Introductory Neuroscience & Neuro-Instrumentation
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Lecture - 6
Neocortical Circuits

Introductory Neuroscience and Neuro-Instrumentation, Neocortical Circuits.

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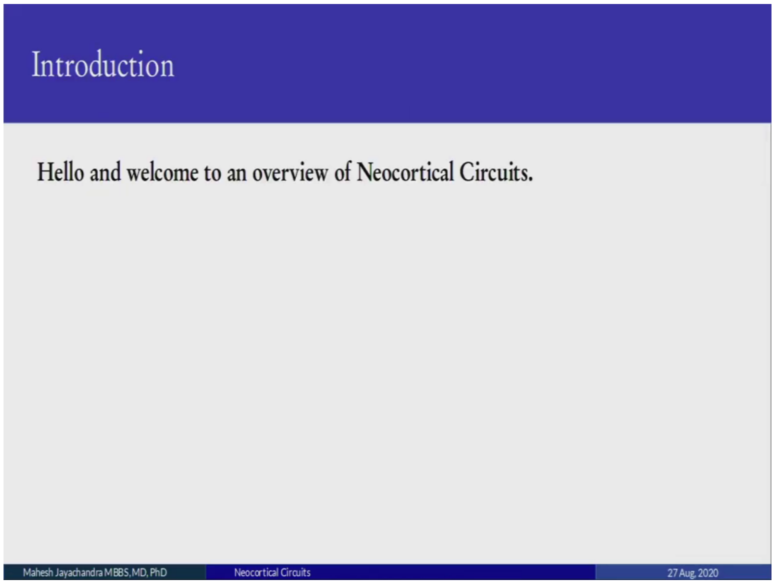

Hello and welcome to an overview of neocortical circuits. These are different circuits in the brain, and this is going to be a little complicated, and you will need all the information we went over in the earlier lectures on histological anatomy of the brain.

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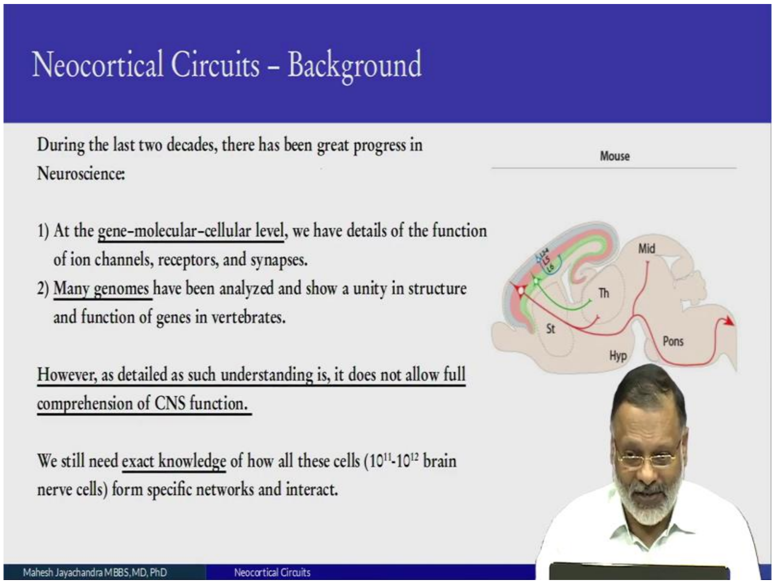

The background, during the last two decades, there have been great progress in neuroscience. We have had a explosion of knowledge at the gene, molecular, and cellular levels with details of ion channels, receptors, and synapses all being worked out.

Also, many genomes of animals have been, different species have been worked out and they show a unity in structural and functional of genes invertebrates especially. However, as detailed as such understanding is, it does not allow full comprehension of the central nervous system function. We still need exact knowledge of how all these cells, we have 10 to 11 to 10 to the 12 cells in the brain, how they form specific networks, and interact.

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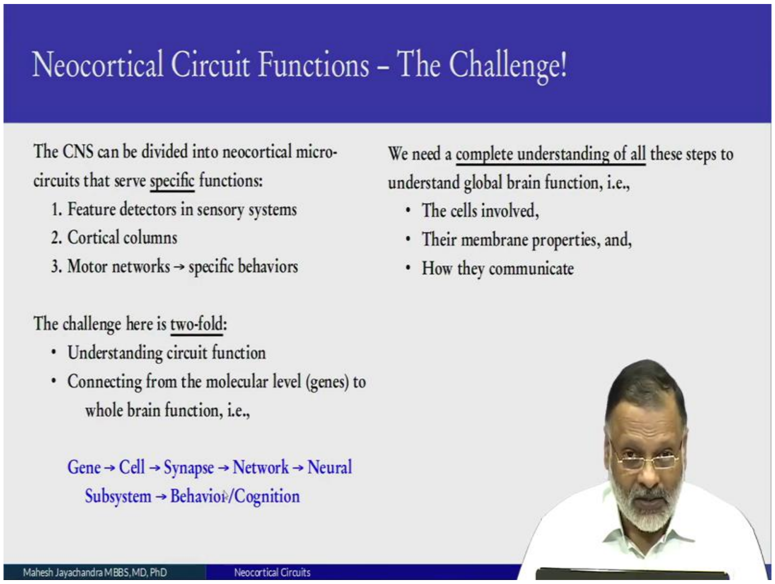

The central nervous system can be divided into neocortical microcircuits that serve specific functions. One, you have feature detectors and sensory systems. Then you have cortical columns, and then you have motor networks which lead to specific behaviors.

