Nanobiophotonics: Touching Our Daily Life
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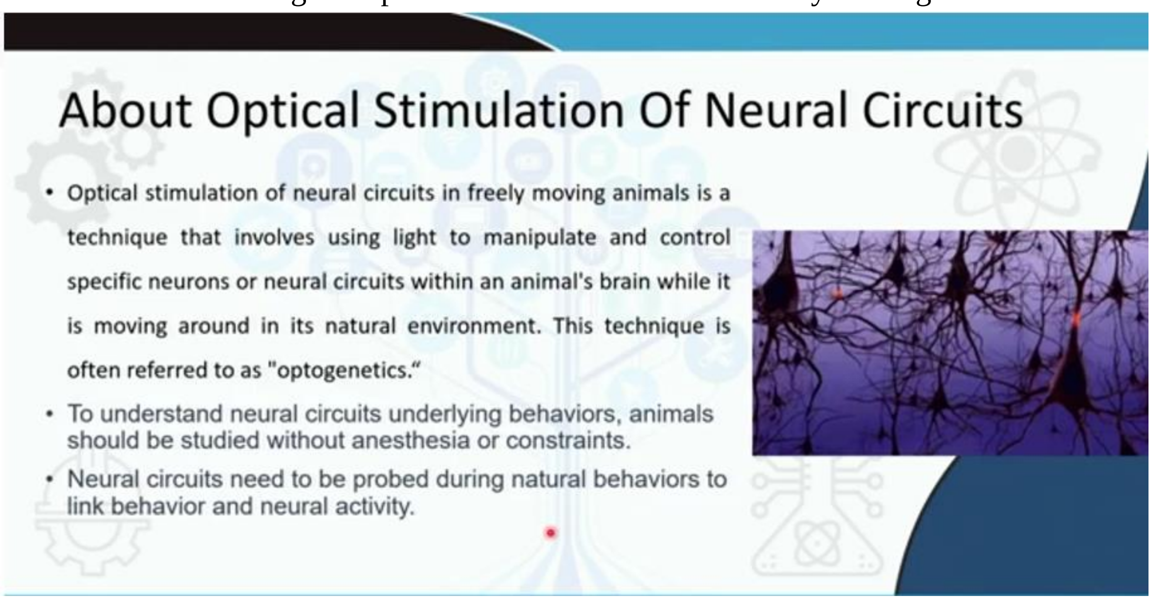
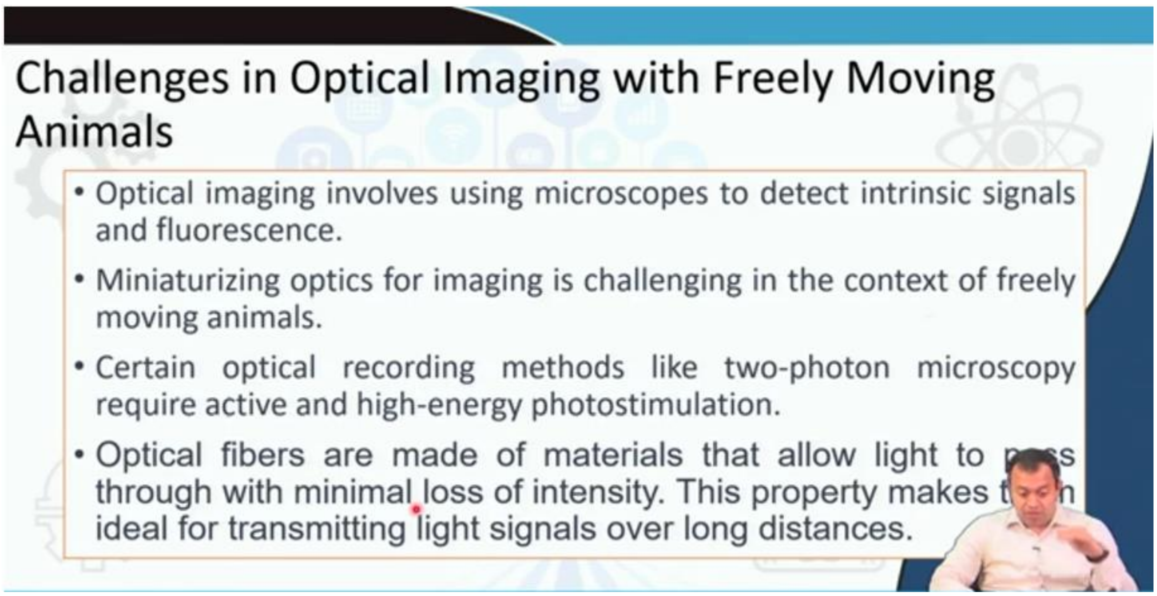
Lecture No. 53
Optical Stimulation of Neural Circuits in Freely Moving Animals

Welcome back. We are still continuing our discussion on applications and emerging research areas in Neuro Photonics. And today the topic is how to ah stimulate the neuronal circuits of a freely moving animal. So, see it is one thing to dissect the brain take it out put it in a petri dish and look it under the microscope and try to see how the neurons look. And even sometimes fire it through artificial means through some kind of in vitro ah simulations. But what has challenged or plugged one of the basic shortcomings that we are finding these days in ah neuroscience and neuro ah photonics and optogenetics research is how do we deliver light at specific areas of the brain in a freely moving animal not dead.



