PROFESSOR: So, no quiz today and no quiz Friday, but I am posting a homework that will be due Friday, very late on Friday. We can't officially have them do after Friday, but I felt the homework would be more useful to you in getting ready for the final. I wrote eight questions. We want you to write on six of them at least. If you want to write on the extra ones, if you have time, that's fine. We'll give you extra credit for that.

All right, now, from the last session, what we didn't finish was talking about-- we talked about stem cells put in the brain as a treatment for Parkinson's. And I want to talk about the cells that are being generated normally in the adult brain. This was first discovered here at MIT when Joseph Altman was in the department, before he took up a position at Purdue University where he's spent over sense.

He discovered them in two places. We talked about one of those already, the new neurons that are generated in the olfactory bulb. But he also discovered that they were generated in adult rats in the hippocampus, specifically in the dentate gyrus, the granule cells of the dentate gyrus, similarly in the olfactory bulbs. They were the granule cells that have turnover, about a 40-day turnover in rats, and they migrate from the lateral ventricles to the olfactory bulbs and in the hippocampus.

Similarly, they're generated in ventricular layer, and they migrate to the adult position, there's turnover of those cells. It's not that we're getting a bigger and bigger dentate gyrus, because we learned more and more, there's actually turnover.

There are data obtained by some labs that indicate that there's a much lower level of generation of new cells in other places as well, including neocortex. But it's been a lot more controversial. When you're just looking at Nissl stains, it can be very

difficult to discriminate some glial cells, some astrocytes from neurons.

But with all the reports that have appeared and the studies that have been done, there are antibodies that allow them to discriminate, that there appears to be some new neurons generated in the adult brain. But we really don't know anything about them and their function, except in the hippocampus where they've been studied.

These are just pictures to remind you about-- I noticed here, looking at these old *Scientific American* figures by Kemperman and Gage, where they were talking about the new cell generation in the hippocampus, they have this picture and they show this box here. And then, here's the blow-up. And the blow-up is from down here. Because, notice, down here the dendrites, the cells would be here and the dendrites would be going up like this. Well, there, the dendrites are going down.

But these are the way those little cells and the dentate gyrus. This is a study I did put in the book because it gave a demonstration that these two cells are being generated in humans as well. These were people that were being treated for cancer, and in taking tissue from the cancer, they needed to know how much new cell generation was there.

You know in a cancer there's abnormal proliferation of cells. So they give them bromodeoxyuridine, which labels the newly generated cells. So in patients who died, they were able to get some tissue. This is just an example of that, where they show up, BRDU-labeled granule cell, indicating that it was generated around the time that BRDU was injected.

All right. Now, the studies of this cell generation in rats, they not only look at the cell generation, they look at it's rate and what conditions are affecting it. And this is from an earlier study where they had shown that if you enrich the environment-- this is an enriched environment. These-- are these mice or rats? Well, it happens in the both of them. I think these are rats. That shows they're small rats. And they show-- and all kinds of toys, a place to run around. They're changing these toys a lot so they keep some novelty there.

So the rats are always exploring. And when they have an environment like that, instead of just putting the same number in a small plastic cage where there's not much to do, these animal show a lot more neurogenesis in the dentate gyrus. There's a picture showing different rate of neurogenesis.

Now if you look online, you'll see that the more recent studies have extended this kind of work. They found that animals that are under a lot of stress-- I mean, if you give them learning to do, but it's very stressful and they're being shocked or this or that, animals under stress produce fewer new cells in the dentate gyrus so the cell turnover is much less or slower. Whereas, the happy animals, the animals that are getting reward, and it's not stressful, they are generating more cells.

So people with-- these are fairly new findings, but it should apply to humans as well. It's a good incentive to get married and be happy because you'll be happier and you'll generate more. You'll remember things better.

AUDIENCE: Is there any advantage for making less cells when [INAUDIBLE]?

PROFESSOR: Yeah, what would be the function of that? It's a good question. That's what we have to think about. We need the research. But if you look online, you will see there is some recent work in this area. I suggest in the book that we know that young neurons in the brains with a lot of young neurons, in other words, that are developing animals and people, the amount of learning they do is much, much greater than in adults.

Think of acquiring language. Kids are learning many new words every day. That's a lot of learning. They're learning many other things as well. So it just could be that young neurons are going to be more plastic, and the data indicate that that's true.