The challenge here is twofold. First, we must understand how the circuits function, and then we have to connect from the molecular level to the whole brain. So that means we go from the gene to the cell, to the synapse, to the network, to the neural subsystem which finally gives rise to behavior and cognition.

So, I again emphasize, we need a complete understanding of all these steps to understand global brain function. So the cells involved, the membrane properties, and how they communicate.

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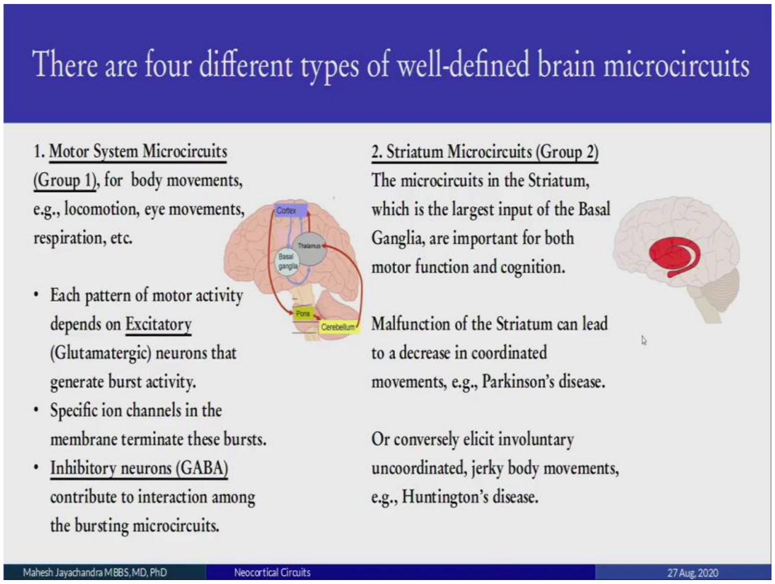

There are four general types of well-defined brain circuits. One is the motor system brain circuits which as the name indicates, control body movement from locomotion to eye movements, to involuntary movements such as respiration, movements of the GIT, so on, and so forth.

Each pattern of motor activity depends on excitatory which you learned from a previous session is subserved by Glutamatergic neurons and inhibitory GABA neuron, these act in tandem and also you have specific ionic channels in membranes which terminate these bursts, otherwise they will just become runaway excitation.

These are the motor circuits and they are basically present in the motor area of the cortex, parts of the Basal Ganglia, thalamus, ponds, and also cerebellum, we have not talked much about the cerebellum, but a lot of motor activity is controlled over there.

The next major group of circuits are the Striatum micro-circuits. This is the largest input for the Basal Ganglia which you have studied earlier in gross anatomy and it is important for both motor function as well as cognition. For example, this is the Striatum and the schematic over here, it is kind of a curved structure.

Malfunction over here can lead to, for example, Parkinson's disease where it usually occurs in older people and they have difficulty in walking, there is start hesitancy, it is difficult for them to begin walking, and their stop hesitancy is difficult for them to stop walking and there are various motor problems. The face as no expression, so on, and so forth.

The converse of it is something called Huntington's disease where you have involuntary uncoordinated jerky movements which are not on your control. Both these pathologies occur because of dysfunction in the striatum.

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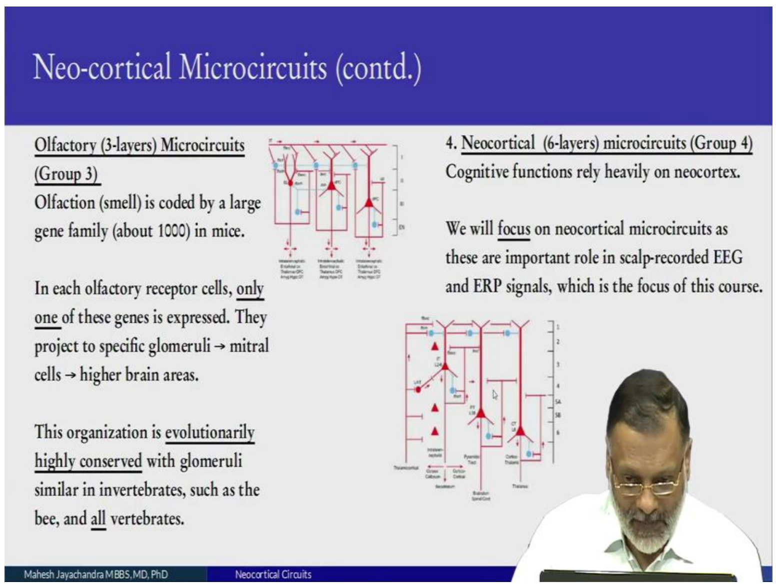

Then we have the primitive brain, the smell brain. The part of the brain which we use to smell, the olfactory system, that is the primitive brain and that has only three layers. And this is encoded by a large set of genes, more than a thousand in mice, and in each receptor, only one of these genes is expressed and they project a specific glomeruli, which is a higher-order structure than to mitral areas and to higher brain areas.