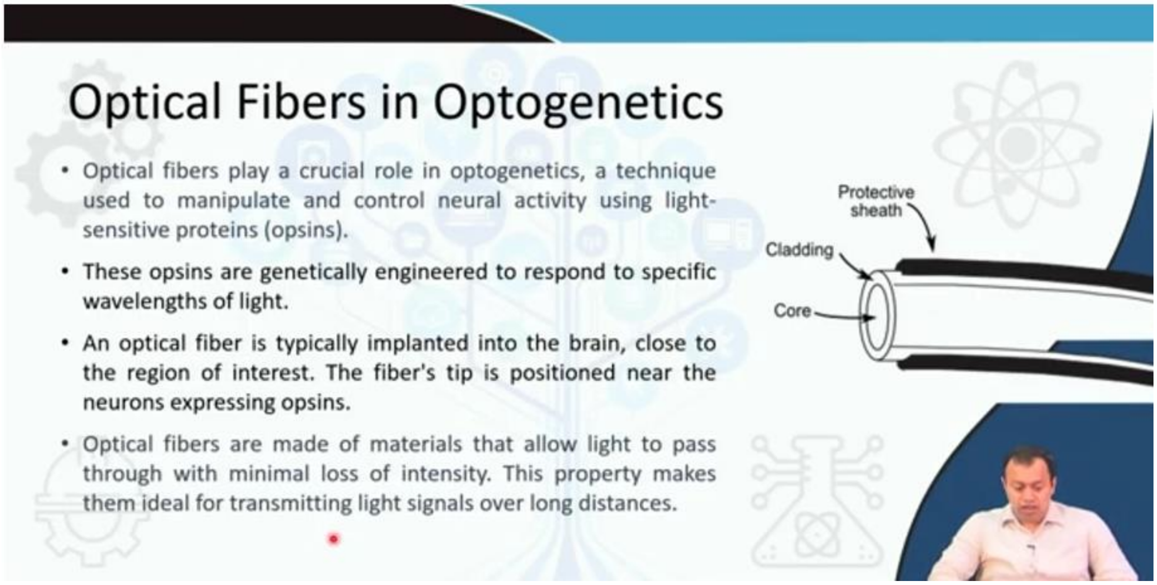
Basically not dead not sleeping not drugged not anaesthetized not bound freely moving a normal animal we want to target specific section of the brain. Now, understand this yes, we have you know change the gene modified the gene added cofactor and what not. So, different area of the brain of the animal is ah protein ah light sensitive. The proteins are present at different parts of the brain and they are light sensitive if light is activated if light is triggered the the the molecules the proteins activate and behavioral change is there how do you deliver that light.

Yeah we saw you you make a hole in the skull and insert ah optical fiber, but is that you know first ethical and be is that by itself not modifying the change I mean how do you differentiate would you differentiate between an animal who has a big hole in the skull versus a non hole in the skull mouse non hole in the skull animal. Some sort of modification is going on as soon as you have inserted a huge ah optical fiber inside the brain of of of of a ah mammal and this thing will only go the complications will only start to rise as ah you go on look for higher ah life forms say for example, primates monkeys and chimpanzees can you ethically remove a portion of the skull of a monkey or a chimpanzee and insert you know a tube and then trigger light into it and then try to see how the chimpanzee is behaving and do you think that will be giving you a non biased result right. So, this is one of the challenges that optogenetic is facing how to deliver light at specific areas of the brain without actually affecting the organism ah you know in in in in a such an invasive manner. So, optical stimulation of neural circuits in freely moving animal is a technique that involves using light to manipulate and control specific neurons. Neural circuits needs to be probed during natural behavior ah to link behavioral neuronal activity we know the challenge.