AUDIENCE: [INAUDIBLE]?

PROFESSOR: In stress, yes.

AUDIENCE: [INAUDIBLE]?

PROFESSOR: In other words, the growth itself is taking up energy, interesting.

AUDIENCE: [INAUDIBLE].

PROFESSOR: Very good, this is in Ki Goosens' lab. They've been studying stress affects since she's come to MIT and joined the faculty here.

I just want to show you briefly this experiment with implantation of stem cells. I thought I had done this last time, but it's here. This was an earlier work. And this has been going on and it started just a this little before this. But you will see this kind of work going on right up till the current year. There's a lot of it and a lot of competition in the area now to find sources of stem cells that can be used in treating human patients, including Parkinson's, but other things as well.

This was an experiment just to prove that in rats you can get these cells to survive. So in this picture of a brain from the medial side that you've seen before, I show the level of a frontal section that goes right through the basal forebrain and septum, with some neocortex at the top.

And here's the picture from the rat. And what they've done is they've injected a cannula that goes down like this. They're injecting into the basal forebrain here. Here's the septum area up here. These are the basal forebrain structures; olfactory tubercle there at the bottom.

And they've taken the pictures of histological results where they made the section right through where the cannula went through the tissue. And as they put it in, some cells, of course, leaked out of the cannula, even though the main injection was down here in the basal forebrain. And there you see labeled cells. Four to nine months, they got results. Four to nine months after these were put in they got these results indicating that these cells are surviving over a long period of time.

And in the area of the injection, you can see many living cells that weren't native to this brain. They were put in, so they know. But what do they become? Do we even though that they're neurons? And so, they tried staining for neurofilament protein, staining with glial fibrillary acidic protein to label astrocytes.

And they saw that they got both astrocytes and neurons after these implantations. And then by looking at the other proteins, they showed that some of these cells are cholinergic, like the basal nucleus, medial septal cells.

Various cells in the basal forebrain, from the basal nucleus on up into the septum, use acetylcholine as a transmitter and some of these stem cells are differentiating, not only acetylcholine cells. But they're picking up signals from the local environment that affects their differentiation. Remember, they're stem cells when they put them in, totally undifferentiated. And then they are maturing in the brain and differentiating.

And here, I just mentioned that it's being done here at MIT in Rudy Jaenisch's lab. And he had various collaborators. And this is the reference to a paper they published in the proceedings of the National Academy of Sciences in 2008. And notice that it involved Martha Constantine-Paton in Jaenisch's lab and various people that helped with that research.

And you'll see other publications in that year, and there's been a number since. Means of methodology for large scale generation dopamine producing cells that will differentiate into dopamine galecic cells from stem cells. They have various sources of these stem cells. Ideally, if you can get stem cells that you can generate from the patient themselves, it's the best.

All right, let's talk about neocortex now for the rest of the class. In this first class, I just want to talk about evolution and functions of endbrain structures. So some of this will be reviewed, because I want to bring things together and make sure you're understand major points about the endbrain, a number which I've been talking about at various times in class.

So in this first class, we'll talk about evolution and functions. And next time, we'll talk about cell types and how their connected, different regions of the neocortex, major fiber roots in and out of the endbrain. And then we'll talk about the thalamocortical system and about association cortex, where are they getting their thalamic input, the transcortical connections that interconnect these association areas. And I'll say

a little bit about evolution of that thalamic structures.

And then finally, this is the last chapter of the book, chapter 34, we'll talk, go back to development to talk specifically about neocortical development, because some of it is a little different from the spinal development that we focused on initially. We also talked a bit about development of the tectum, and then cortical plasticity, especially with an interest in adult plasticity and the structural changes that have been found.

All right, so this is a picture we've seen a few times. It was one of the early studies using gene expression patterns to show how gene expression patterns for certain genes. Here, this is these two genes. It looks like I screwed this up. I didn't take the right one. Because what they actually did, as I remember, is EMX-1, and then the gene that's expressed in the green areas there. Sorry about that. It's correct in the book. I checked that and double checked it.

But anyway, regardless, it always shows this kind of pattern, where you-- the cortex in mammals expresses EMX-1. The same gene is expressed in the frog in the dorsal cortex. And dorsal cortex there including the medial pallium, which become hippocampus. So that would be way over here in the mammal. And it also includes a large part of the olfactory cortex.