So here you see a typical three-layered schematic, a three-layered cortex schematic and even the hippocampus is we have not discussed that much, it is a deep brain structure for spatial coordination and orientation in space. So that is also a three brain, three-layered structure.

This organization in the olfactory system, for example, is highly conserved and it is similar in all invertebrates and in all vertebrates studied so far. This is the primitive part of processing and it is an older, archaic if you will, part of processing in the brain.

The neocortex which is the main part of the brain which is involved in primate cognition that consists of six layers and cognitive functions heavily rely on the neocortex. And we will focus on neocortical circuits because they are important for scalp recorded EEG and event-related potentials, ERP signals, which is the focus of this course. So below here is a picture of the six-layered cortex, a schematic again.

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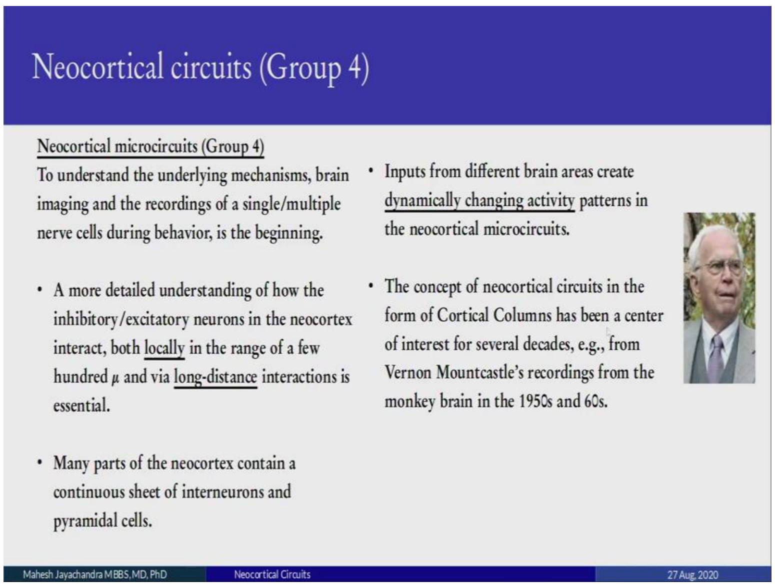

Continuing on what do we need to know really in these neocortical microcircuits, so we and how do we do it? One is we record, we do neurophysiological recordings. The other thing is we do imaging of these nerve cells during behavior. So, but we also need a more detailed understanding of exactly what inhibition, excitation occurs both locally within a few microns of the neuron as well as by long-distance interactions between different areas of the cortex.

So many parts of the neocortex just have a continuous sheath of interneurons and pyramidal cells and these inputs from different brain areas create a dynamically changing activity, it is like Charles Scott Sherrington said, an enchanted loom; you constantly have it flashing and turning and different things are happening.

So the concept of neocortical circuits in the form of cortical columns has been the center of research interest in many labs over many decades and this all stemmed from Vernon Benjamin Mountcastle's recordings, classic recordings from the monkey brain in the 1950s and 60s.

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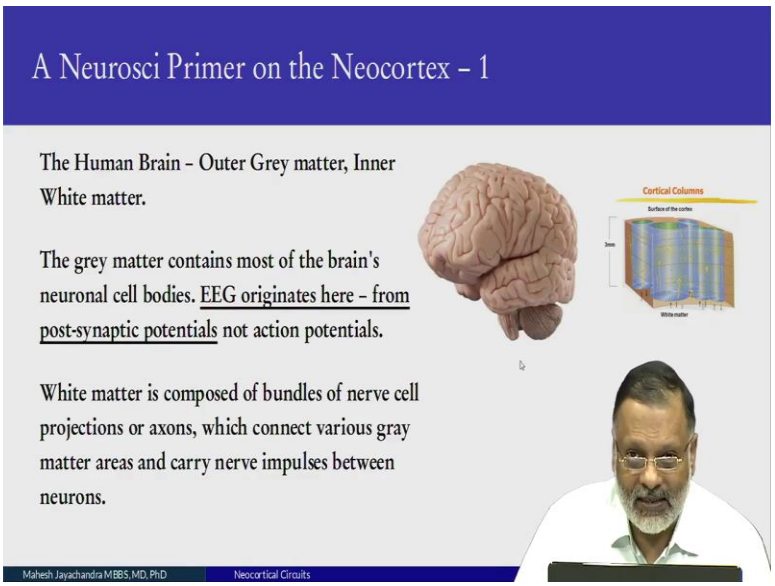

So just a primer, just to refresh your mind. The human brain consists of the outer grey and the inner white, we are talking of the neocortex, this guy. And the outer grey is just a 1 to 2-millimeter thin bed sheet of cortical neurons which cover the brain and go through the sulci and gyri. So this consists, the grey matter is consists of most of the neuronal bodies.

EEG originates here from post-synaptic potentials, the synapses between neurons, excitatory neurotransmitters, so those potentials are not from action potentials this is an important point. The white matter is consisting of bundles of nerve fibers projections, it is a network, it connects one area from the brain to the other and carries the impulses different areas.