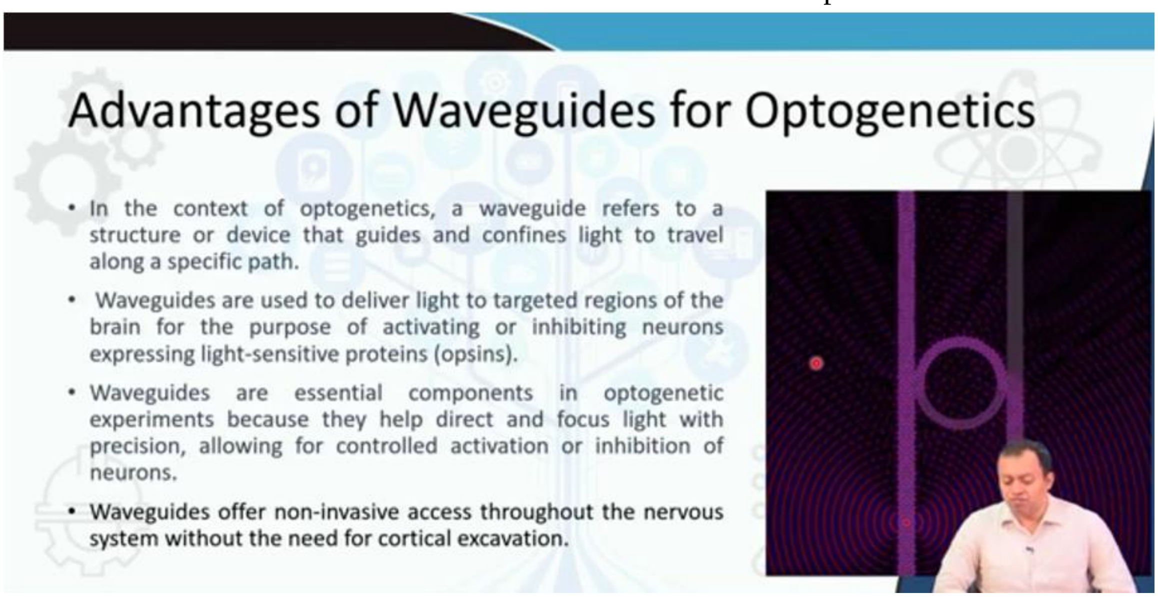


We know the problem statement the challenge here is optical imaging involves using microscope to detect how will you detect is there any physical change taking place inside the neuron miniaturizing optics for imaging is challenging you need to put not only an optical fiber, but some kind of a microscopic system that this is the neuron light is falling up and then the neuron is either expanding closing who is there a movement is there a physical change that is taking place. So, how do you how do you measure do you put a lens along with the optical fiber do you put a lens microscope and putting a lens inside some organism's head brain which is the most important yet the one of the most ah you know affected areas how exactly is going to happen. Miniaturizing optics for imaging is challenging in the context of freely moving animal you simply cannot put a microscope miniaturized microscope inside some animal's head creating optical recording methods like 2 photon microscopy you cannot put another microscope 2 photon that to inside the head of an animal optical fibers are made of materials that allow light to pass through with minimal loss of intensity this property makes them ideal fine. But they are only for the light to be delivered granted that is going to help us tremendously, but what if I want to image and what if I want to not insert a tube inside the head of an animal well we do not have many options and this is something where I think both optics people not photonics optics people instrumentation people mechanical people all of them needs to combine their you know with their their intelligence along with neuroscientists and biologists and medical people to see that how do we make some kind of an implant you know pacemaker you have pacemaker that is put inside the heart and that triggers ah for the heart to beat properly. Some kind of this miniaturized device very small ah can be inserted inside a specific portion of the brain which can both image and it is ah sending light pulses periodically and at the same time through an antenna wirelessly transmitting the results outside.

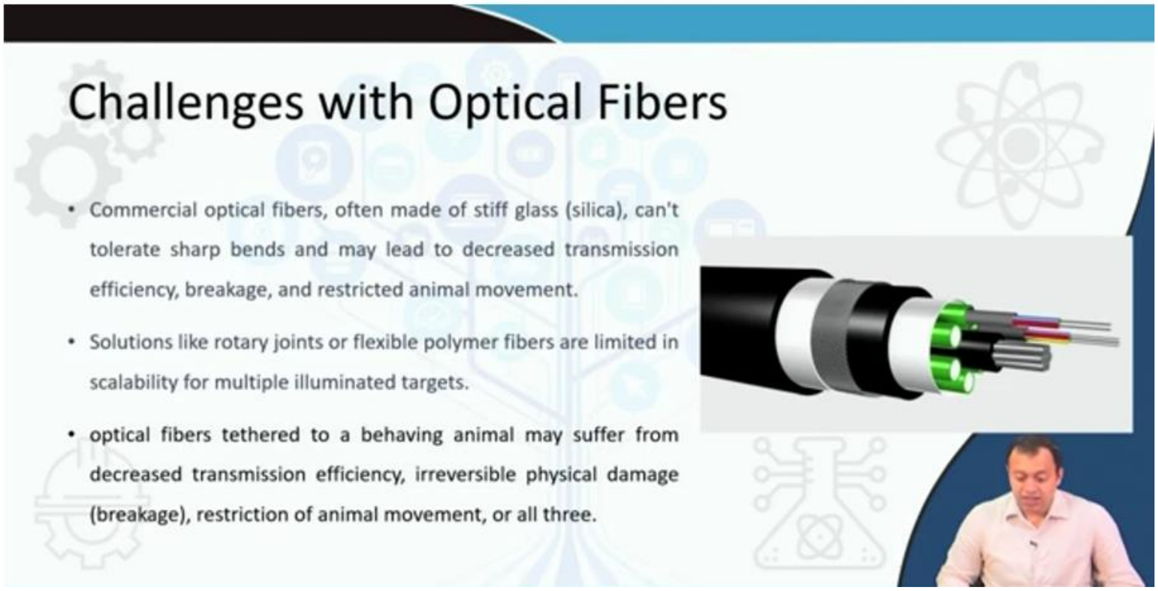
You do know that IOT internet of things those things are quite popular these days implanted chips GPS chips you can track somebody inside must have seen it in Hollywood movies even the pacemaker inside the ah heart has some sort of a transmission system that that connects it with ah that connects the person the patient with the hospital in case some some problem starts with the brain it immediately sends information. However, those techniques are fully not matured wearable electronics you can wear it in your hand and the from the skin it can monitor and send results IOT and connect with your doctor etcetera, but as soon as you put that implant inside the human body and ask it to transmit as well as monitor things starts becoming extremely complicated. Getting a signal which is connected with my skin throughout and getting a signal inside the body deep inside the body that to a very very small ah implant with an even smaller antenna is challenging needless to say. So, ah well optical fiber you know is the best option thus far that we have these opsins are genetically engineered to respond to specific wavelengths of light ah optical fiber is typically implanted into the brain close



