Advanced Neural Science for Engineers
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Lecture 50
Deep Brain Stimulation/Recording for Parkinson's-I

Hi. Welcome to this series. There are 2 different lectures but part of the same topic which is on Parkinson. Now I, we have discussed about epilepsy. We have seen several videos which included craniotomy, then removal of the cortical layer, implanting the device right, and we talked about surface versus deep implantation. Whether we talk about macro-needle or we talk about flexible device? Whether it was 32 channel or 10 channel? Whether it was non-bio reservable or bio reservable but both biocompatible?

Bio reservable when it resolves in the body. Biocompatible when it compatible with the body environment, compatible in in vivo study. So what we are looking at is the biocompatibility things in the implantable devices because the device will not harm the other organs when you implant it in the brain.

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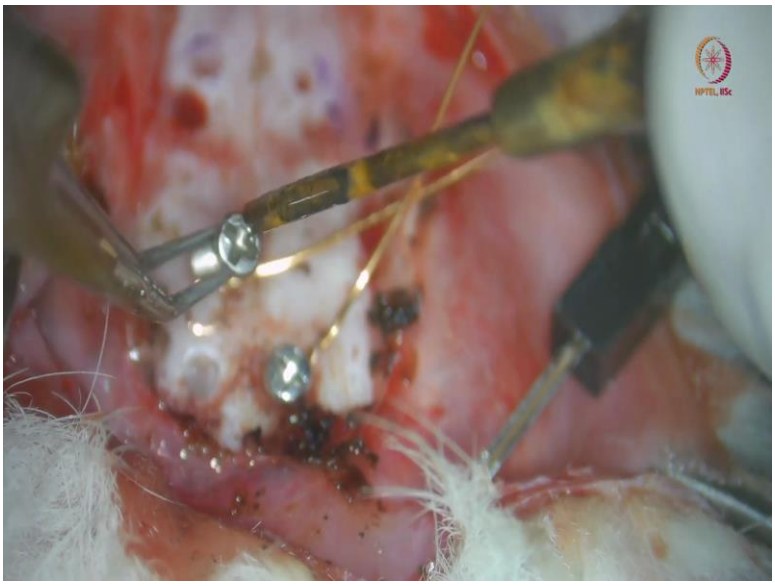

So in the last video, if you recall what we have seen is that in video number 4, if you recall we have seen that there was a cranial drill instead of a complete craniotomy because we wanted to just place the wires, electro-wires into the brain. So we do not require a complete craniotomy.

Then we saw that the wire electrodes can be used for recording the electrical signals. Again, if the tip of the wire is conducting, then we can just connect and touch the neuron and if you do that, then you can record the action potentials.

But if you look at the group of neurons and you are measuring something from the entire column, which is a cortical column, then you can talk about the LFP's which is local field potentials.

We have also seen how we can drill the ground and reference electrodes using the screw electrodes and that is important because when you are acquiring the signal or applying at the electrical stimulation there should be a reference and there should be a grounding.

We then saw that how we can seal the holes on the skull to fix it and finally, we have seen how the micromanipulator attached to a stereotaxic operators can used for implantation because it should be very precise. If you are not in the correct position then the whole purpose is defeated. So you require a micron precision to go deeper inside the brain in the area of our interest. So that is the use of your micromanipulator.

Now, what we are going to do in these particular 2 sets is we look at how we can first understand what is Parkinson, a little bit about Parkinson, and then see that how the gait is affected. I have a video to show it to you that when a person walks and when the person is turning then they actually the difficulty of the turning happens because the gait is affected in Parkinson. You have seen Parkinson is nothing but the vibration or the loss of the motor skills in a certain way.

So for people who have Parkinson's their hands are shaking or when they turnaround, it is difficult or when they hold the pen and they write it is a lot of shake, when they eat something with spoon it is shaking. So this is the motor which is affected.

Now why it is affected, how it is affected is a biology but can we treat it? Can we, what is the current technology to treat it and what alternatives we can present using the micro-fabrication that we have learned at this, at the part of this course. That is our focus.

So we will not only look at the deep brain because in Parkinson, the way to treat Parkinson is by inserting the electrodes deeper in the brain and applying electrical stimulation and looking at the effect of electrical stimulation. But how about if we have the electrical stimulation to the surface of the brain? We do not have to go deeper into the brain.

Now there is a reason why people go deep. But we want to just study how the effect of surface versus deep would be there when you are treating a person suffering from Parkinson's.

So for that we have neurosurgeon working with us who helps us with the surgery, Dr. Sabri Girishan. I am sorry about that. Dr. Sabri Girishan. He is an associate professor in Ramaiah Medical College and he is a neurosurgeon. His interests are in the motor area and an excellent

person to work with because he actually performed surgery and we learn from him. What we are delivering, what we are designing is the electrodes that can be used for study.