And then, this is the striatal area, which expresses different genes. And these intermediate areas express other genes that they didn't study in this initial work, but that corresponds in the mammal mainly to the amygdala area in the claustrum, the amygdala region. And they find that gene is expressed in the dorsal ventricular ridge area of the reptiles and the birds.

We don't call it dorsal ventricular ridge in the adult bird. We call it the nidopallium and subcomponents of the nidopallium. We keep calling it dorsal ventricular ridge in reptiles and turtles. You see it's there in frog also, but not in the same configuration.

All right, so we think it's not just gene expression patterns that indicate this. We think the neocortex of mammals evolved from the that dorsal pallium or dorsal cortex of the ancestral vertebrates. And the dorsal cortex of amphibians and reptiles evolved

from that same area. And the hyperpallium of birds evolved from that region in the birds. So we'll show pictures of that part of the hyperpallium we call the wulst. It can be compared to neocortex, quite specifically, in terms of its connections.

And this refers to the amygdala, which now the gene expression data I should point out, is actually much more complex than this indicates. And there's been a lot of it, and there's multiple genes. And sometimes, the expression patterns don't lead to as clear cut a conclusion as others.

So in the book, basing that kind of complexity, I do site that kind of data. But I've stressed function and connections because I know it's the connections that ultimately are determining behavior. It's not those gene expressions that determines the function. It's the, connections and what they become. And we'll see, the neocortex is actually made up. We've already seen that. You get contributions from various structures, not just that ventricular layer of the neocortex. They come from subcortical regions, too.

And the same actually is true for these ventral structures like the amygdala and the anterior olfactory nucleus, which is part of the amygdala. Again, it's partly pallial, partly striatal. And the neocortex itself is like that. So that's one of the complexities we're faced with.

So I looked at the amygdala and I study the connections, its inputs and its outputs, and its connections with itself, different components of the structure, and I see that it is a single structure in terms of function. So that's the approach I take because I'm interested in function primarily because I know that that's what drives evolution. It's the functional adaptations.

So what sensory modality and what projections in that modality underlie the two major types of learning that I've been talking about in this class, so important in evolution of the forebrain? So what are those two types? And what are the structures in the center of? One of them? Sensory motor habits, the other spatial learning, knowledge place and the things in those places.

So that's what we usually talk about when we talk about long term memory. But it is separate from habit formation, the striatal learning. So what was the modality? The initial one that dominated the endbrain, the primitive endbrain, which was olfaction. Olfaction initially totally dominated the endbrain. The endbrain is basically an outgrowth of the olfactory system, which developed up there in the rostral end of the brain in front of the primitive diencephalon.

So these are the two kinds of learning. So we talk about object-- identification of objects and places. Very different kind of learning from the midbrain, because the midbrain, remember, when this was happening in the forebrain, animals already had this huge-- had a midbrain, a midbrain, that in some animals, became very, very large. Remember, the predatory fish, the enormous optic tectum and little endbrain.

But what kind of learning goes on the midbrain? Not these kinds of learning. You don't have reinforcement learning and habit formation. You don't have a long term memory for places. What you have is innate recognition, triggering of innate responses. Think of the frog and his feeding.

So we talk about-- I think ethologists give the best descriptions of that behavior, when we talk about visually elicited fixed action patterns, where the key stimuli for eliciting them are visual, many of them dealing with optic tectum. The plasticity is just sensitization and habituation in the tectum. But in the endbrain, you've got a lot more than just olfaction. You have these new forms of plasticity, the two types I just mentioned.

And I just spell that out. You can read any of this. And here, I just spell out some details about the ancient inputs to the object learning system and the original outputs. They're very much like the connections to the amygdala and ventral striatum we've already gone over. And then, the learning, place learning, allowed anticipation of odors reaching the nostrils, and the possible act they could anticipate, the actions needed, again, evolved largely out of the olfactory system.

And of course, later, the non-olfactory inputs became more and more important.

And certainly, in the primates they become dominant. In most primates, though in some primates olfaction is still very important. And we know that the medial pallium is the most critical structure, important for those functions that evolved in the hippocampal formation.