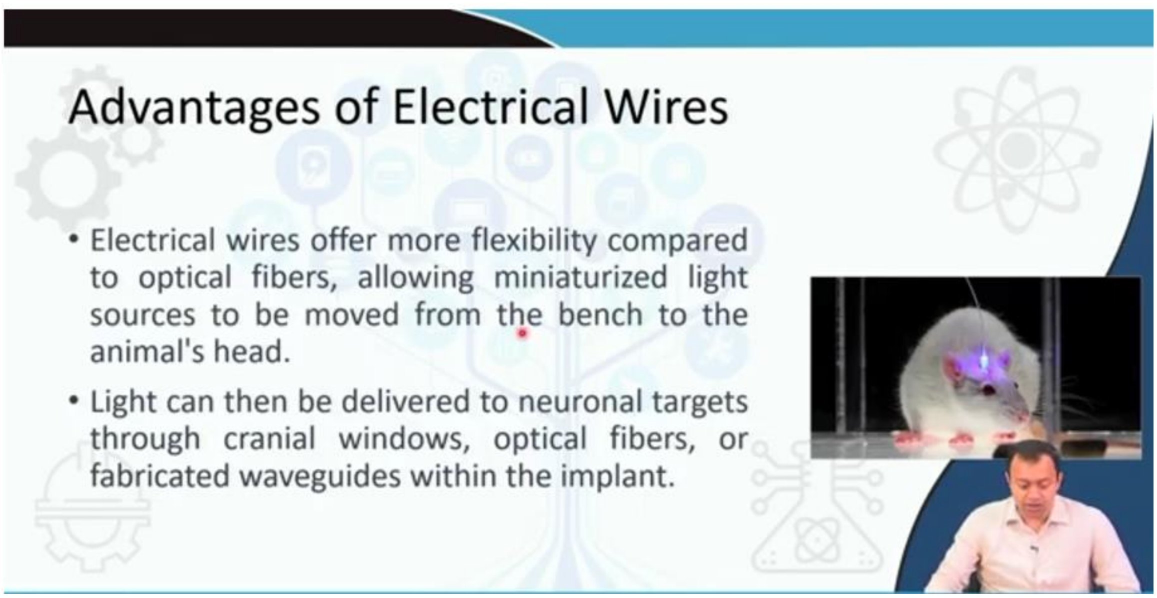
to the region of interest, the fiber tips is positioned near the neurons expressing opsins optical fibers are made up of materials that allowed light to pass through we have discussed optical fiber before. So, we can utilize multiple optical fibers one is for transmission and one is for reflection we have couplers in between.



So, the light can simply couple and pass through the other in the context of optogenetics a waveguide refers to a structure or device that guides and confines light to travel along a specific path waveguides are used to deliver light. So, you can use waveguide inside the ah optical fibers or you put some sort of an implant waveguides are essential components in optogenetics and they can be utilized. So, this this light is through via this coupler this this light is via this coupler is then passed through this ah challenges with optical fibers are plenty commercial optical fibers often made of stiff glass can tolerate sharp bends and may lead to decrease transmission efficiency basically has the have the