So this is the human brain but when you look at just the grey matter, the outer layer, you have it is about as I said, 1 to 2, 3 millimeters and it has six layers, and the white matter is below. Let us consider it in more detail.

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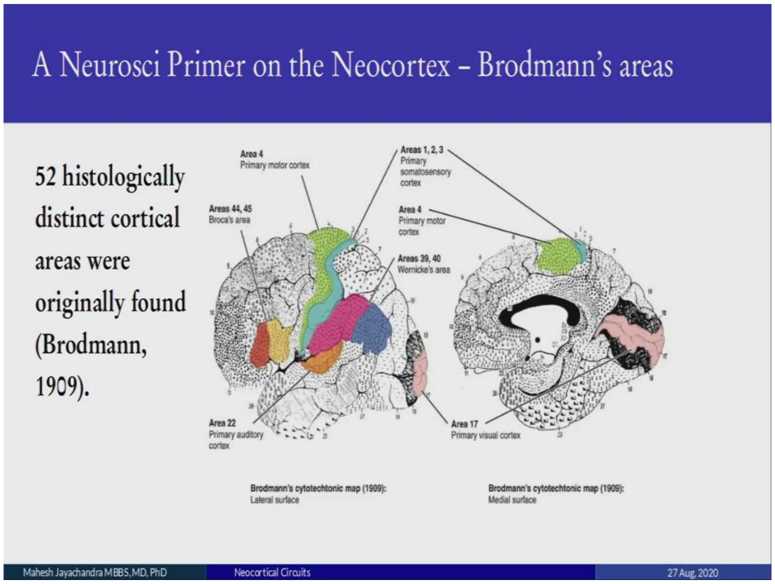

So Brodmann was an anatomist, he did a lot of histology in the early part of the 20th century and he, by on basis of gross histology, he showed that there were these histological areas of the brain which subserved certain specific functions. This is the left view or the view of the brain from the left side and you have area 1, 2, and 3 which is the primary sensory cortex.

Area 4, which is the primary motor cortex. Broca's area which is for language, Wernicke's area is also for language, and area 22 which is inside is the primary auditory cortex. And this is a section looking at the medial surface of the same brain. So, he found 52 distinct areas, and this is based on histology.

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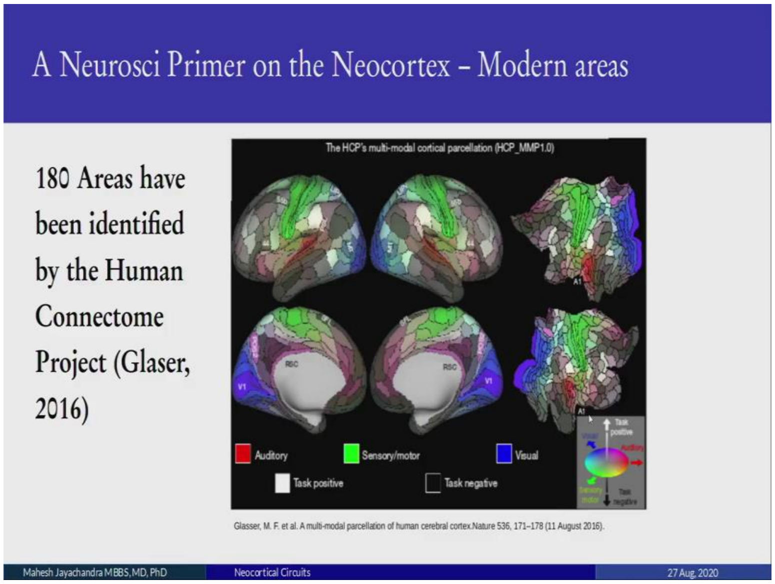

So a fast forward to the 21st century. So based on other imaging methods fMRI and stuff and tensor techniques, we have more than 180 areas which have been identified by the Human Connectome and new areas are being discovered all the time.

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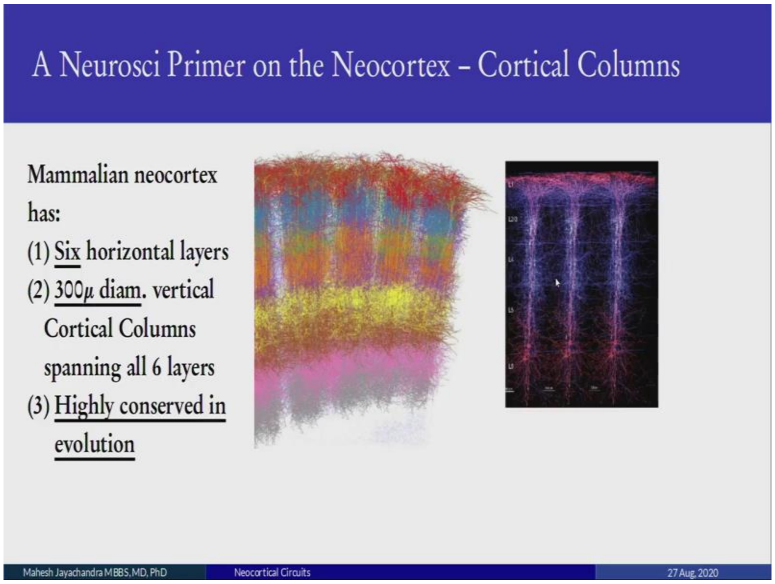

So the cortical column, what is it? So these are remember the 2, 3-millimeter grey area, I mean grey layer, so here you have layer one, two, three, four, five, six and you have this horizontal structure. You also have a vertical structure in the form of these columns and these columns are approximately one-third of a millimeter, 300 mu in diameter, and they span all the six layers.

