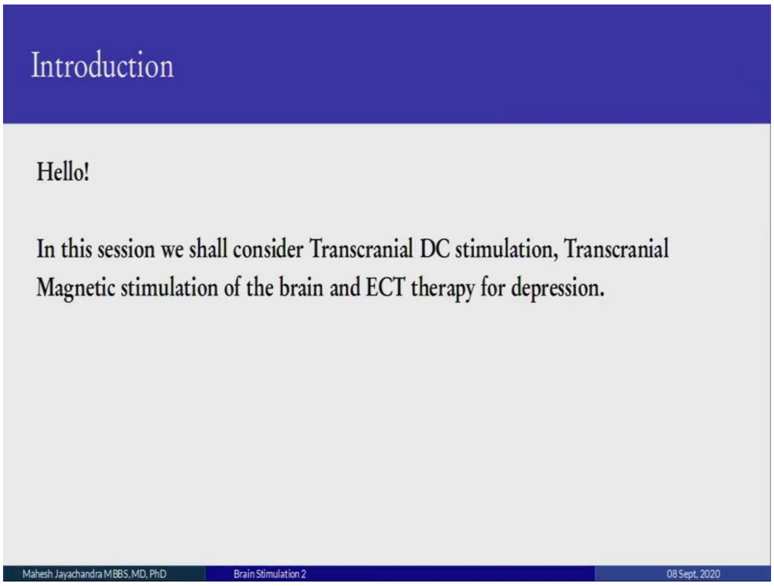
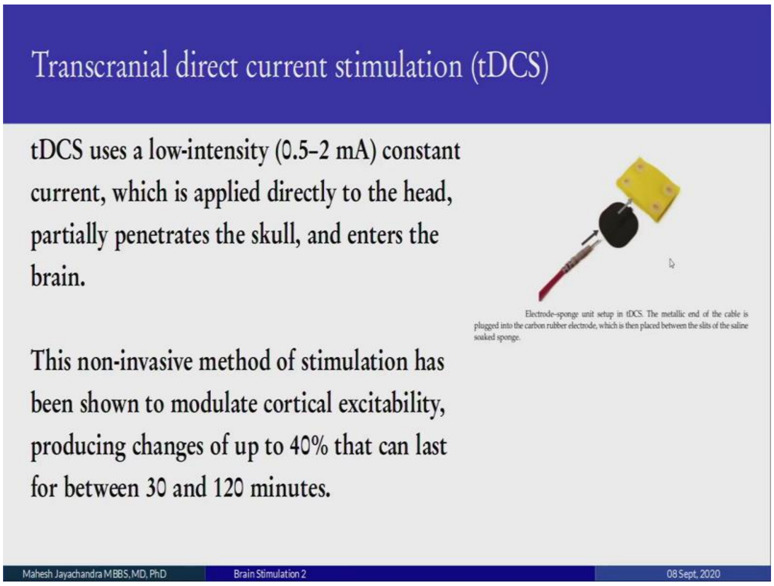
Introductory Neuroscience and Neuro-Instrumentation
Professor Mahesh Jayachandra
Center for Bio-Systems Science and Engineering
Indian Institute of Science, Bengaluru
Electromagnetic Stimulation of the Brain – 2

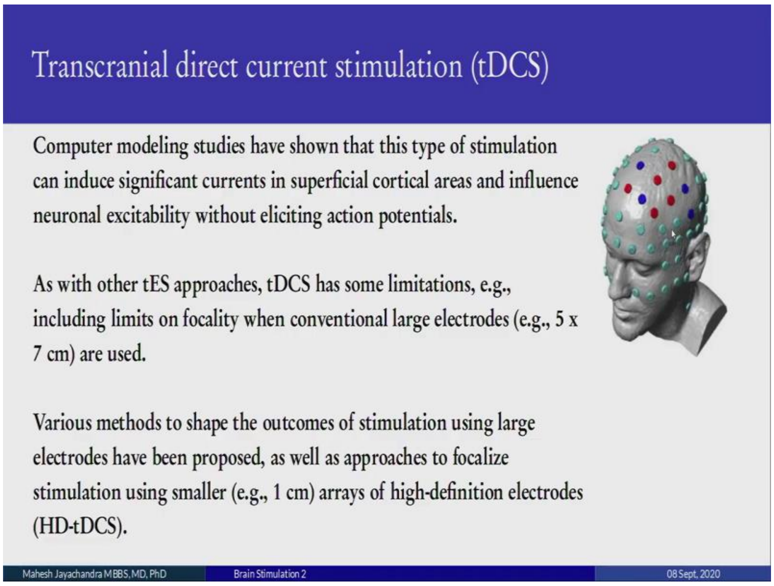
(Refer Slide Time: 0:22)



So, Introductory Neuroscience and Nero-Instrumentation: Electromagnetic Stimulation of the Brain, part 2. So, in this session, we shall consider Transcranial DC stimulation, Transcranial magnetic stimulation, and Electro Convulsive Therapy for depression. Electro Convulsive Therapy is interesting because when people think of brain stimulation, they think of ECT. So, I have decided to, and most people ask me about ECT. So, I have decided to add a section at the end to give an idea of ECT.

(Refer Slide Time: 0:54)





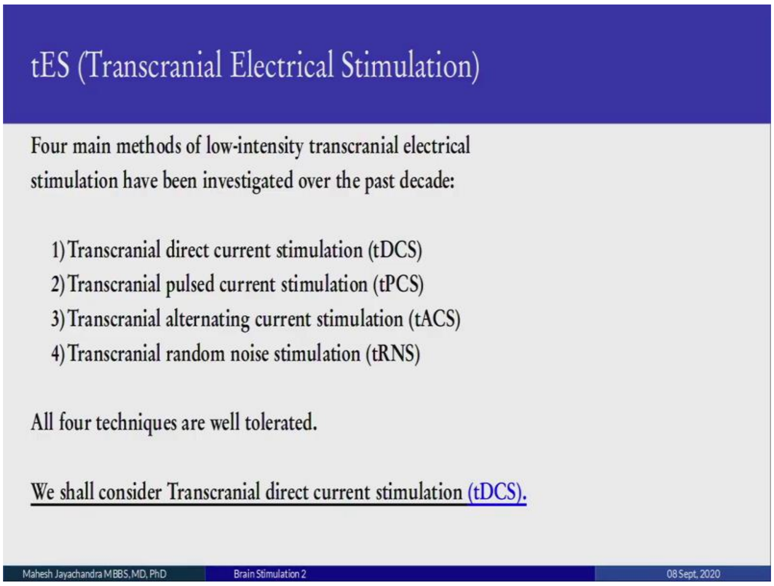
So, we will start with Transcranial direct current stimulation. tDCS. So here, you use a very low current, 0.5 to 2 milliamps. It is a constant current and it is applied directly to the head. It partially penetrates the skull and enters the brain. So, typically, you have an electrode, which is an electrode sponge unit. So, you have the metallic end of the cable is plugged into a carbon rubber electrode, which is placed between the slits of a saline-soaked sponge.