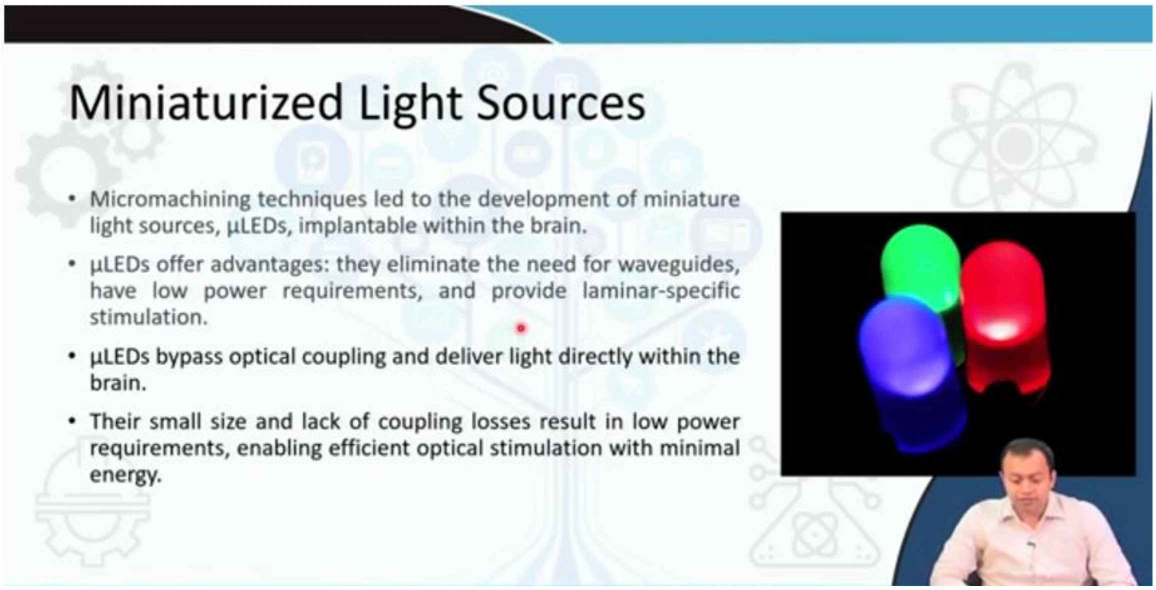


risk to kill the animal solution like rotary joints or flexible polymer fibers are limited in scalability optical fiber tethered to behaving animals may suffer from decreased transmission efficiency irreversible physical damage you think restriction of animal movement and all you are making a hole inside the head of a animal and you are calling it freely moving sure it is freely moving, but it has a gap its skull is opened up its head is opened up right yeah this is it.

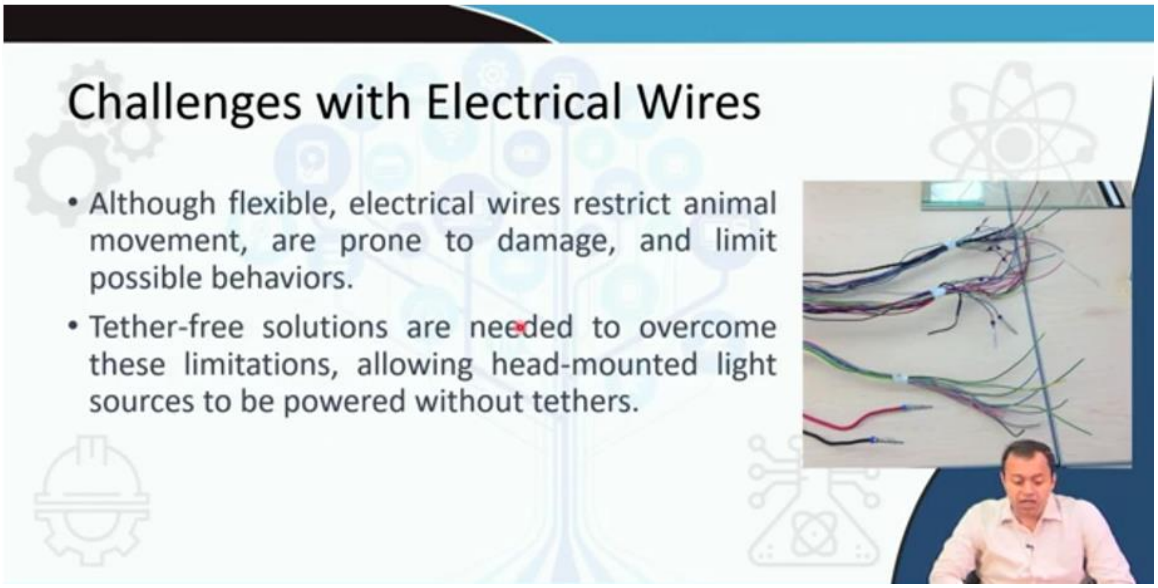


Advantage of electrical wires electrical wires offer more flexibility compared to optical fibers allowing miniaturized light sources to be moved from the bench to the animals head light can then be delivered to neuronal targets. These electrical wires are these electrical connections you have you can bend it and several different organic polymers plastic electronics this organic conducting polymers or conducting organic polymers can be used to ah connect with insert inside the brain and they can also glow ah at a particular electric current being passed through these and that light.