The interesting thing is they are highly conserved in evolution, rats have it, whales have it humans have it, all mammals have it. Some form of if they have a neocortex, they have cortical columns and that is what is been shown in all the animal studies so far.

If something is so highly conserved in evolution, it is probably very important and many people feel, many scientists feel that this is the fundamental computational unit in the neocortex. It is like a VLSI, a very large scale structure IC, integrated circuit structure, which does all this computation. It is very different from ICs what you have in the electronic world, but this is a metaphor for us to think about.

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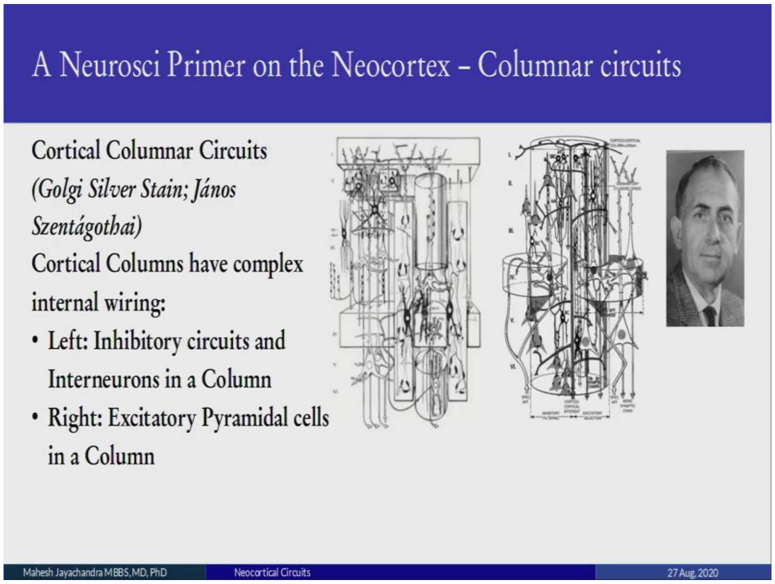

This was some work done early last century by a very famous neuroanatomist Janos Szentagothai and he used something called the Golgi Stain and you have on the left a Golgi Strain but the inhibitory circuits are highlighted. This was all painstakingly drawn with the camera lucida and they are very faithful to what is seen on the microscope.

On the right, you have the emphasis on pyramidal cells, all the excitatory neural circuits and if you remember the excitatory neural circuits, they use glutamate, and while the inhibitory interneurons, they use GABA.

This is complex but it is actually much more complex because he used something called the Golgi Stain. Now the Golgi Stain is a silver stain which is very interesting because it when a cell takes it up, every single part of the cell takes it up. But weirdly enough, only 1 to 2 percent of cells do take the stain.

So actually, what you are seeing here is only 1 to 2 percent of the packing density. If you had all the neurons shown, it would be just a blend of, a band of black; you would not be able to see any structure. So this is a very schematic, and very few elements are actually shown over here it is high, it is far more densely populated but it gives you an idea of the complexity.

And all the arrangements are not haphazard, there is a specific pattern and a rationale behind the arrangement, behind the connectivity both in the inhibition as well as the excitatory part of the cortical column.

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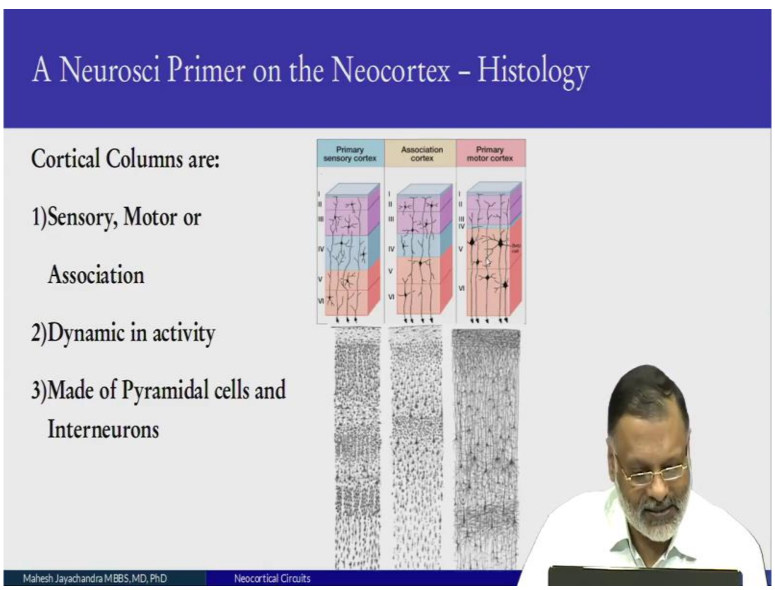

Cortical columns can either be sensory if they are in sensory areas where they have a particular structure or they can be motor in the motor areas. And in the motor areas, you have these big pyramidal cells, they are the biggest cells in the brain. If you remember from our earlier session, the pyramidal cells are the best bets. They are the biggest cells pyramidal neurons in the brain, and this is the actual histology below it.