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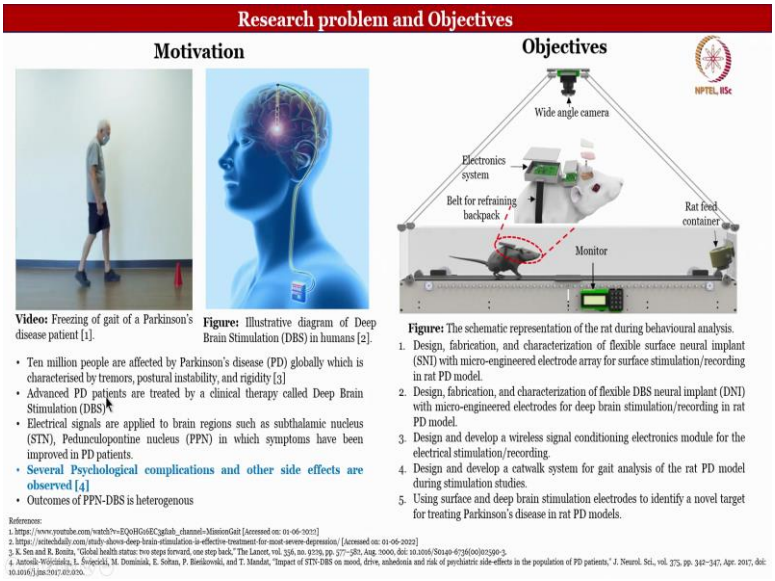

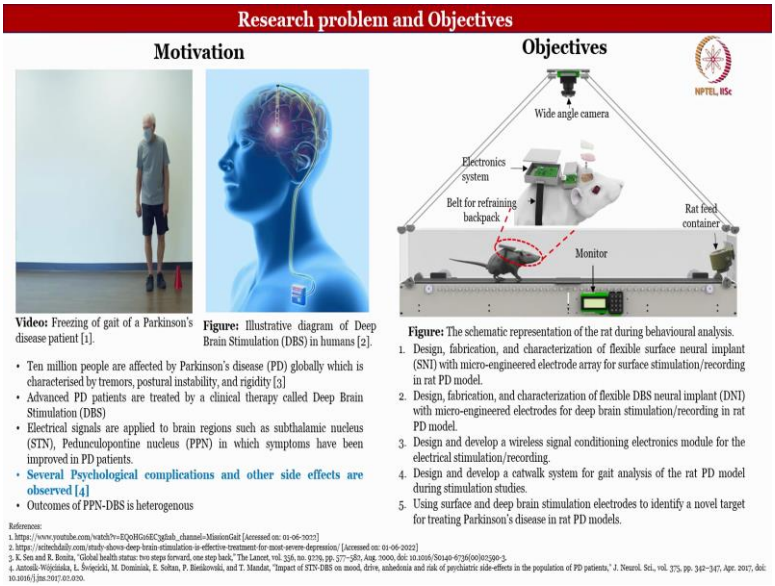

So if you see the slide this is a video that I am playing and you can see the person walking. And then when a person is turning around, you see, see there is lot of difficulty to turn around. As soon as the person turns around, the gait becomes normal. See. Now walking, see is easy. So what is this? This is an example of freezing of gait of a Parkinson disease patient.

Now how to treat it is by diagram, it is an illustrative diagram of deep brain stimulation in humans. And in terms of numbers, 10 million people are affected by Parkinson's disease. In short form we call it as PD. This is well, the numbers are global which is characterized by

tremors. I have told you about shaking of the hands. Hand shaking is different, okay, and the tremors are different. So the instability, postural instability and rigidity.

The generally again like any other disease, the Parkinson is also treated by a drug, some drugs. One of the drugs is Parkin and depending on the amount of Parkinson, the drug is advised to a patient. Most of the patients under the drugs, they are they can sustain but for the patients who have advanced Parkinson's disease, for them a clinical therapy called a deep brain stimulation which includes the surgery and implanting the electrode deeper inside the brain is advised.

Now in this case, the electrodes will apply the electrical signal to regions in the brain such as subthalamic nucleus also called STN or Pedunculopontine nucleus PPN very difficult name in with symptoms have been improved in PD patients. So this PPN has a better than SSN but sorry STN but still these studies are undergoing.

Several psychological complications and other side effects are observed when you use the STN region and outcomes of PPN-DBS is heterogeneous. So we want to see can we use an alternative region along with the surface stimulation and will it be better for treating Parkinson's?

Now to do that first we need to show it in animal models. So here you can see the animal model, the figure which is shown here. It shows a schematic representation of the rat during behavioural analysis. What is behavioural analysis?