And this you put on one side and that you put on the other side and that is your tDCS stimulation. So this non-invasive and you can barely feel it if at all, most people cannot. This non-invasive method of stimulation has been shown to modulate cortical excitability and it produces changes for up to 40 percent and that can last for between 30 to 120 minutes, it is transient. And computer modeling studies have shown that this type of stimulation can induce significant currents in the superficial cortical areas, it does not go deep.

But anyway, we are interested in the superficial cortical areas, the grey matter. And it influences neuronal excitability without causing action potentials. This is important to note, no action potentials are produced. Just the membrane potentials are modulated and changed. So it has some limitations as with other electrical stimulation, Transcranial electrical stimulation methods. And if we use such big electrodes, you cannot focus the site for electrical stimulation. So various methods, algorithmic as well as the shape of the electrodes have been proposed.

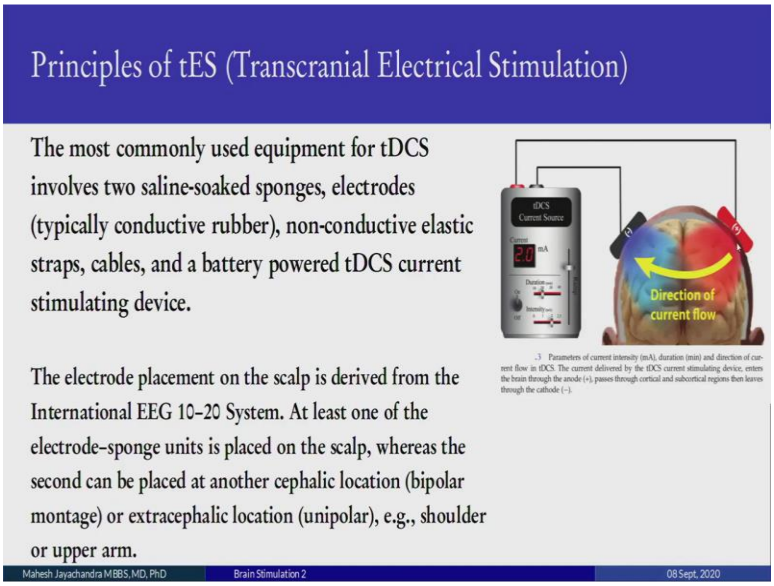
And one method where people have found relative success is using smaller, for example, like here 1-centimeter arrays of high definition electrodes, HD-tDCS. It is getting cumbersome over here. So this allows some limited amount of focality. Remember, between the electrode and the brain, you have the scalp, you have the skull, you have the meninges, then you have the cerebrospinal fluid. So, all these tend to blur the stimulation signal.

(Refer Slide Time: 03:10)



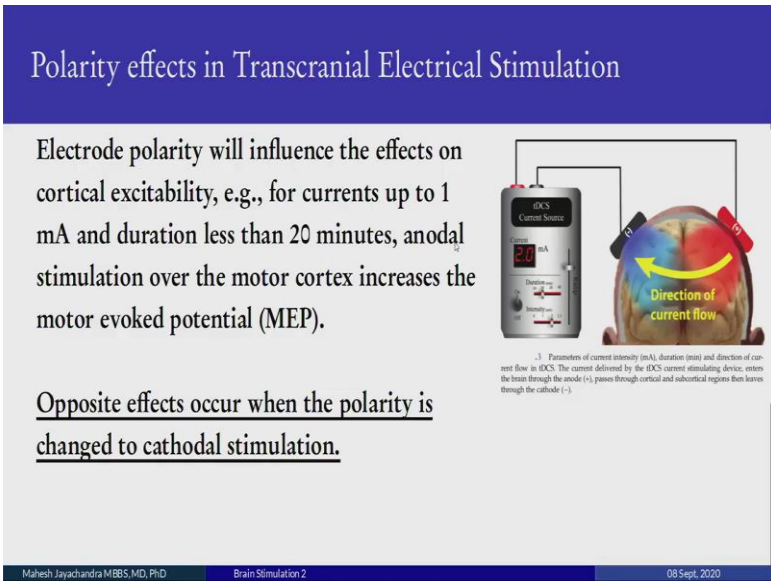
So as far as Transcranial electrical stimulation is concerned, there are four main methods. One is we just saw, Transcranial direct current stimulation. You also have pulsed current stimulation. We have pulses of electrical stimuli. Then you have, these are DC. You can have alternating current instead of DC. And then finally, you can have random noise stimulation. So all four of them are well tolerated, you cannot feel it. The current is very low. But mostly for our purposes, we will consider Transcranial direct current stimulation.