The part of the brain which is neither primary sensory nor primary motor cortex, we just lump it together association cortex and it can be very variable in different parts of the brain. One thing to bear in mind is that these cortical columns are dynamic in activity, their activity keeps changing. They can be a part of other circuits, they can be primary, as I will show you in subsequent slides, and of course, they are made of pyramidal cells excitatory and interneurons which are inhibitory.

However, there are also a whole bunch of supporting cells. So typically, in a mammalian column, they have estimated they are only about 120 pyramidal cells and about 10 times as much as interneurons, and 10 times that number of supporting cells like glial cells and smaller cells which do nutrition stuff.

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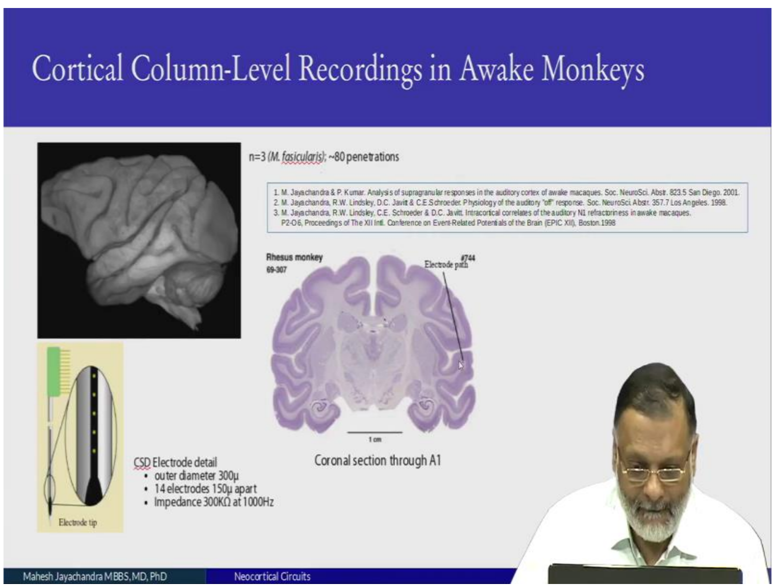

So now, I am going to get into actual data because so far it is theoretical, it is nothing like getting your juices flowing if you actually see the real data which we record from the brain. And these are cortical columnar level recordings, they are from awake macaques, I did these recordings during my post-doc working with Dr. Schroeder and Dr. Javitt and Albert Einstein Nathan College of Psychiatry in New York.

This is a monkey brain, Macaca fascicularis, that is the brain, and we are interested the Heschl's supratemporal plane, inside here is auditory cortex. If you take a coronal section, so we make the electrode, the Barna electrode with 15 points and we insert it right through stereotactically until it reaches the auditory part of the brain.

Now how do we know it is the auditory part of the brain? Well, we do stereotaxis, so we know X, Y, Z coordinate, where the auditory cortex is, and also to be sure we check the histology at the end of the experiment and to make sure the electrode is where we think it was. Without histology, we are not sure, so histology is a very important part. So that is why anatomy is a very important part of neuroscience.

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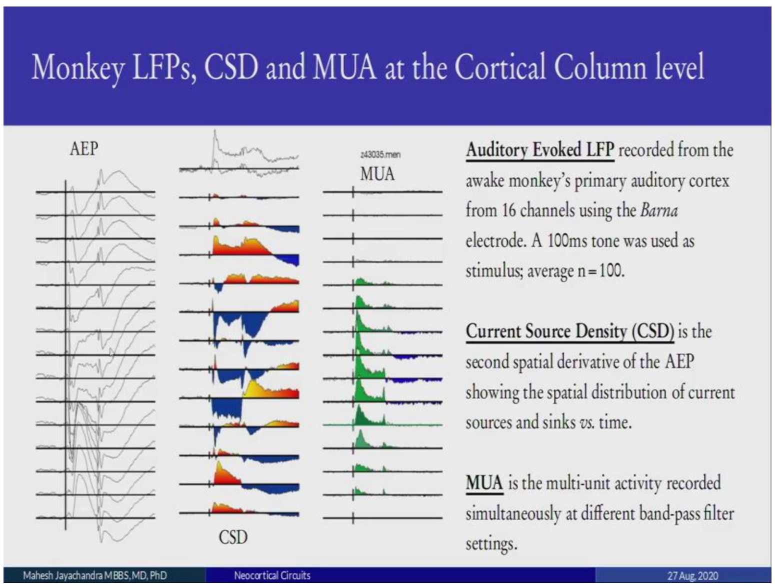

So now we have inserted the electrode and, on the left, you see the local field potential or the, of the auditory work potential because we were giving clicks and tones, you can actually see the tone. Over here it is 100 milliseconds and there is an on response and there is an off response and the regular auditory work potential.