That I suppose I put a rat feed container, suppose I put cheese here, alright, and then if the rat is walking on this one, okay? Rat walks on this. So this walking is because there is a treadmill like you have seen treadmill that we use for walking, jogging, same thing a rat treadmill is what we can design. This is commercially available as well, and rat will walk towards this cheese. There is a behavioural analysis.

But if you create a Parkinson in the rat’s brain, then the gait will get affected. And if you do the surgery and apply the DBS similar to this humans in the rat’s brain then whenever there is a gait which is affected due to Parkinson, when you apply electrical signal the rat should be able to walk in a normal way. So the gait that is affected can be recoverat and the gaiting becomes better when you apply electrical signal in the certain area of our interest.

Now, like I said, we are not only interested in the deeper area but also the surface of the brain. Can you use both deep plus surface to see whether it has a, combined effect as a better outcome?

So for this, you need to have a wide angle camera because you need to study the gait of the rat. There is a backpack which applies the electrical signal to the rat's brain. We have the surface electrodes that can be placed on the rat's brain. We have deep brain stimulation electrodes that can go deeper inside the rat's brain, alright?

So let us see how we can do that and in fact, we have at the end of this entire lecture, I will be talking about acute and chronic studies. Like I said that there is a video which will show you what is the difference between acute studies. That means that once you have performed the studies, you can euthanize the rat, you can euthanize the rat and when it is chronic studies that means the rat is kept alive for a certain number of days to study the effect of electronics or drugs or whatever it is.

Then we will also show you when we keep the rat in the cage how the rat is recovered and how the signals can be measured at 3^{rd} day, 7^{th} day and so forth. Which signals? Brain signals. So which are those signals? ECOG. What is ECOG? Electrocardiography.

Particularly studying this we can understand the behavioural analysis of the rat. In the video we can also will also see the step and behaviours related to the recovery. That is that how the free moment of rat in the cage will affect the signals. When it is sniffing and searching for the food, then what happens? How it looks like? When it drinks water, how it looks like? When the rat is taking rest, then what kind of signals we can observe? Right?

We have seen alpha, beta, gamma, theta all these things. So each signals has a certain characteristics because if it is a sleep mode or it is an active mode or it is an attention mode, then the signals will change correspondingly.

Finally, what we will be looking in the video would be the gathering the accustomed to the implant like how we are getting the signals from the implant, the background of recorded signals and how it can be improvised after it is customize.

That means that once you have acquired the signals, how can you remove the noise from the signals, how can you improve the SNR, whether the signals are the baselines, when there is a Parkinson's what kind of changes happens, when we apply electrical signal what kind of

changes happens? So this is the final, final study but we will see some part of it as a part of the video at the end of these 2 lectures, okay?

So to study this Parkinson's, now, if you go to the objectives of this study, you see the first objective is on design, fabrication, and the characterization of the rat during behavioural analysis.

This is the first study but for that we need to first fabricate the treadmill and then we can also need to fabricate, we also need to fabricate the flexible surface neural implant which is SNI, surface neural implant.

So as we call it as SNI and there is using the micro-fabrication technology and it will be nothing but a micro-engineered electrode array and that can be used for not only the recording the signals but now we are talking about the applying the electrical stimulation to the certain part of the brain.

The second one would be to design, fabricate, and characterization of flexible DBS. DBS stands for Deep Brain Stimulation. You can see here deep brain stimulation implant which we call DNI. Surface, we call SNI; deep brain we call DNI, again with micro-engineered electrodes for deep brain stimulation recording in rat's PD model. PD is Parkinson's disease model.

The next one would our objective should be to design and develop a wireless signal conditioning electronics because if there is a wire again, it is a difficulty. So how about we have wireless electronics that can there is a signal conditioning unit for electrical stimulation in recording.

The next objective which is number 4 is to design and develop a catwalk system right. We call it treadmill catwalk system which is this entire system. We can design. Once you understand how the motor works, how to control the motor how the how to put the belt, what is what how can I control the speed, and how can I capture the images you can easily design such a system.

This catwalk system can be used for analysing the gait of the rat during for the rat PD model, where the rat is in a given a Parkinson's disease and when you apply the electrical stimulation so they can use this catwalk system to study.

The last point which is to using surface and brain stimulation electrodes to identify novel target for treating the Parkinson's disease in rat PD models. So we need to find a novel target regions particularly which has surface and deep brain stimulation, how it can help to identify the new or novel target regions.

So this is the problem of Parkinson. I told you that there are currently the electrical stimulation for advanced PD patients. It is given in the area which is STN. The alternative area which is studied is PPN and we are trying to look at not only STN, PPN but also the effect of the surface electrical stimulation.