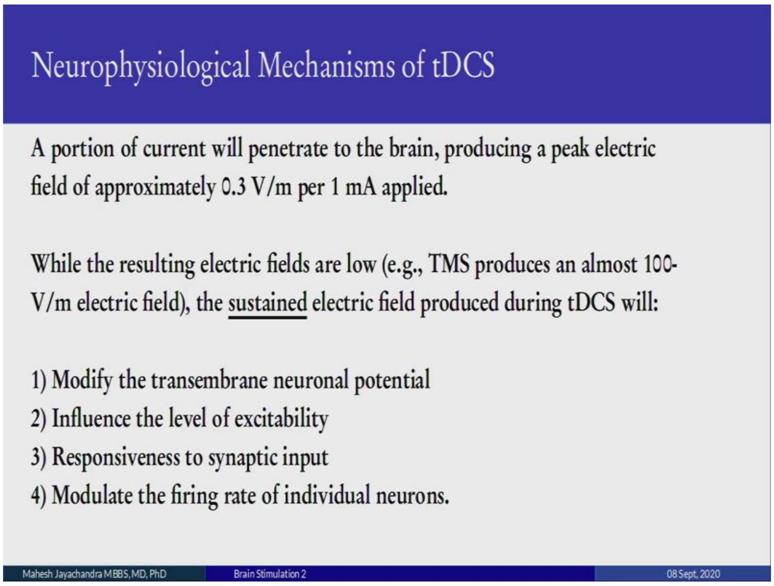
(Refer Slide Time: 03:45)



So as mentioned before, we have two saline-soaked sponges. And a conductor rubber electrode, nonconductive elastic straps, cables, and a battery-powered tDCS current stimulating device seen over here. So where do you place the electrodes? It is based on the 10-20 system for EEG electrode placement. And at least one of the units is placed on the scalp. The other one can be on the scalp or it can be at the extracephalic side, like for example, the shoulder or the upper arm.

(Refer Slide Time: 04:20)





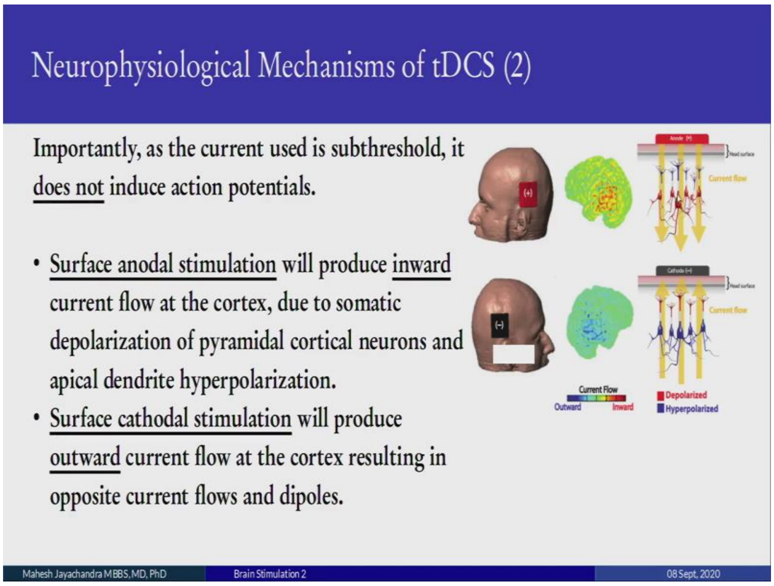
So, the polarity affects Transcranial stimulation. So, electrical polarity will influence the effects on cortical excitability. So for currents up to 1 milliamp and duration of less than 20 minutes, anodal stimulations, positive electrode over the motor cortex, that is in front of the central sulcus, increases the motor evoked potential. Now, what is a motor evoked potential? We will come to know in just a bit.

So opposite effects occur when the polarity is changed to cathodal stimulation. So here, you have the current source, you have the anode, you have the cathode. And the electrical stimulus enters the brain through the anode, passes through cortical, subcortical regions that we are not sure and then it goes out to the cathode. So, what is the, what happens when you do this? A portion of the current will penetrate the brain. So, it produces, most of it does not. Because as I said, all these blurring layers are in between.

And when it does penetrate the brain, it would produce a field of approximately 0.3 volts per meter per milliamp of current applied. So, this is very very low compared to magnetic stimulation which is almost 300 times as massive. But it is a sustained field, the magnetic stimulation is transitory, this is sustained. So what does it do? So these are some of the things we speculate it does, one is it modifies the transmembrane neuronal potential.

Your resting membrane potential, all that is modified. It also influences the level of excitability. It influences the responsiveness to synaptic input. And it modulates the firing rate of individual neurons. However, it does not cause action potentials, it just modulates the firing rate, maybe they fire faster, maybe they will fire slower but does not cause action potentials. So, we just mentioned that. So since it is subthreshold, it does not cause an action potential.

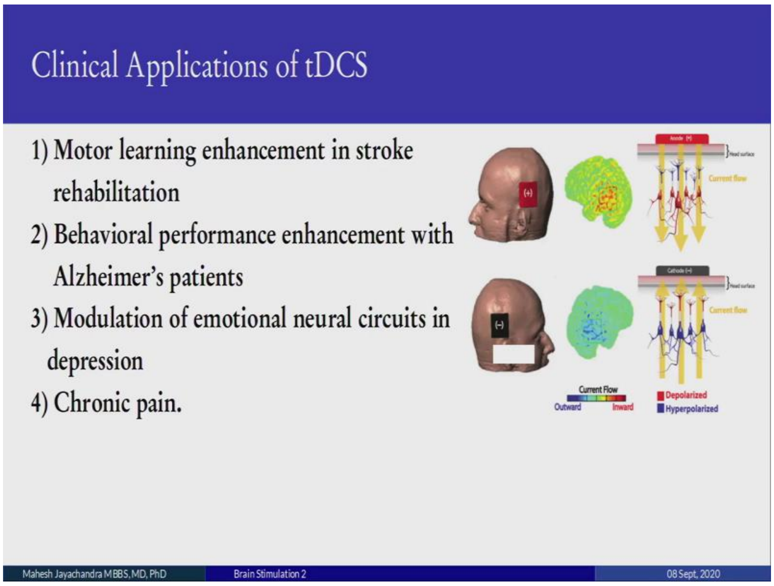
(Refer Slide Time: 06:21)