This will all make sense to you much more later, but these are the local field potentials. And over here, the MUA on the rightmost column are the multi-unit activity where the electrode records a population of a single neuron, single units. Now, in between is an interesting way of visualizing data.

We take the auditory work potential and then we take the second spatial derivative and that shows the sinks and sources called current source density calculation, this is in one dimension. So that shows where the current is coming out and where the current is going in and it is an easier way to visualize things what is happening at the columnar level than the LFP by itself.

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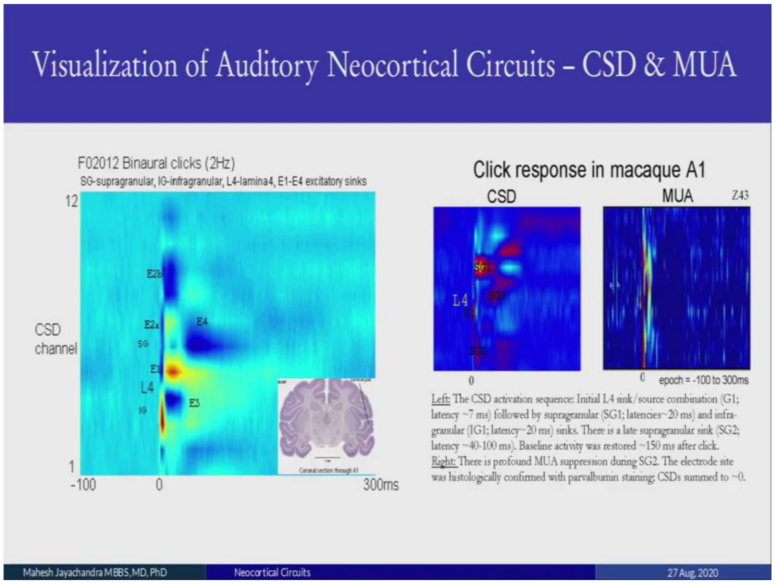

So now, let us see what happens when we give a click. So over here, as I showed the electrodes is in the auditory cortex. And this is a visualization of the current source density, what we saw in the previous slide and this was visualized on MATLAB.

And here, we can actually, this is at layer four because that is where the activity comes and that is our anchor and that landmark which tells us where we are because you cannot do the histology with the electrodes inside, so this is why we are doing the experiment. And then we have all these excitatory sinks, different sinks at different times happening.

And this is another response to a click and simultaneously, we are recording the multi-unit activity and it just shows that the activity immediately there is activity with the click, and then it goes into a depression, there is not much activity and then it comes back to normal. This is baseline same as this.

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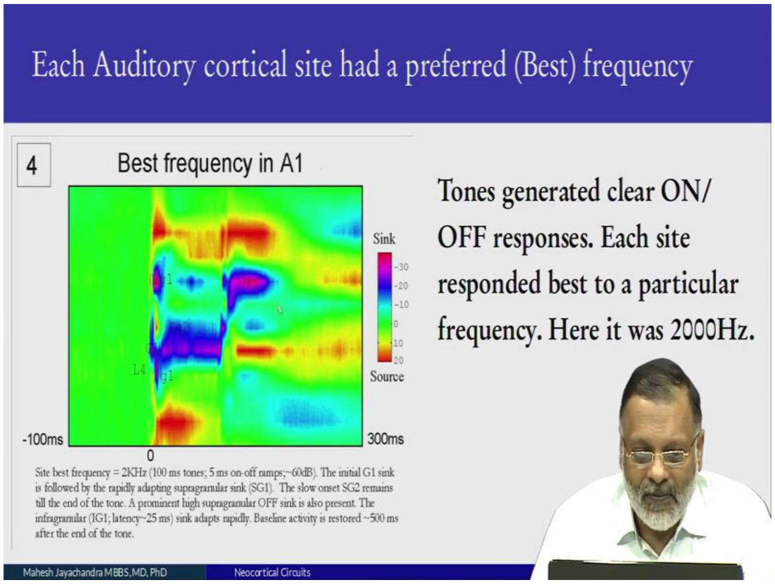

And interestingly enough, if you play different frequencies to the monkey and the electrode is in the auditory cortex, every point in the auditory cortex will respond to tones but it will respond to a particular frequency, it is called the best frequency. So in this particular site, the best frequency was 2000 hertz. It was a tone, so you have an on response and there is a tone, and then you have an off response.

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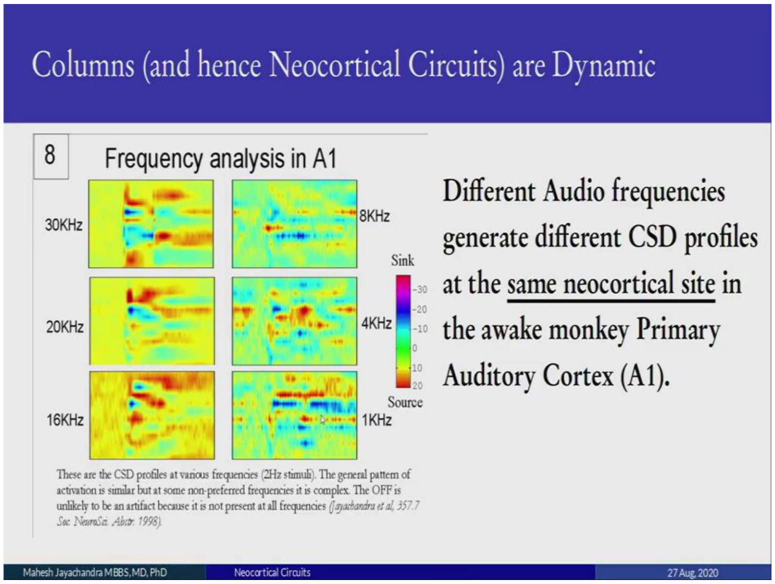