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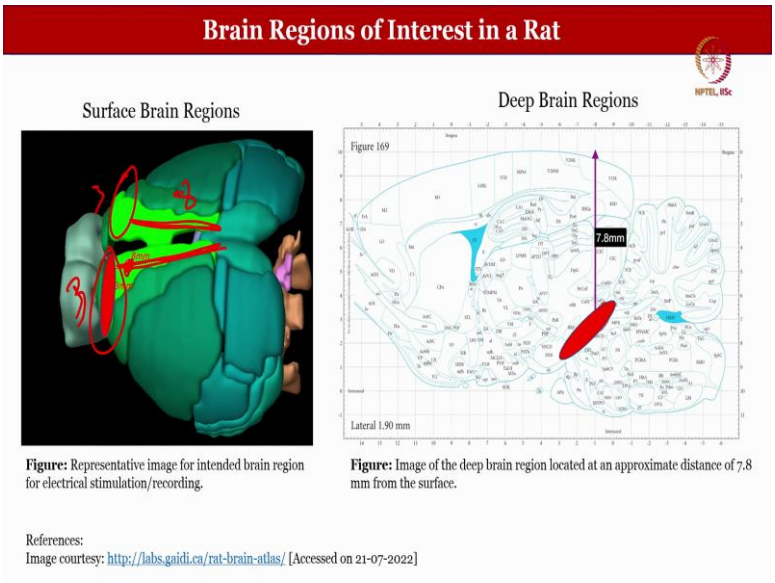

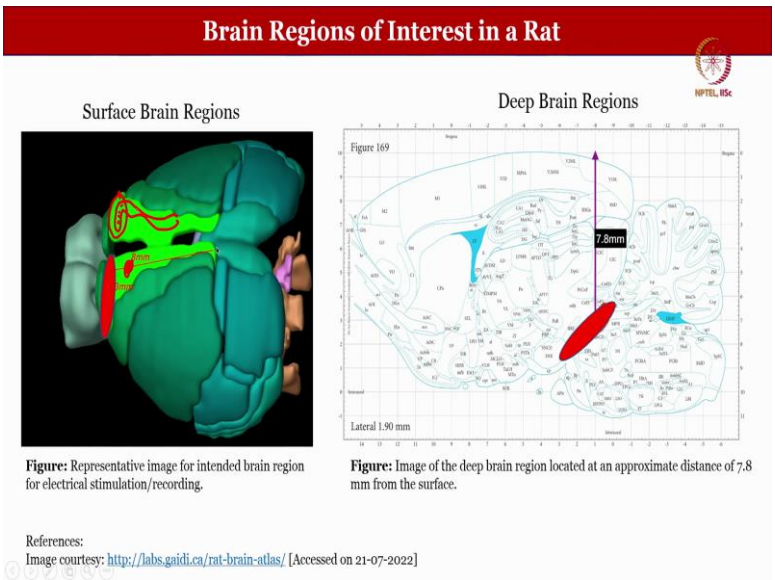

Now, if you see that in one of the videos I was talking about this particular region, deep brain stimulation region, this region where it is almost 7.8 millimeter deeper in the brain. Now we

are talking about the image of the deep brain located approximately 7.8 millimeter from the surface for the treating the Parkins, okay?

And here the representative image on the left side is for the brain region for electrical stimulation and recording. Here you can see is about 3 millimeter. This is about 8 millimeter. Same thing here- 3 millimeter, this is 8 millimeter. So this is 8. This is 3. This is 3. And that is why our electrode should be designed such that the deeper one we do not worry about it. We can go deep inside in this region.

But the surface one should be such that it should not be exceeding this region. So can we have electrodes that can come here and can go sit here and can come there. So we can put electrodes like this. alright? So we need to design such electrodes using micro-fabrication technology.

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Now, the question is that are commercially available surface grids for rodent brain will work for these applications? Now there is no definitive answer because again these electrodes are used for certain other applications but not really for Parkinsonian in the case where how we are targeting, okay, the regions that we are targeting.

The one that you can see from Cambridge NeuroTech, the (a) one which is this electrode alright? These this is a zoomed in version of the same one. Like this one, this is a zoomed in version, is the image of surface ECoG arrays grids connected to a connector. This is surface one connected to this one.

While the (b) which is this one shows a schematic layout designs and (c) which is here shows ECoG electrodes from Cambridge NeuroTech. So you can very clearly see that the one which you can see, we can also, we also have the NeuroNexus products, the electrode arrays and this one particularly this one is from Cambridge NeuroTech and all these are surface recording electrodes or the electrical stimulation electrodes or ECoG.