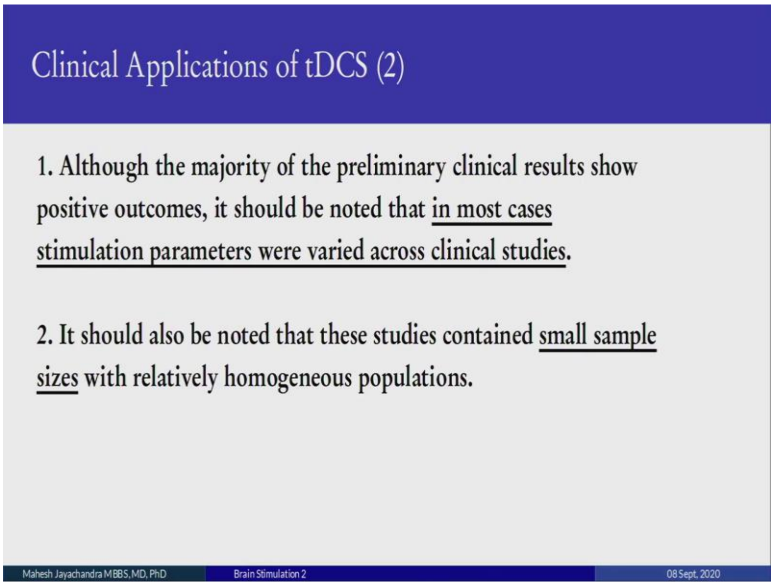


And a surface anodic current and cathodic current. So just consider the anodic current first. So you have current flowing from the anode into the brain and it causes an inverted current flow because of somatic depolarization, depolarization of the cells, and apical dendrite hypopolarization over here. Cathodal stimulation is the produces an outward current and resulting in opposite current flows.

So here the soma are hypopolarized and the apical dendrites are depolarized. And if you model it and look at the surface of the brain, what is the area activated, it is a big area, you cannot localize it. So this is the anodal area of the brain under the anode, and this is the area of the brain under the cathode where current exists.

(Refer Slide Time: 07:22)





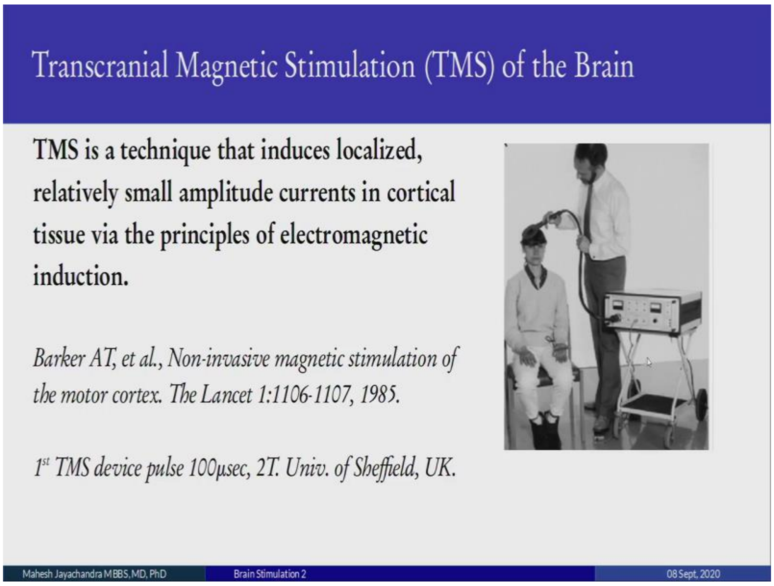
So what are the clinical applications? So, one-third of humanity suffers from stroke. So a lot of research has been focused on stroke neurorehabilitation. And apparently, motor learning enhancement occurs with this tDCS which is useful for stroke management recovery. Another very important cognitive disorder dysfunction that occurs in older humans over 65 is Alzheimer's where there is a cognitive decline and typically manifests as unable to remember, memory functions are disturbed.

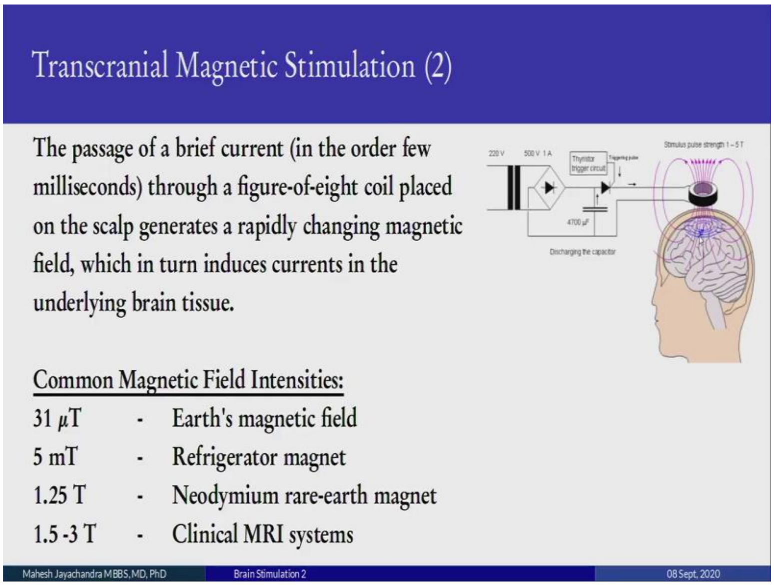
So tDCS has been shown to improve behavioral performance in Alzheimer's patients. Then depression. So patients with depression, depression is endogenous, we are talking about something a problem, not reactive where you are depressed because you did not do well in your exams or somebody is dead. This is endogenous where there is no obvious cause but the person feels sad and sometimes medication does not work. They found that tDCS help in modulation and causes some relief. And finally, in chronic pain.

Many kinds of neuropathy do not have a definitive treatment and electrical stimulation is one of the therapies which have been considered for chronic pain. So one caveat we have to bear in mind, two. So although the majority of preliminary clinical results show positive outcomes, it should be noted that in most cases there is no standardization of stimulation parameters. They are very variable across clinical studies. So we have to bear that in mind and choose the optimum possible parameters for your study.

And also these studies typically are very small sample sizes. So, for statistical testing, we need much larger sample sizes, and also they were done on homogeneous populations, so we have to do heterogeneous populations to see if these findings, this alleviation of problems occurs in everyone and it is not confined to one particular population. So we have to bear these in mind before you go ahead and start using tDCS.

(Refer Slide Time: 9:55)





Transcranial magnetic stimulation. So this is a technique where you induce localized small amplitude, relatively small amplitude currents in the cortical tissue via principles of electromagnetic induction. So this is Professor Tony Barker, University of Sheffield. So, he was the one who first made this transcranial magnetic stimulator at the University of Sheffield. So the pulse duration is approximately 100 microseconds and the pulse strength is 2 tesla, which is huge.