However, every part of the monkey's brain responds to tones, when there is activity it is different. So while the, in this particular penetration of the auditory cortex of the monkey, it responds better 30k, 30 kilohertz; but at the same site when you play different tones, it responds to all of them but in a very complex patterns.

30, 20, and 16 it seems to be kind of similar but there is no pattern really discernible between 8, 4, and 1. So the whole brain acts all the time and also it has some preferred stimuli which it reacts to.

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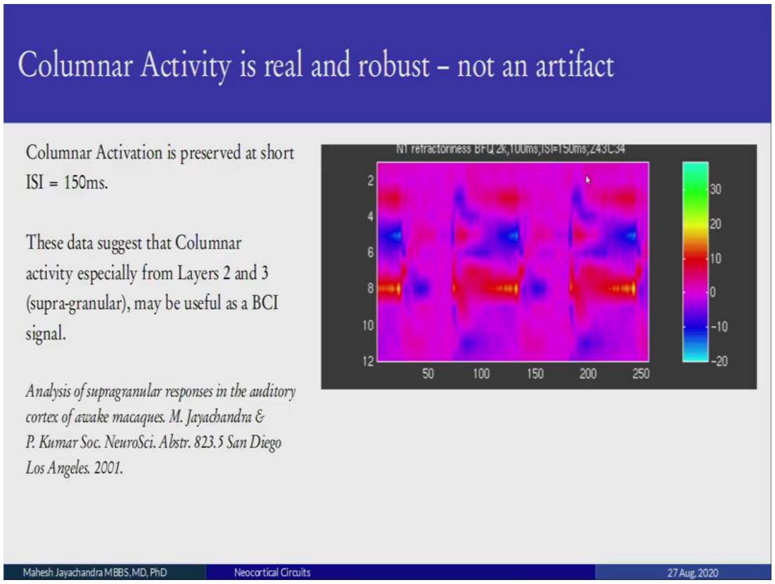

So you might say, hey this is a pretty pictures and they are just nice but are they real? So is it robust or is an artifact? So here we push the brain instead of giving stimuli at once a second, once in two seconds, we pushed it and gave stimuli at 150 milliseconds and you see the cortical column is very robust the activity, and it follows at 150, it does not disintegrate.

I mean, of course, if we make it smaller and smaller, then to stimulus interval, it is going to fragment and disintegrate. But we had some system limitations, we could not go below 150 milliseconds. So, it also suggests that some of these signals if you were to record from inside the brain could be useful as a signal for BCI, Brain-Computer Interfaces which we will consider later.

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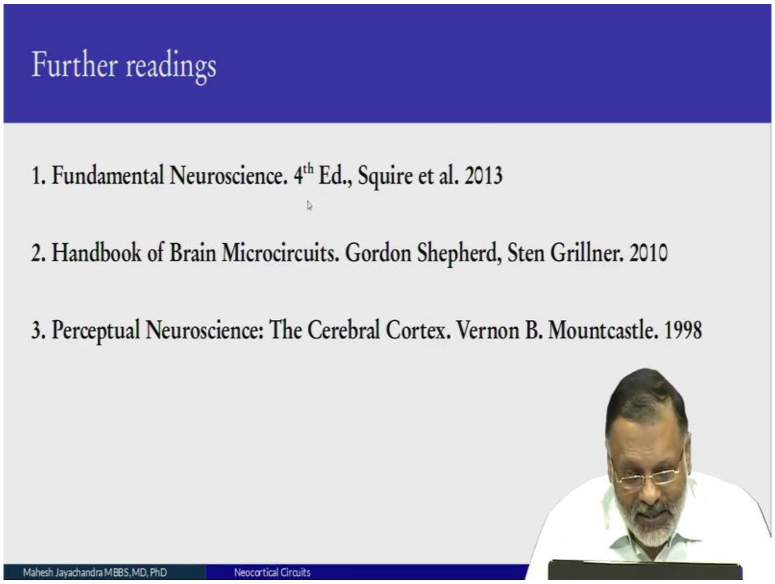

If you want to do further readings on these matters, I would strongly recommend the following textbooks. One is Fundamental Neuroscience by Squire et al, which is kind of a comprehensive survey of all the circuits and stuff what we have been talking so far. If you want to specifically get into brain microcircuits, Gordon Shepherd and Sten Grillner, highly recommend it.

And if you want to hear from the big man himself, Vernon Mountcastle, Perceptual Neuroscience; it is a little old but still remains one of the best sources for information on cortical columns and the physiology of the circuitry inside. So thank you very much.