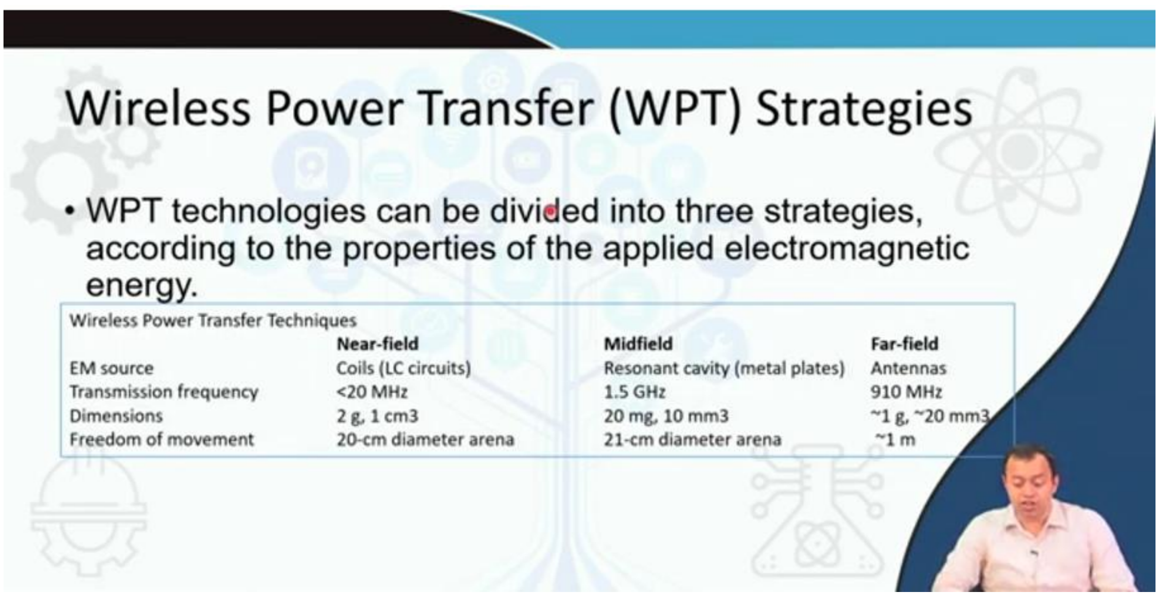
So, think about it you have a conducting polymer inserted inside the brain of a mouse other end of the polymer is connected with some kind of a voltage source that voltage source is sending electric current that electric current is resulting glowing of the wire conductive polymer wire the glowing of a light at a particular wavelength triggers the proteins presence inside the brain of the animal which is then resulting in some sort of a behavioral change and you are measuring it right. We also need to have miniaturized ah miniaturized light sources micromachining techniques led to the development of



miniature light source micro LEDs implantable within the brain micro LEDs offer advantages they eliminate the need for wave guides having low power requirements. So, micro LEDs mostly made up of quantum dots combination of quantum dots these days perovskites and ah those kinds of ah materials are coming up, but still you have to understand that this is not being used in a sterile environment you are not utilizing them for solar cell development especially for halite perovskites etcetera you are ah putting it into a brain right. So, you have to be extremely careful of what exactly you are planning to do. So, micro LEDs offer advantages they eliminate the need of wave guides have low power requirements and provide laminar specific stimulation micro LEDs bypass optical coupling and deliver light directly within the brain they are implanted at specific areas of the brain you can trigger them by wireless ah wireless signaling their small size and lack of coupling losses result in low power requirement enabling efficient optical, but their biggest problem is cytotoxicity it is one thing to put a new ah nanoparticle somewhere inside the brain it is another thing to put a LED light emitting diode with you know all those connections electrical connections and what not inside the brain of a organism and try to consider it whatever behavior it is doing as normal and thereby measuring normally.