So then I talk about that invasion of non-olfactory inputs. You can read through this just to remind yourself of that when you read these slides. And what that did-- this is the questions I put in. So from what part of the primitive pallium in pre-mammalian reptiles did the neocortex evolve? What do I say earlier in the class? What is it called? Dorsal pallium or dorsal cortex.

What part of the mammalian cortex does this pallial region in modern reptiles most closely resemble? Well, how do you study that? Look at connections. So when I asked this question, I was surprised that anatomy books never do that. I just loved to see studies of dorsal cortex in reptiles, and I found some. And I looked at the projections. They're all light connections of parahippocampal areas in the mammal. They're not connections like neocortex at all. Although, there are connections from non-olfactory modalities come in there.

Part of it does get direct olfactory input, but much of it doesn't. Most of it's multi-modal, but sometimes you even have uni-modal areas developing. But the outputs are going into the medial pallium, which is the major, thickest part of the pallium in these animals. Remember that very thick medial pallium of the frog, for example.

And yet, that area is-- that dorsal cortex is the part that changed in the mammals as the neocortex evolved. And what structure in the bird endbrain evolved in a way that resembles the way neocortex evolved in mammals? It's got a couple of different names. Any of you remember?

The wulst is one name we use for it, and I'll show pictures of that. We also call it the hyperpallium. Now they call all those structures pallial, probably because of their homologies with mammals and also because of how they develop in the embryo. They are originally pallial.

So this is just about what I just said. So why did mammals evolve a neocortex and birds evolve a wuslt? You know, it's a very good question that Altman takes up in his little book. He describes the avian wulst as much more efficient. What does he mean by that? This is a picture where I show the structures when we talked about the visual system.

I'm showing the geniculate pathway carrying visual information to neocortex, and a pathway through the tectum, the superior colliculus. It goes to the lateral thalamus, a part of the pulvinar. Usually, we call it LP in the lab animal, the little animals we use, the rats, hamsters, and mice. And it projects primarily to the extrastriate visual areas. By primarily, I mean where the densest projections are. They do project more broadly as well, but these are the main projections.

But if you look at reptiles and birds, they also contains these two pathways, one homologous to the geniculostriate system. And that one goes to this dorsal lateral cortex in reptiles. And it goes to the wulst, the hyperpallial area in the birds. And in very visual birds that have a large endbrain like the owl, the wulst is quite large. And, it's in fact, much thicker than the neocortex here.

This other pathway doesn't go to the wulst. The other pathway here in reptiles goes to that dorsal ventricular ridge area that stays subcortical. So it's a subcortical structure. But it's not-- it used to be called striatum or neostriatum, but we don't call it that anymore because it's not homologous in its connections or its development to the striatum. And that's been supported by those gene expression studies.

The striatum is down here. The stratum is down here in birds. But this whole area in between the real striatum and the wulst is called the nested pallium, or the nidopallium. We subdivided the part that gives the visual projection here from the tectum to nucleus rotundus, which is much larger than this area that gets direct input from the retina. It goes to this area called the entopallium.

That was one of the discoveries made here at MIT by Harvey Karten, who I've been in touch with recently by the way. He's interacting with me a bit about the book. I

send him a copy of it because he's been such an important player in this field, and he's still quite active in the San Diego area. He's in La Jolla.

So this is Altman's simplified picture of neocortex and that much thicker wulst area. wulst means bulge. And you can see how in this section how it bulges out from the rest of the endbrain in the owl. It's a little bit-- we picked an owl and an owl monkey, but any monkey would do to make such a comparison. But we're going to talk about this simple lamination of the neocortex. The wulst lamination is much-- there are many more layers, and the cells are different. We have the pyramidal cell in cortex. These neurons in the wulst are generally stellate in shape.

So to get the same processing power that you have in the wulst, mammals have evolved multiple visual areas that are interconnected. It seems to work extremely well, but with two disadvantages. You've got a lot more axon. Here the axons are shorter, interconnecting the different parts of the wulst because it's a thicker structure.

So we have to ask, well, what are the advantages? Just look at neocortex first. This is a well known type of illustration, illustrating cortex in three different histological stains. At the far right is a Nissl stain, where you see the shape of the cell body and the density of the cells and their size in the different layers, which are numbered here. Layer one is always a layer of very few cells at the top. And you see here on the Golgi picture that that's mainly a layer of dendrites and axons. Here in an axon stain, you see that. A lot of axons, including many transversely running axons in layer one.