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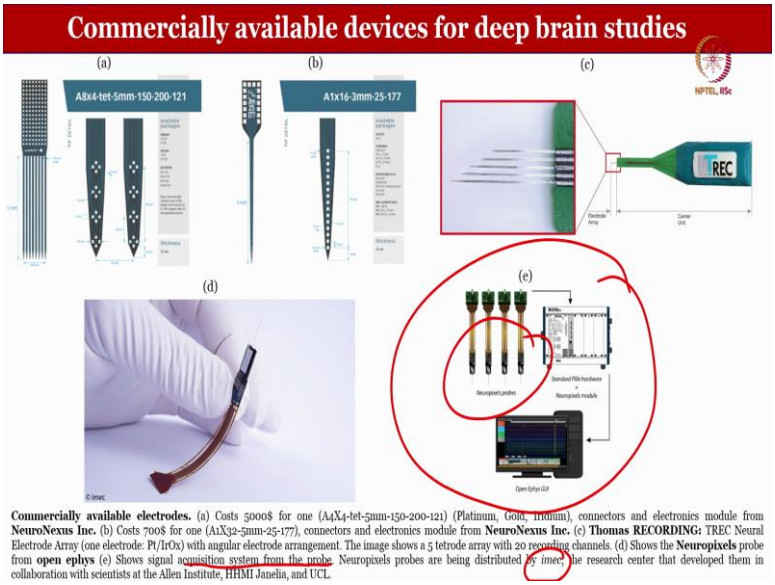

There are other commercially available device as you can see in this particular schematic. The company that sells it is called NeuroNexus and also there is a Thomas RECORDING: TREC Neural Electrode Array. There is also Neuropixels probe from open ephys and same thing we can also show this particular (e) one is from Allen, this is developed signal acquisition system is developed which is Neuropixels probes are being are distributed by imec. This is the, this one is from imec and research center that develops them in collaborations with scientist at Allen Institute, UCL an HHMI in Janelia.

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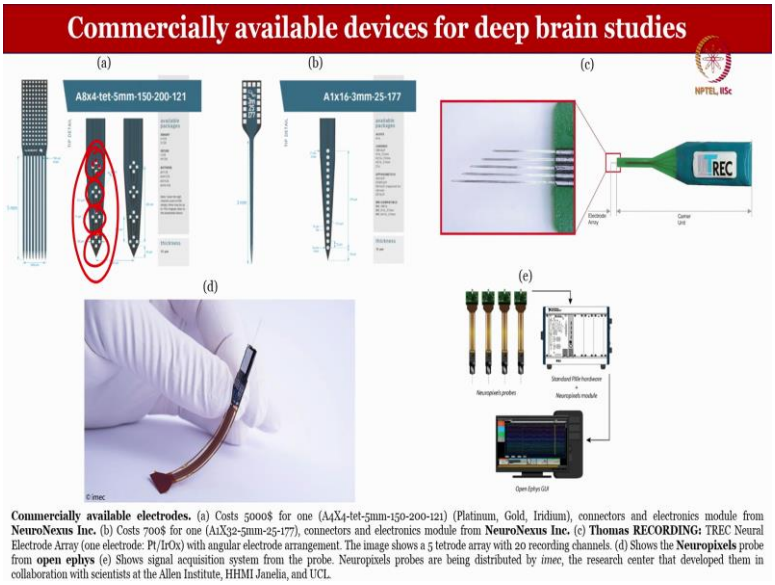

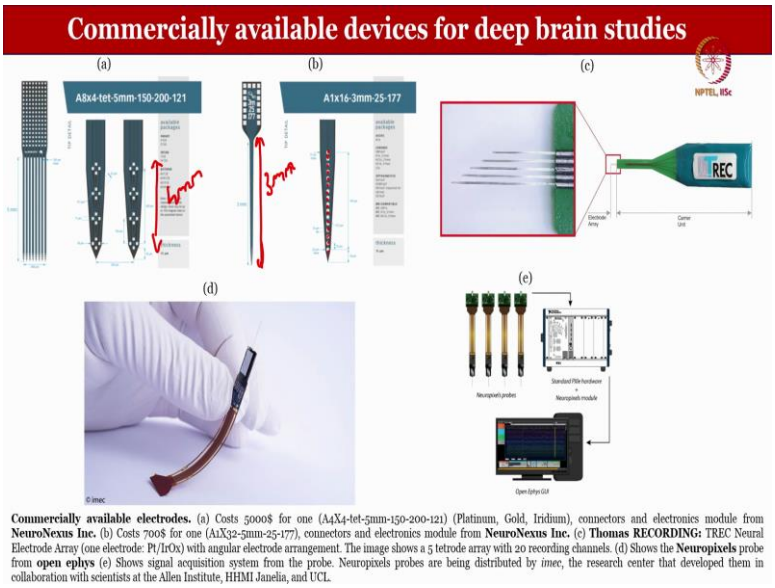

So let us go one by one, okay? Let us not get overwhelmed with the slide. So if you see this this particular needle it looks like a needle and this needle has a tetrode. You can see 1, 2, 3, and 4. Right? So these are all tetrode. Now, how many tetrodes are there? 1, 2, 3, and 4. So 4 tetrode across the needle on the surface of the needle.