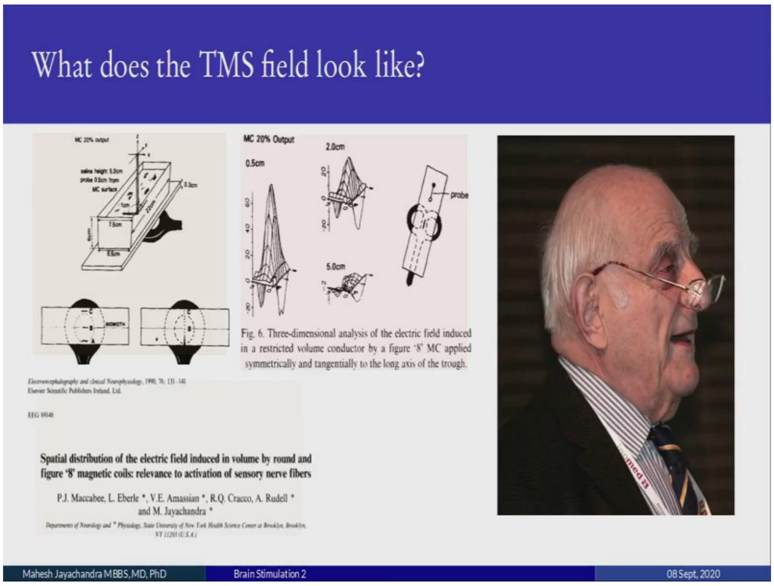
And here you see him stimulating the right motor cortex of a subject. Now TMS is very interesting. In that, you cannot perceive the stimulus. Our brains do not perceive a magnetic stimulus, stimuli. So it is painless. You do not know. You might have some other effects like feeling heavy in the head after much TMS stimulation, but there is no perception of the stimulus itself. So on the right, you see the circuit.

Essentially, it is a huge capacitor bank and it gets charged and then it suddenly discharges through a coil which sets up a transitory very strong magnetic field. Now this magnetic field induces an opposite magnetic field, electromagnetic induction principles in the brain. These lines of force cut through axons and the motor cortex and the axons from the motor cortex are very fortuitously placed so that they cut it as it bends into the perimiddle track and the spinal cord.

And that is why it is very useful for eliciting motor system responses. Just for comparison, a typical TMS machine would be about 2 to 5 tesla. As Tony Barker used 2 tesla. Now the earth’s magnetic field is microscopic compared to this, about 30 microtesla. A refrigerator magnet is much more powerful, it is about 5 milli tesla. So a rare earth magnet, these are very powerful magnets and you should be careful. You have two of them and your skin gets caught in between.

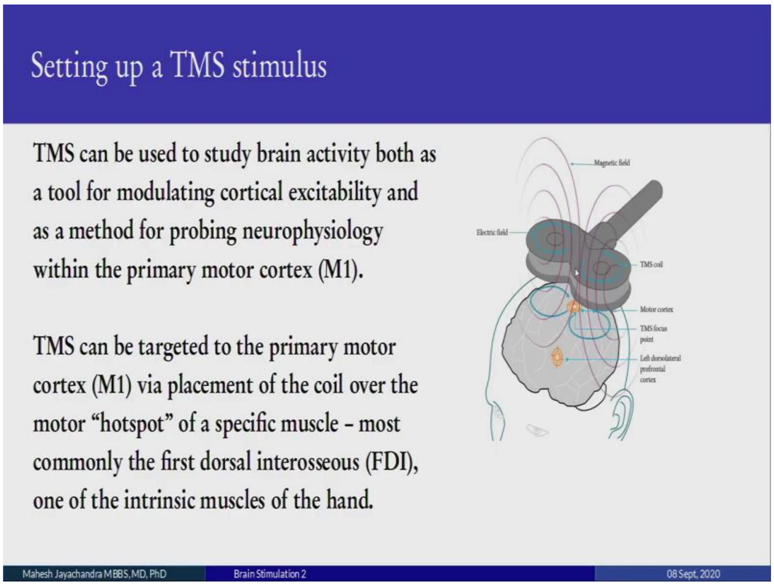
It is impossible to separate it, very difficult. So that is much high as 1.25 tesla. And then the clinical MRI systems are up to 3 tesla and research MRI systems can go up till 7, 10 tesla, especially animal systems. So, the magnetic field induced by the coil is quite major. But it is only, it is transitory, it does not last for more than microseconds.

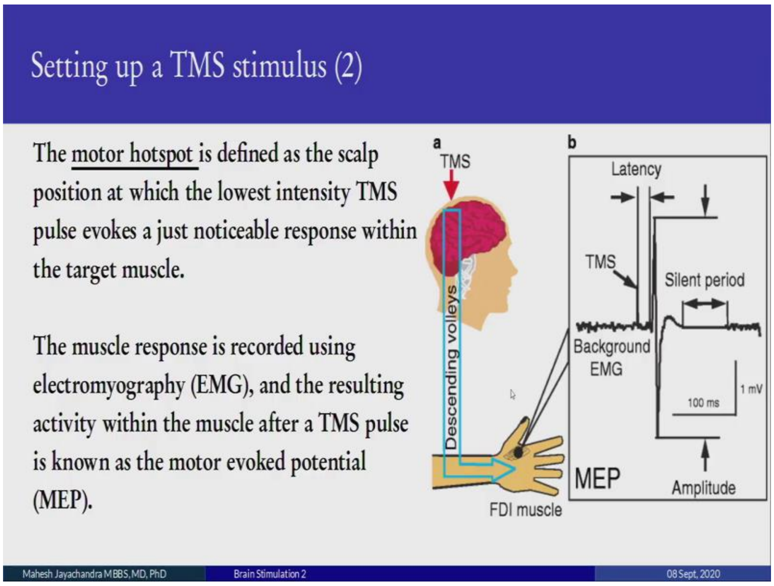
(Refer Slide Time: 12:44)



So, what does a TMS field look like? So, this is how it looks like. So, this was done in Professor Wahia Masin's lab, my thesis advisor, in SUNY, Brooklyn. And we modeled the field and the sensor was a little 1-centimeter coaxial cable stripped at the end. And with the magnetic coil below, we induced currents in the sensor and we plotted it out. And we see that it is very sensitive for distance, if it is half a centimeter, you have a huge focal magnetic field. If it is 2 centimeters, much smaller. And with 5 centimeters, practically not there. A lot of the initial clinical work and transnational work for TMS was done by Professor Vahe Euge Amassian in Brooklyn.