And layer two and three are the smaller pyramidal cells of cortex. And you see them here in the Nissl, where the really big pyramidal cells are down here in layer five. And that's where you find the cells that give rise to the long outputs to subcortical regions.

Some of the pyramidal cells in layer three or three B here are pretty large also. They're the ones with long transcortical connections. And then in layer four, this varies a little bit with the species and the stain you're using. You can see here, int

good Nissl stain they're always small cells. And if we look in the Golgi, we see that there are these stellate cells that are generally not pyramidal cells.

And there are other non-pyramidal cells scattered through the cortex. Here in the fiber stain, you see a couple of additional things. For one thing, you see that there's more than just six layers. Even in the Nissl stain it would be easy to name more than six layers. Layer six is always going to be divided into usually at least three layers.

But to make sense out of all cortex and using the same kind of terms, we name just six layers, and then we talk about sublamination. Fiber stain show some additional layers because of these layers of transverse fibers. And then we see these fibers that travel perpendicular to the surface of the cortex that divide the cortex up into these different columns.

And we want to know what those axons are. What are the transverse fibers? What are these vertically travelling fibers? And this is just a more-- just look at the Golgi stain. I took one here from Poliakov, a great Russian anatomist, and some of his pictures of the cortex which are quite elaborate and nice, and we see more of the cell types here. You see some of the stellate cells in very dense, dendritic arbors and axonal arbors. You'll see some of them are-- well, you'll see in the book that there's a picture there showing different cell types in the cortex.

It's actually in chapter 33, which you may not have looked at. But the first two pictures in chapter 33 show some interesting things about these cell types in the cortex. 33-1 one shows two major types of cells, the excitatory glutamatergic cells, and then the other type are all inhibitory. Also, the first type is spiny. The second is non-spiny.

So they're different in their morphology. Both groups include some stellate cells, but especially the cells using GABA, the inhibitory interneurons. In the Golgi stain you can't see which of these-- most of these are, in fact, inhibitory interneurons. The main excitatory interneurons are the neurons in layer four.

In this chapter and in this particular question I'm asking for descriptions of different

types of axon projections, axons that start in the cortex and end in the cortex. Remember, we talked about propriospinal connections. Well, these are propriocortical connections. And some of them are just connection within a column. Others are across columns. And the others are long transcortical connections. And those generally go into the white matter. They go down in the white matter, and then they travel over a long distance to another cortical area, where then, they go back up into the layers of cells.

So this is my picture of a single column where I've taken the cells and axons and I pulled them apart a little bit to make it broader than it really would be so you can see the different types and how they're connected. I show one of the large pyramidal cells in the deep part of layer five. It has an axon that goes out, generally to subcortical areas. And I simplify the dendrites because if I drew all of them, then you wouldn't see the rest of things, the rest of the cells.

So I'm just giving examples of the major dendrites, the basal dendrites and apical dendrites, and I'm showing that they arborize-- these dendrites arborize up in layer one. I show a few cells in layer one with a dendritic spread, and then, longer axon distribution that's mostly interconnecting adjacent areas of cortex.

Then I show the pyramidal, smaller pyramidal, cells here. I show the small granule cells in layer four that are receiving input from the white matter. This would be an axon coming from the thalamus. I show where it's main connections are in layer four.

There are other connections. They also go to layer one and layer five and six. In fact, they really go to all the layers. But they're much denser in layer four, so we often picture those terminating in layer four. And they're terminating on these excitatory interneurons, which then have axons that connect to the overlying areas, primarily.

And then I'm showing connections from these layer six neurons, some of which go out. They go to the thalamus. And others go to the other layers. So these are inter-columnar axons, several types in layer four, in layer six. And also from these upper

layers where you see-- this is axons. They almost always have collaterals, even if they're going to another area.

And this, what do we call this type? It goes down into the white matter, goes to another area, then goes back up. We call it a U-fiber because it's going down, over, then up. Those are the U-fibers. These others are intercortical axons that are not U-fibers. They never go into the white matter.