That means when you apply and how big it is? It is about 400 micrometer which is close to 4 millimeter. This is 3 millimeter and you can see here in this case there are linear electrode arrays. Now we have seen this thing earlier when we I was showing you about the linear electrodes. So these are also linear electrodes.

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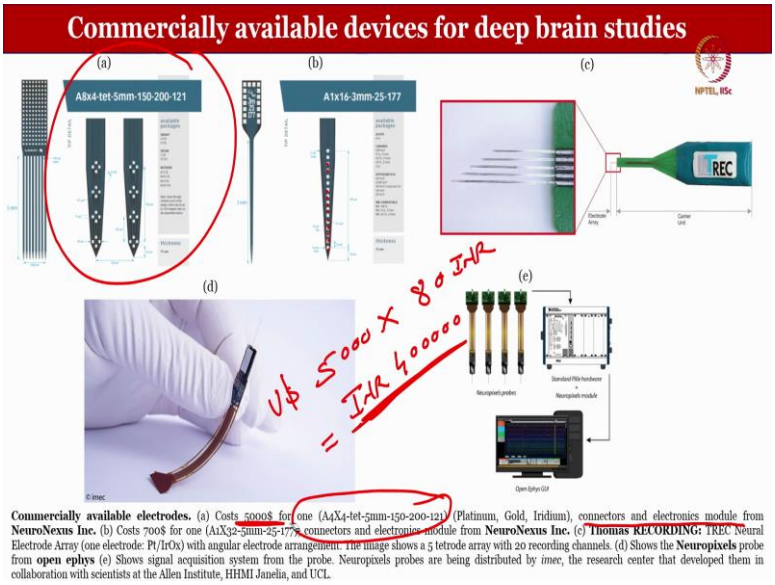
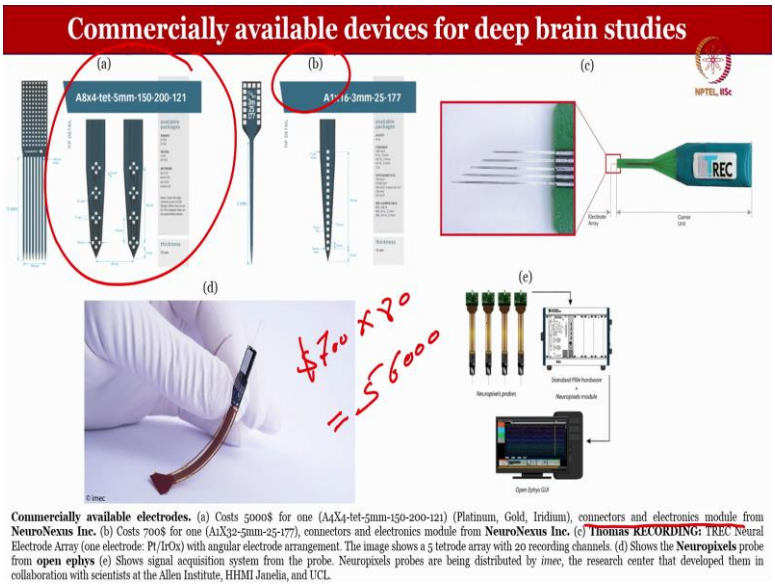


Commercially available electrodes. (a) Costs 5000$ for one (A4X4-tet-5mm-150-200-121) (Platinum, Gold, Iridium), connectors and electronics module from **NeuroNexus Inc.** (b) Costs 700$ for one (A1X32-5mm-25-177), connectors and electronics module from **NeuroNexus Inc.** (c) **Thomas RECORDING:** TREC Neural Electrode Array (one electrode: Pt/IrOx) with angular electrode arrangement. The image shows a 5 tetrode array with 20 recording channels. (d) Shows the **Neuropixels** probe from **open ephys** (e) Shows signal acquisition system from the probe. Neuropixels probes are being distributed by *imec*, the research center that developed them in collaboration with scientists at the Allen Institute, HHMI Janelia, and UCL.



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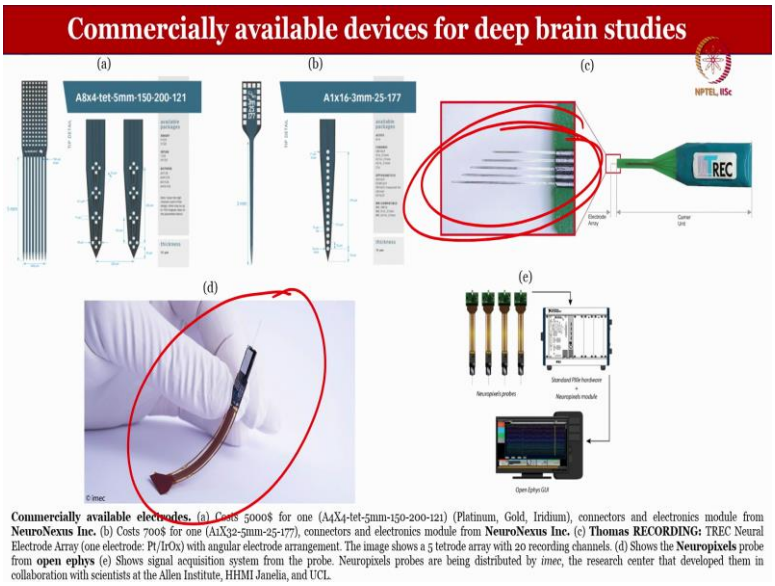