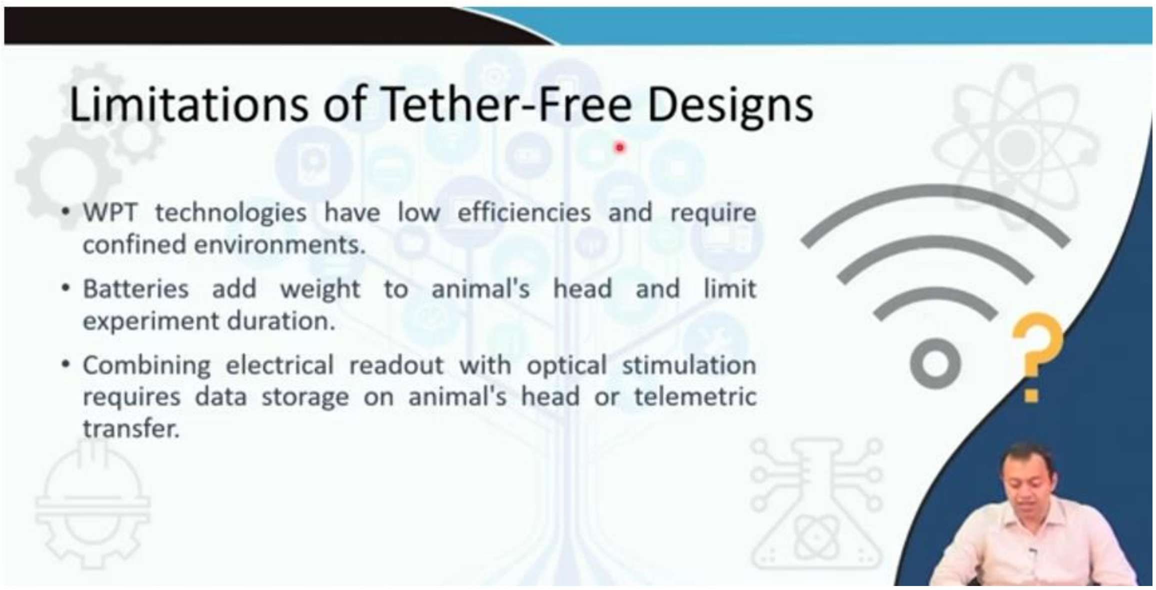


Challenges with electrical wires all the flexible electrical wires restrict animal movement are prone to damage and limit possible behaviors tether free solutions are needed to overcome these limitations allowing head mounted light sources to be powered without tether tether are this connection those those those this is the tether this is this this this then get connected with computers will you consider it as free this is connected with some sort of a you know display device. So, wireless power transfer strategies are then being explored WPT technologies can be divided into three stages

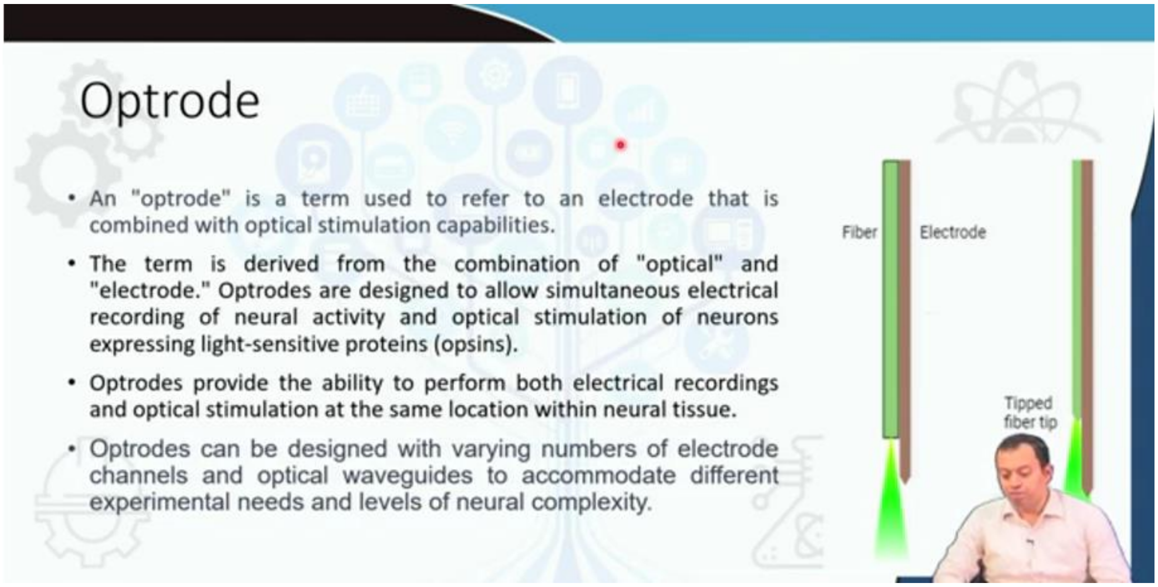


near field mid field and far field you need to have antennas ah LC circuit or metal plates RF and microwave people know this very well the transmission frequency in 20 megahertz

1.5 gigahertz that is basically 1 g or 2 g ah level ah 2 g in this here means dimensions gram milligram this is weight 2 gram 1 centimeter cube 10 millimeter cube the size and etcetera freedom of movement 20 centimeter diameter arena where the mouse can move and far field you can have 1 meter area where the mouse can move what wireless power transfer is ah still being explored inserting think about it would you like to insert a Wi-Fi router in your head you will never lose signal you will never lose signal with your mobile phone because you have the router inserted in your head powered by a battery and that battery is getting charged from the food that you are consuming think about it how how you know peculiar or bizarre it will happen, but many people I think will be interested they will never lose signal. So, we are trying to do something very similar like this with the animal model right WPT technologies have low efficiencies