This is very typical of a-- it's a very simplified picture of the columnar arrangement that's repeated throughout the cortex. This just shows some-- These aren't from Golgi. They're injected cells in more recent studies. This is the work of Charlie Gilbert, I believe, who worked a lot with Hubel and Wiesel, and has published a lot on these neuron types in the visual areas of the cat and the monkey. There's another one where he shows the stellate up in layer two and three, elaborate dendrites and axon.

So to just talk briefly about the basic sensory motor functions of the cortex. We know in the sensory cortex that when you have motor cortex devoted to a given area of receptors, you have more acuity. So if you look at the foveal representation, visual cortex is much greater than the representation of the lower acuity regions of our visual field. The same is true for somatosensory cortex.

So what are the big parts of somatosensory cortex? Parts representing the fingertips, the tongue, lips; the parts where our acuity is the most. The same is true of animals. Remember when we showed picture of the raccoon. It's actually got a different gyrus for each digit-- very high acuity in their front paws.

And the same thing is true in the motor system where we could talk about motor acuity or dexterity. We're talking about the hands. But it's true for other parts, too. The spider monkeys has high motor acuity in his tail, so he's got a lot more cortex representing the movement of that tail.

And of course, that's true for the tongue. We don't just have high sensory acuity in the tongue, we have high motor acuity. We need it not only for speaking, but for

manipulating food and for all the various things we do with our tongue. We're probably the best kissers in the animal kingdom because of that, tremendous control of our tongues.

All right, so, then I bring up this-- I like to refer to Mesulam because he made this so clear in his recent writings. He pictured the paralimbic cortical areas as divided into two main regions. Now these are-- the paralimbic cortical areas are sort of in between the neocortex and the limbic areas. Some people would say, well, there really are neocortex. But if you take a strict structural definition of neocortex, they don't really have the same kind of six layers. You could easily name six layers there, but they're a little bit simpler cortex. But they're always in between neocortex and limbic areas.

In fact, a lot of the connections going both ways from these paralimbic areas, but the two regions correspond to what we've been talking about, a place sense and object sense. So let's just look at his picture here. Here, I put this in the book. I think we redrew it, but not very much.

And it shows the cingulate gy-- all the away from parolfactory just beyond the anterior cingulate here, through the entire cingulate gyrus and retrosplenial cortex, and then continuous with the whole parahippocampal area. So the parahippocampal gyrus in humans is part of that. So that's hippocampocentric. These areas all connect with parahippocampal areas, which connect to the hippocampus. They connect to entorhinal cortex, for example.

These other areas he called olfactocentric. This is interesting because the connections of all these regions are different than the ones-- than the hippocampocentric areas. They go, for example, they're heavily connected to the amygdala and basal forebrain, the areas that are evolved. They're closely connected to the olfactory system, and to these systems that evolve for object discrimination or our affective responses to objects.

And then, I go through one other thing that played a critical role in evolution of the somatosensory system that were one of the somatosensory areas specialized for

controlling fine movement, and that's what we call primary motor cortex. What's the evidence that it actually-- the motor cortex evolved out of the somatosensory area? For one thing, it does get some somatosensory input. It's adjacent to, just rostral, to what we call somatosensory area one.

But in some animals, it's actually not separate, like the Virginia Opossum. Remember this? Do I have a picture here? I guess I didn't put it here. But that motor cortex was so critical, except we can tell which area it is because the ventral anterior nucleus and the ventral lateral nucleus, the parts the anterior to the somatosensory part of the thalamus, project to the motor areas, the VL and the VA.

We usually can separate them, even in the opossum. The VL gets the cerebellar inputs primarily. The VA gets striatal outputs primarily, and it projects to the premotor areas. VL projects to the motor cortex. But in the opossum, these nuclei project to the very same cortex that the ventral posterior nucleus projects, so it's somatosensory.

All right, and what evolved as association areas right in front of these motor areas are the areas involved in anticipating and planning became the locus of the executive functions of the prefrontal cortex, which is so critical for human behavior. But it's very important in animals, too. This ability to anticipate, to get inputs from posterior areas, like from the visual system, to tell them where the locations of things that were just in the environment, scanning, that we're scanning. Retain that information briefly in working memory, and that's affecting where we move our eyes, where we choose to move our eyes.

All right we'll come back here with this slide. And then we'll go on and talk a little bit more about structural details in the hippocampus next time. But please read through all these qualities. And they're all online, so we won't have to spend so much time with the rest of this particular group of chapter 32 things.