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The difficulty here is that look at the cost, okay? So we are not ready to see. (a), this one cost $5,000. Let us see in Indian Rupees considering that $1 is 80 rupees which is not the correct figure. It is 82 but it is okay. We are paying INR 4 lacs, 4 lacs. Huge number for Platinum, Gold, Iridium, connectors and electronic module from Electrode Array and with angular electrode arrangement.

But the point is if you go for (b) which is a single needle with linear electrodes. This one. It costs about $700. How much? 56,000 rupees. Crazy no. So, this is from NeuroNexus. Very costly.

See my point is these are really good electrodes okay I am not we should not just learn something from the entire course is if the technology is there, we should appreciate the technology. None of my lecture is against the technology. It is in favour of technology. Right?

My whole focus is that the technology should be available to people who wants to use it at an affordable rate. The companies, their company should make profit because that is what companies are for. You take any start-up. In fact, we are having so many start-ups because of beautiful policies that are coming up and that is a good thing.

Number of start-ups, number of ideas, number of products and number of businesses growing, people are hiring and then the start-up makes money the whole business grows. Every company that is there has to have some profit. That is called business. Otherwise, what is a business.

But the point is, is 4 lacs value or 56,000 affordable to scientist who knows how to use this electrode in the rat's brain can use those? When you are learning neuroscience, when you learning how to do the experiment in neurophysiology, when you want to implant those electrodes, would you be given as a student a electrode of 4 lac and said to go and do it? That is difficult right.

So what I am suggesting now, is this not the something which is available here. This is a beautiful technology that is developed by the companies.Whether it is NeuroNexus, whether you talk about imec you talk about HHMI, Janelia, UCL, Allen Institute, the collaboration is how the things comes up.

My point is, can we fabricate these kinds of electrodes at one-tenth of the cost or even lesser so that the researchers can use it and they can fabricate it. Why the cost is so high? There should be some reason.

One is of course, that is their business. What are other reasons that we need to learn? Is the electronics very high? Is the fabrication cost very high? If the fabrication cost is very high, can we fabricate at a lower cost? Can we fabricate indigenously here?

What do you require? You require a Fab Lab. Do we have Fab Lab? Yes, we have a Fab Lab. Can you try to fabricate it? Yes, we can and we were able to fabricate it.

You require an optimization strategy to fabricate those electrodes that is affordable, that can be used for such application, whether it is epilepsy, whether it is Parkinson's, and so on and so forth. Right? So it is about the affordability so that many people can explore.

When many people works in the into focus on the area of neural engineering, there will be lots of solutions that would be available for the surgeons to take up and the technology that can be developed from not only fewer countries but from several countries.

So that is the whole idea of telling you about this probe. It is not just cost, it is about the, it is not about the technology as well. The technology is excellent. We can use it where can we fabricate it here.

You see this one, this beautiful electrode? And there is a reason of having different length because where what is an application right, where you are actually placing those electrodes? If we talk about hippocampus, then the then the whole design would be different.

So these are some commercial devices that we understood. The (c) which is the one that I have just talked about. IR is Thomas RECORDING. It is called TREC neural electrode array with an angular electrode arrangement.

The image shows a 5 tetrode array with 20 recording channels. This is with 20 recording channels. Okay?And finally, the (d) which is here shows the Neuropixel probe from open ephys and so on and so forth.

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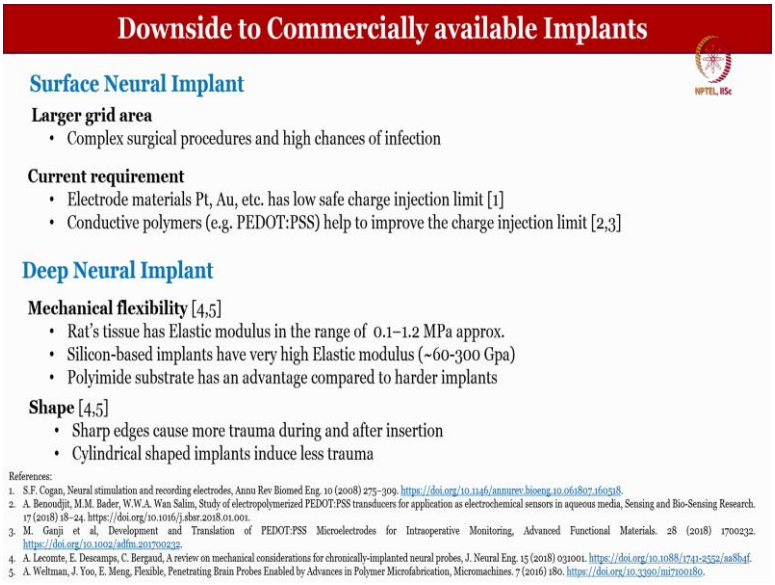