(Refer Slide Time: 13:41)





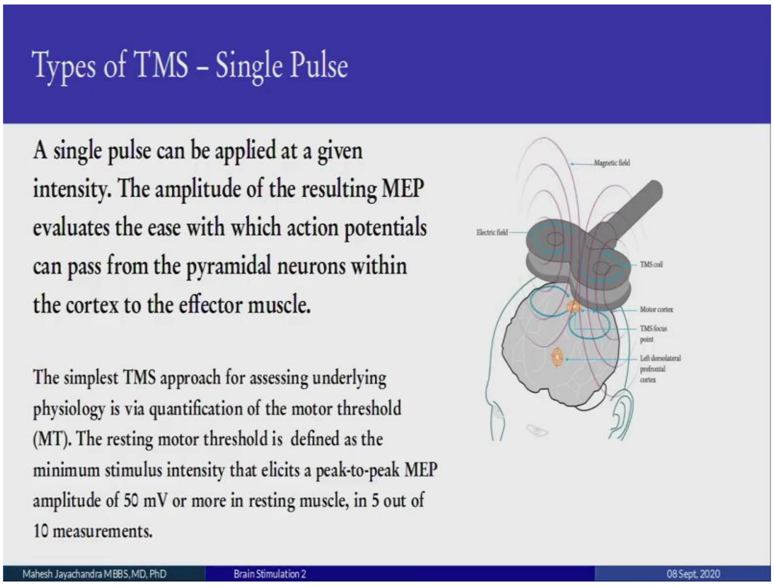
So, how do you set it up? So, again, if you look at the schematic on the right, you have a magnetic coil. Now, this is a slightly different magnetic coil from around coil. It is called a figure of 8 coil or a butterfly coil. And it kind of focuses the field on one area rather than being so diffused. So this is typically used to stimulate the brain. And it is easy to stimulate the motor cortex because it is right over here.

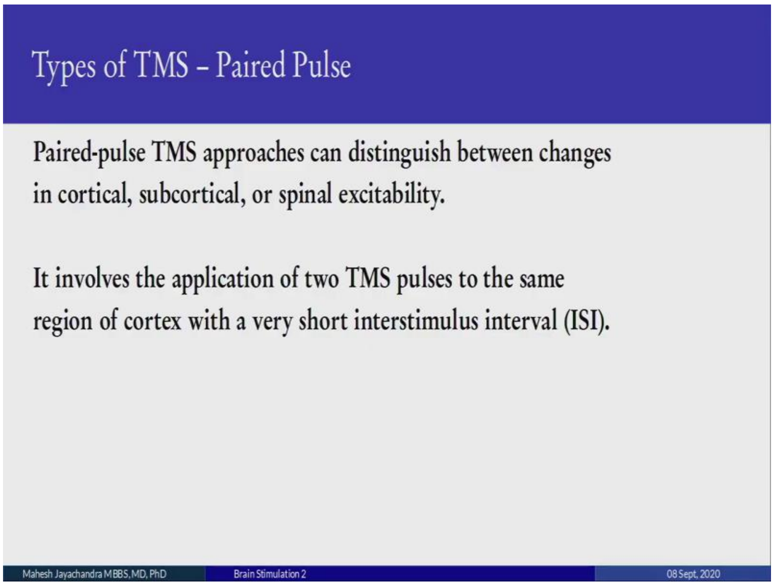
So you can put the coil-over here and you stimulate the contralateral motor cortex. And we have to move the coil a little bit to find a hotspot. And usually what we do is use the first dorsal FDI. This is the dorsal surface of the hand. This is the interosseous muscle between these two. And we place the coil on the contralateral side and when we see a small tremor or a twitch, that is a threshold. We know that it is at the appropriate place and we can get a motor evoked potential. So let us do some definitions.

The motor hotspot is defined at the scalp position at which the lowest intensity of the TMS pulse elicits a just notable tremor or fluctuation over here. You can see it. But typically, we do not go to the site. We record this with EMG, electromyogram. We have not talked about it, it is very similar to ECG, in fact, the same thing. The recordings are 1000 times bigger in millivolt range compared to brain waves. So you put an electrode over there and as soon as we see the response, then we know the coil is on the hotspot.

So if you look at this image on the right, this is the motor evoked potential. So you are stimulating with the transcranial magnetic stimulus in the motor cortex and you see this twitch over here. So this is the background EMG. This is nothing. So, here comes the stimulus. And then you have this nice response and this is the motor evoked potential. After the response, you have a silent period and then the background electromyogram, EMG, the background muscle activity starts again. So this is the motor evoked potential, very different from the sensory evoked potentials we talked about because this activates the motor system.

(Refer Slide Time: 16:10)

