Neurobiology

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Week - 01

Lecture 1.2: Recent History

In the last video, we saw that people have been trying to understand the brain for thousands of years. But they could only make limited progress because they were not able to see the brain in a great amount of detail. They were limited by the tools. And this began to change with the invention of microscopy in the last few hundred years. So with microscope, you could see the brain in much more detail. But that still did not resolve the problem completely.

And the reason was this. So even if you put the brain under a microscope and look at it, you basically find that it is still too dense to see anything clearly within the brain. It is just too densely packed. And you are not able to resolve the individual units that make up the brain.

So that has been, that remained a pestering problem for a while. And the solution was not clear. So try to think that if, let's say you were living a hundred years ago and you had access to a microscope, what would you do to be able to see more detail in the brain? Let's try to think about it. So I guess one kind of ideas could be that maybe you will take thin slices out of the brain and then try to look at them. But if your slice is a few microns thick, it might still be too dense to see anything clearly within an optical microscope.

Now, if you had access to an electron microscope, you could go deeper, but that technology did not exist at that time. The other kind of thing you could try to do is to maybe dissociate or sort of expand the volume of the brain and loosen the parts. But then of course you lose the detail of how things are connected. So there was no easy solution at that time. So to solve this problem of the dense brain structure under a microscope and not being able to say anything clearly, the scientists at that time thought that maybe if they use a dye and put the dye in the brain, then maybe that will increase the contrast and they might be able to see something clearly.

But even after trying various dyes, they still found that it was just too dark. I mean, it was just too dense and dark. You could not see anything, could not resolve. A breakthrough was finally achieved in 1873 by the work of Camillo Golgi. You might have heard of Golgi's name in the context of Golgi apparatus or Golgi bodies, which are cell organelles.

What Golgi developed was a method in which he would put two salts in the brain tissue and those would be randomly taken up by certain units. Only those units will be labeled. Because the probability of taking up this salt was very low, it basically converted a dense tissue into a lightly sparsely labeled tissue and then it could be imaged under the brain. So that this sparse labeling basically solved the problem of the dense brain structure. And with that, it became possible to obtain images like this.

So this is the drawing of hippocampus based on an image that Golgi was able to see under the microscope. And now for the first time, one could see within the brain regions what kind of connections there might be. So all these fibers, now we know these are axons of neurons. Although at that time it was not clear to them what they are seeing, but at least they could see these fibers as parts of the brain. And the way Golgi interpreted these images was that, to him all of this looked like a densely interconnected network with lots of fibers.

He could not see distinct cells in there. So he thought maybe the brain is slightly different from other parts of the body in that the brain is made, is basically a dense mesh or a network of tissue. But more than Golgi himself, the person who really took advantage of this training method to make fundamental discoveries about the brain was Santiago Ramon y Cajal. Cajal was a Spanish biologist who just had a passion to look at the brains under the microscope. And he was also good at drawing.

So he could draw these beautiful images like the one shown here on the right of what he was seeing under the microscope. And after looking at hundreds of these images, he was finally able to come up with a few insights about the brain. So based on his observations of the brains under the microscope, Cajal found that Golgi's idea that the whole brain is just a single interconnected network without any individual cells was not right. In fact, Cajal was able to see that the brain is composed of separate cells, which we now call neurons. And so this idea is now known as the neuron doctrine, which really came up after the work of Cajal.

And in fact, both Cajal and Golgi got the Nobel Prize in 1906 for their work on the brain, even though they were giving competing theories. Now we know that Golgi was wrong and Cajal was right. The brain is indeed made up of neurons. In fact, billions of neurons. And although these neurons can vary quite a bit in terms of their shapes or sizes, they tend to have some common components.

So most neurons have a cell body, which will contain the nucleus. And then there are the branches coming out of the cell body called dendrites. These are the branches that receive information from other neurons. And then there is one long branch typically that goes out. And this branch is called the axon.

And then this branch branches out into axon terminals, where this neuron transmits information to its follower neurons. And this axon may be covered by a layer called the myelin sheath, which helps in insulating the neuron. So far we have seen how we came to know how the brain is organized in terms of various brain regions and down to the level of neurons based on the work done by people like Vesalius and later Golgi and Cajal. Now let's think about how the brain functions. And one of the key things about the brain that we know now is that electrical activity plays an important role in the functioning of the brain.

And first hints about this were seen in 1780, much before we even knew that there were neurons in the brain, based on the work of Galvani and his colleagues. So they were doing some experiments with static electricity and they were using frog skin to generate the static charge. So the story goes that on a table they had a frog whose skin was recently removed. So the frog had died, but only recently. And accidentally they touched an object that had a static charge with one of the nerves of the frog.

And although the frog was dead, they saw that the leg of the frog twist as if the frog were alive. And then they repeated this observation and others also repeated this observation and eventually concluded that electricity does play a role in conduction of nerve signals. Later Helmholtz expanded these studies and he in fact even figured out at what speed nerves conduct electrical signals. And he showed that it was not like infinitely fast and there was actually a finite speed about 30 m/s or so that at which the nerves were conducting these signals. In fact if you are curious I would encourage you to look up how Helmholtz did these experiments.

Now let us look at the drawings made by Carl again. So on the screen here is the drawing of a particular brain region called the hippocampus, which is one of the most studied brain regions in neuroscience. And you can see different neurons in this structure. And if you look carefully you will also see some arrows that are drawn along with the neuron fibers indicating the direction of the flow of information. So remember that Cajal was not doing any functional experiments.

He was not looking at the activities of neurons or how they are responding. He was only looking at their structures. But probably by following the neuronal structures starting from the sensory layer he was able to infer that this must be the direction in which the information is coming in and then must be going to the next neuron and then able to continue the direction. So this is quite remarkable that with very careful anatomical observations he was able to draw or able to infer this kind of directional information. So Cajal not only figured out that the brain is made up of individual neurons but he also looked at the connections between neurons very carefully.

And based on these observations he was able to come up with two more principles. The first one is the principle of connection specificity which basically says that although there are very large number of neurons the connections between them are not random in the brain but they are actually made very precisely and in a particular manner if you compare from brain to brain. And the second principle was the principle of dynamic polarization which says that the information along a neuron flows in a particular direction. So it is not just like a metal wire in which the signals are flowing either way but rather the signal or the information flows in a neuron in a particular direction. And again as I said he himself did not do this kind of electrical experiments or measurement experiments but simply while looking at the anatomy very carefully he was able to come up with these very bold predictions at that time which have now been verified by further experiments. Thank you.