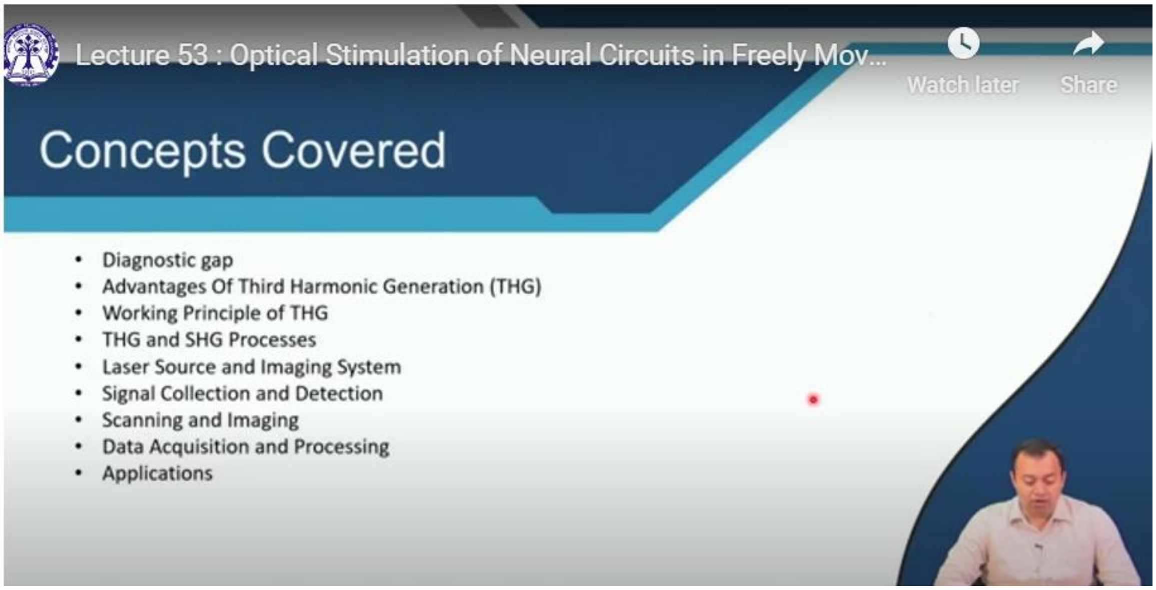


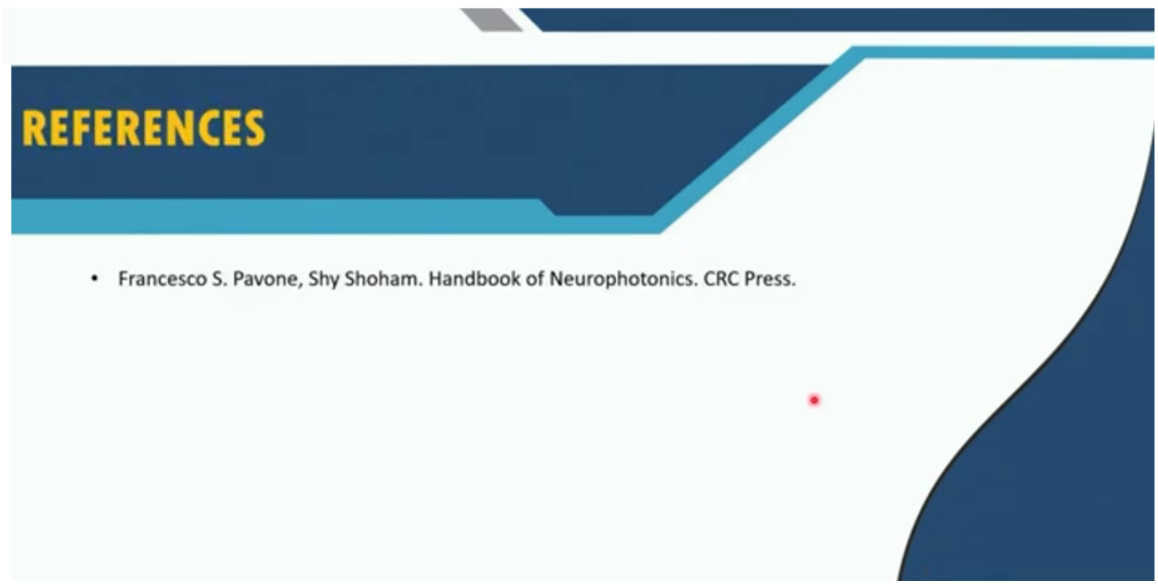
extremely low efficiency whenever you put something inside and require confined environments batteries add weight to the animal’s head and limit experimental duration combining electrical readout with optical stimulation required data storage on animal’s head or telemetric transfer. There is something called optrode that has come up where you have combine optical fiber with some kind of a metallic nano ah metallic wire electrode and fiber calling it optrode optics and electrode and optrode is a term used to refer to an electrode that is combined with optical stimulation capabilities derived from the combination of optical and electrode optrodes are designed to allow simultaneous electrical recording of neuronal activity.



So, you send light and measure the electrical ah well basically electrical current or voltage through this electrode ah metallic electrode it could be ah simultaneously, but they have they can combine optrodes provide the ability to perform both electrical recordings and optical stimulation at the same location within the neural tissues optrodes can be designed with varying numbers of electrode channels and optical wave guides to accommodate different experimental needs combining together an optical fiber an optical fiber connected with some sort of a ah metallic wire whatever the optical fiber is triggering the light is triggering resulting in change of the electrical potential that is then measured by this metallic wires, but still these are quite difficult quite challenging and restrict the overall behavior of the animal and thereby stating that you have fully understood the brain with respect to neurons with respect to behavior still remains a challenge.

So, in conclusion optogenetics is light sensitive proteins being utilized to measure neural activities optical stimulation of neurons using light sensitive optives lead to control behavior combining optical stimulation with ah electrical recording in closed loop system enhance experimental control offering insights into neural circuits etcetera.





So, these are the concepts that I covered for today and these are my references. Thank you very much.