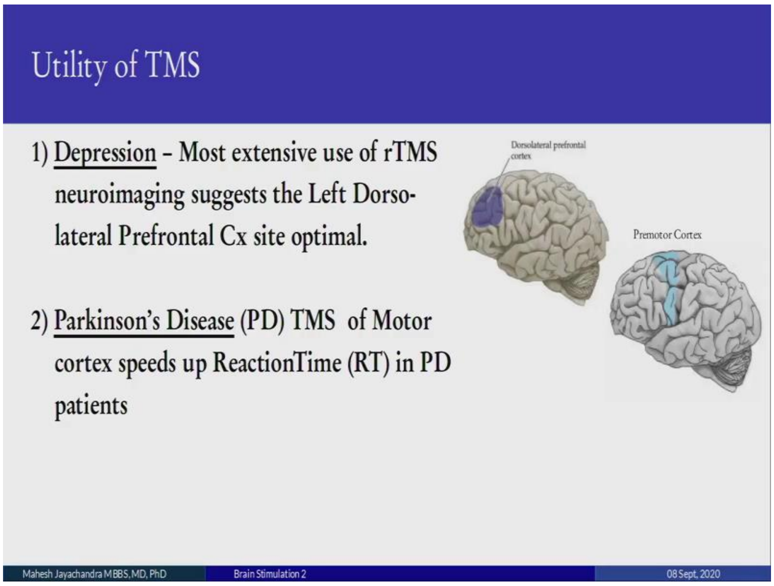


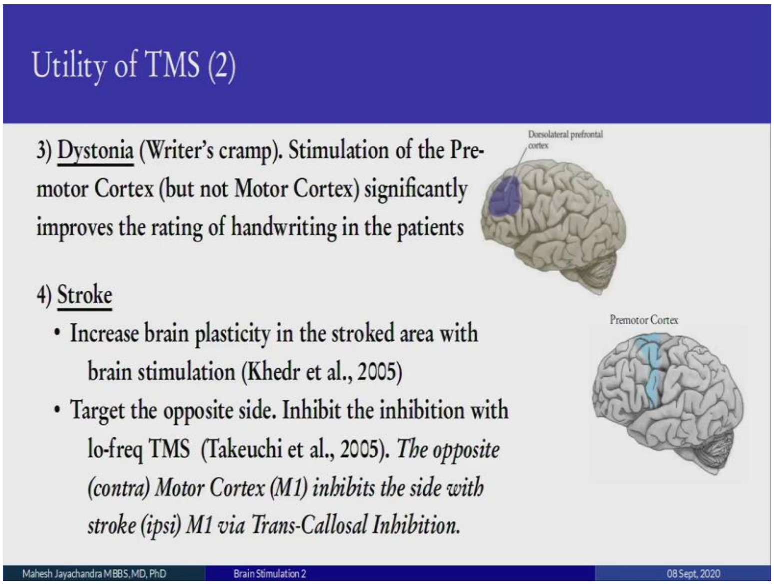


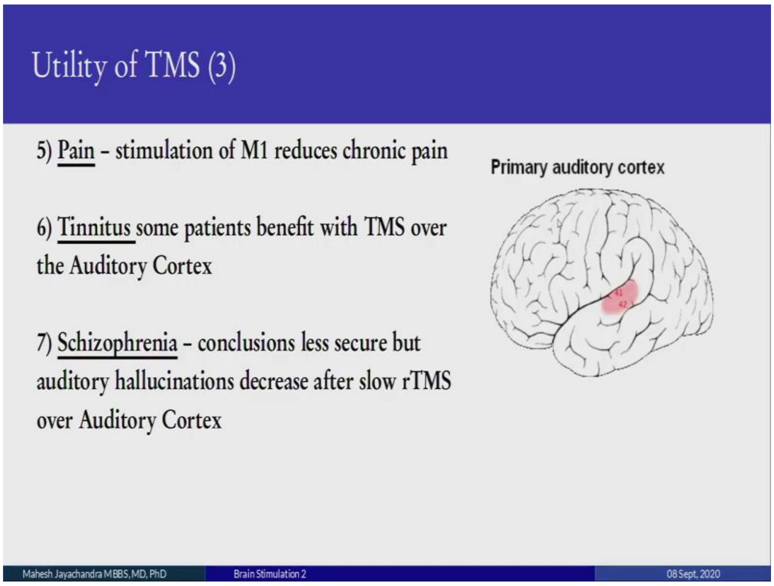
So what kinds of TMS are there? So, you can have a single pulse. So single pulse can be applied at a given intensity. The amplitude of the resulting motor evoked potential evaluates the ease at which the action potentials can pass right from the pyramidal neurons through the internal capsule, pyramidal track, spinal cord, and to the periphery over here. So we quantify the motor threshold and is defined, we define this as the minimum threshold intensity, that elicits a peak to peak MEP amplitude of more than 50 millivolts in the resting muscle in 5 out of 10 measurements.

So this is a very empirical kind of a definition. Then most of the neurophysiology is empirical, nothing is intuitive or can be reasoned out. Alternatively, you can have a paired stimulus. So two TMS stimuli are very close to each other. And this can distinguish between changes in cortical, sub-cortical, or spinal excitability. So, these are two stimuli with a very short intra stimulus interval between them.

(Refer Slide Time: 17:14)







What is the utility? Again depression. So most extensive use of TMS is in clinical depression. This is used, this is the biggest use of TMS and insurance covers it. So the left dorsolateral prefrontal cortex here is optimal for depression. So, you have, the patient comes, comes for a few times, and almost like magic, the symptoms of depression left. And we use this only in cases where the patients do not tolerate medications well. Another place where it is used but more researched, clinical research is Parkinson's disease.

And here you stimulate the pre-motor and motor cortices, and it increases reaction time. What happens in Parkinson's is that they start hesitancy. To do something takes some time. To stop something, it takes some time. This increases reaction time. So it offers some help. Another place where its use is dystonia, a writer's cramp. So, if you keep using your hand and do use it a lot, sometimes you cannot, it is difficult, it is painful to use it. So again, here if you do pre-motor cortex over here, if you stimulate, this helps in patients and improves your handwriting. And stroke. So, in the stroke area with brain stimulation, you can increase plasticity.

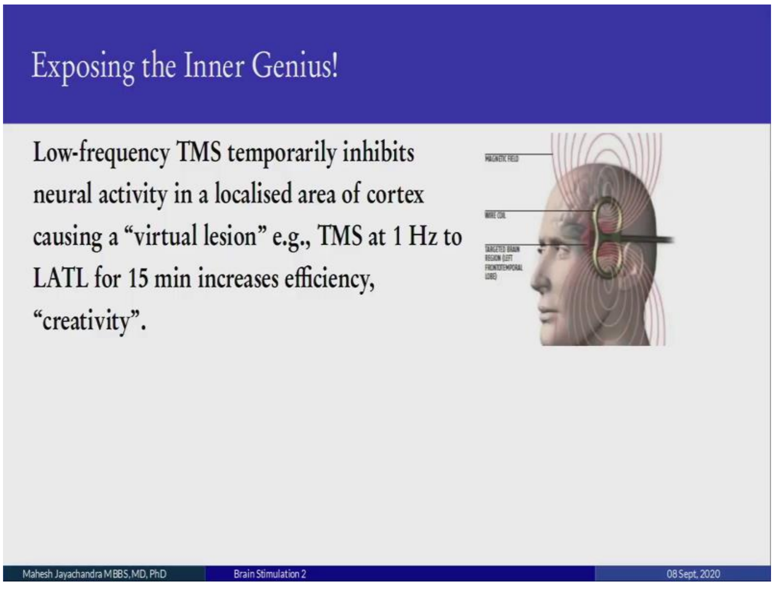
The logic being increased plasticity would help recovery. Also, you can target the opposite sides because both hemispheres are highly connected. And you inhibit the opposite side with low-frequency TMS and the ipsilateral side with a stroke it inhibits a little bit transcallosal right across the corpus callosum. So they found some help, it helps. But again, these are in limited studies, limited populations, homogeneous populations and they have to be applied, extended much more before it comes into regular clinical utility.

