly, you have to deal with the tumor. Sometimes they can reverse the effects just by getting the tumor removed. It's very difficult surgery because of the location, OK. But surgeons have learned ways to get at it. They can actually go through the roof of the mouth to get at the pituitary above it.

All right, what about the other part of the pituitary? I call it here the adenohypophysis. Adeno means glandular tissue. OK. The glandular pituitary or glandular hypophysis, it's also being the secretions from the adenohypophysis, secretions like the hormones that affect the gonads, hormones that affect the adrenal glands, the adrenocorticotrophic hormone, OK.

Gonadotropins, they don't secrete directly testosterone and estrogens. Those are secreted peripherally by the testes and by the ovaries primarily, and also somewhat by the adrenals, OK. But the hormones from the hypophysis here, the adenohypophysis stimulates those hormones.

And their secretion is affected by the hypothalamus from neurons like those here in the median eminence region, this region of the hypothalamus, the arcuate nucleus where I show you, here, cells in that region with axons that are going in to the proximal part, here, of the neurohypophysis and also ending on blood vessels.

But now they're ending on blood vessels that enter this hypophyseal artery, which then has many branches into the adenohypophysis. Those factors, they're called releasing factors, get to the adenohypophysis also through a vascular system.

We call it a portal system because there are capillaries that pick them up, and then they go to a larger vessel, a portal vessel that gets them over to the adenohypophysis. Then you have another capillary bed where they're released. And that's shown here in humans. He shows the vascular system, sort of a cartoon of that here. So a capillary bed, a portal vessel, and then another capillary bed.

I tried to change it in the text from portal vein to portal vessel, because I thought there was a regent who might want to call it a portal artery. But it's so traditional to call it a portal vein that copy editor changed it back to portal vein. So I did try to correct the language. Ha-ha. But anyway, that's the way the system works. It's important to know and it's very important in understanding human pathologies.

So [INAUDIBLE] I already mentioned, I think, the major answer to question four, and I talked about question five, diabetes insipidus. So what are the homeostatic mechanisms associated with the hypothalamus. Are we already way beyond time? I guess we are, so we will stop, and we'll come back-- we're finished right here, we'll come back to question six. And it shouldn't take too long to review that if you've read the chapter, OK. So then we'll continue with the limbic system, and we'll begin talking about connections between hypothalamus, some of them by way of the thalamus, to the limbic system structures.