So let us go to the next slide. The downside again we need to appreciate technology, we also have to see the gaps in the technology. So the downside to the commercially available implants are: 1. Surface neural implant - larger grid area, complex surgical procedures and high chance of infection because of the larger grid area.

What is the second point? Current requirements- electrode materials like platinum, gold, etcetera has shown and has already low surface, low safe charge injection limit, okay.

And if you want to improve it, then the literature shows that if you go for conductive polymers like PEDOT:PSS it may help in improving the charge injection limit particularly important when we are looking at the current requirement, particularly important when we are looking at the electrical stimulation.

The next one is that deep neural implant. So surface neural implant and deep neural implant. So deep neural implant you have mechanical flexibility and shape. What mechanical flexibility? That rat tissue has elastic modulus range of 0.1 to 1.2 mega Pascal approximately.

So the silicone base implants have very high elastic modulus about 60 to 300 Giga Pascal while the polyimide substrate advantage compared to the hardened implants. That is why can we go for a softer material like polyimide instead of using silicone based implants. People have tried and it has shown a better efficacy compared to the harder implants.

Finally, talk about the shape. The shape sharp edges. See the sharp edges, you can see that all these edges are very sharp. Take anything, very sharp because like a needle. So the sharp edges has causes more trauma or has more trauma during and after insertion. Then second

one is cylindrical shape implants induce less trauma. So can we change the shape from short to cylindrical? Right? That will help in reducing the trauma.

Now, for this we have seen what is Parkinson? We have seen what are the commercial electrodes and what are the objectives, the rat-based PD model that we are trying to use for understanding the effect of electrical signals, and finally, what are the commercial implants and its downside.

Now, in the next lecture, we will continue with the fabrication of the devices that are used for surface electrode recording and followed by the materials that can be used for the deep brain stimulation. So till then if you have any questions, feel free to ask me. I will see you in the next lecture.

I have deliberately shortened now this lecture so that it does not become overwhelming. Like I always want to stress on this particular point that if you look at the lecture, whether it is 1 hour lecture also, whether this is the course or any course that you take you just focus for half an hour, take a break for 10 minutes, again, come back and focus on half an hour. Max, you stretch for 45 minutes to 1 hour. That is it.

After 1 hour, you take a break. Come back. There is a reason because the focus and the attention it reduces with time. So it is shown that after 45 minutes or 1 hour of the work, you take a 5 minutes break, just walk come back you can again get attentive. So that is the reason that you can always come back and see or continue with the lectures. So I will see in the next class. Till then you take care. Bye!

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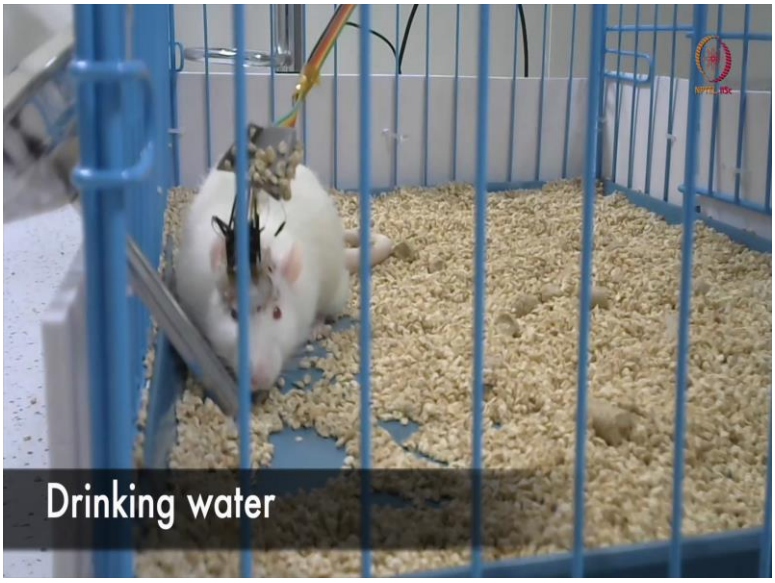
Sniffing and searching for food


Grooming


Drinking water