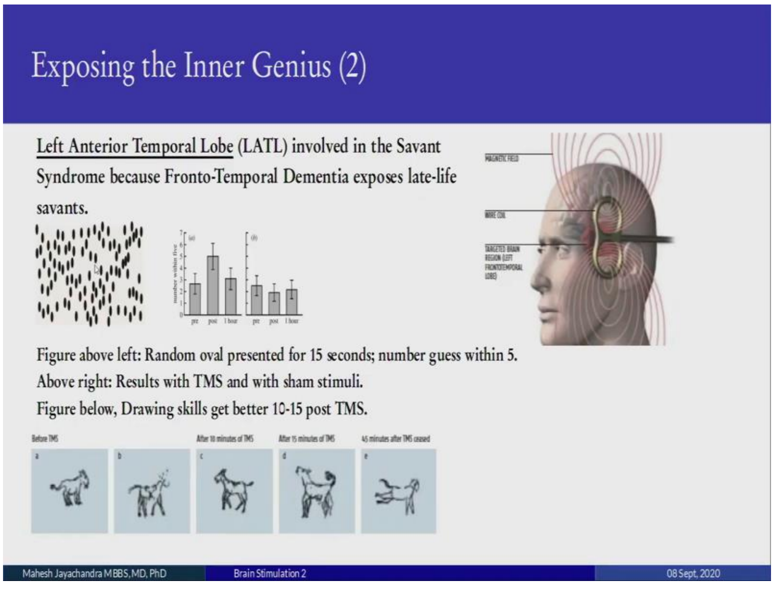
However, depression treatment is now a regular clinical method using TMS. Then other just for completion sake, other areas where TMS is found to be useful, one is in chronic pain. And again, we use motor cortex stimulation. Some people have ringing in the ears, tinnitus, without any auditory stimuli, you constantly have this ringing. So if you stimulate the auditory cortex, this is area 41, 42 vernicase area, but I am close to it. The primary auditory cortex is inside this groove over here, the supratemporal brain area 21, 22.

So if you stimulate this area, apparently it helps. The ringing stops. And schizophrenia, this is a bit controversial. But after stimulation of the auditory cortex same place over here, you seem to have a decrease in hallucinations. So one of the signs, synchonon of schizophrenia is auditory hallucinations. A person will hear somebody talking to them, threatening them at a loud volume. But there is no auditory stimulus.

They are not lying. Because if you do an FMRI, you will find that the auditory area is being activated. Now whether you believe in other elements doing it, whatnot, we do not know. It could be spirits or whatever talking. That is what the patients usually say. However, it is real, they are not lying. And TMS stimulation, slow stimulation, over slow low-frequency stimulation over the auditory area decreases the auditory hallucinations.

(Refer Slide Time: 21:00)



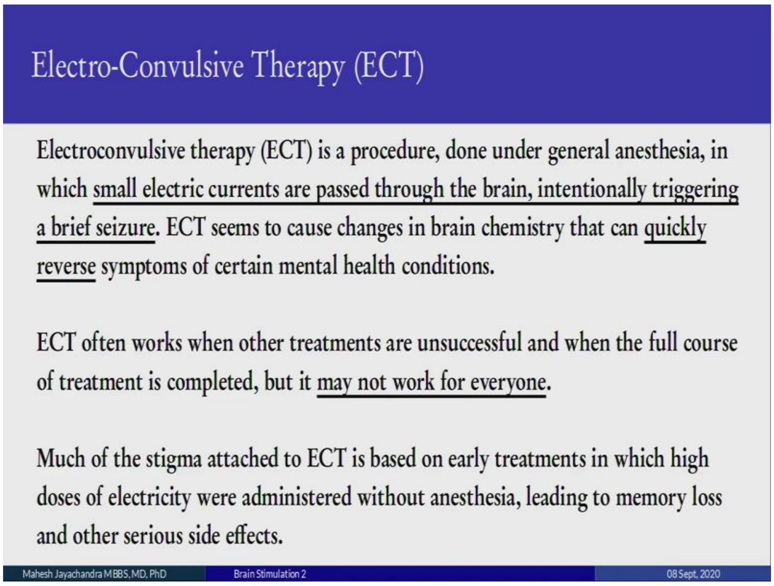


And there is another very interesting thing. Everybody is a genius. I am not being fictitious. There is a particular area in the brain, the left anterior temporal lobe and if that is interfered with for a short time, you become like Shakuntala Devi. She was a person who could process a lot of numbers and she is from Bangalore. Nobody knew how she did it. Even she wouldn't know how to do it, it was just intuitive for her. So this is seen in older people. So typically, you have a grandfather and he is playing bridge and suddenly, he becomes very good at it and he can memorize all the other people, what cards they have.

And apparently, it is called one kind of dementia where it effects the left anterior temporal lobe. And this causes the person’s cognition to increase to a level where they are considered a genius. So, Professor Snider in Australia, he studied this and these were two tasks given to the subjects. So here you have on the left side, you have a bunch of ovals and you have to estimate in a short period of time, within 5, what is the number of ovals present on the screen. And here you see the data, on the left, this is before the TMS, after the TMS it is statistically significant. And then it comes back to normal.

And these are sham controls without TMS stimulation. The other thing he did was he made the draw. So here you see the baseline drawing, it is supposed to be a horse, vaguely looks like a horse, it could be a dog. After 10 minutes of TMS, it looks nice. 15 minutes, really a horse. 45 minutes, again it comes back to his baseline from it. So temporarily, you can make a person’s cognition ramp up. And kind of like a genius, which is nice to have this before competitive exams.

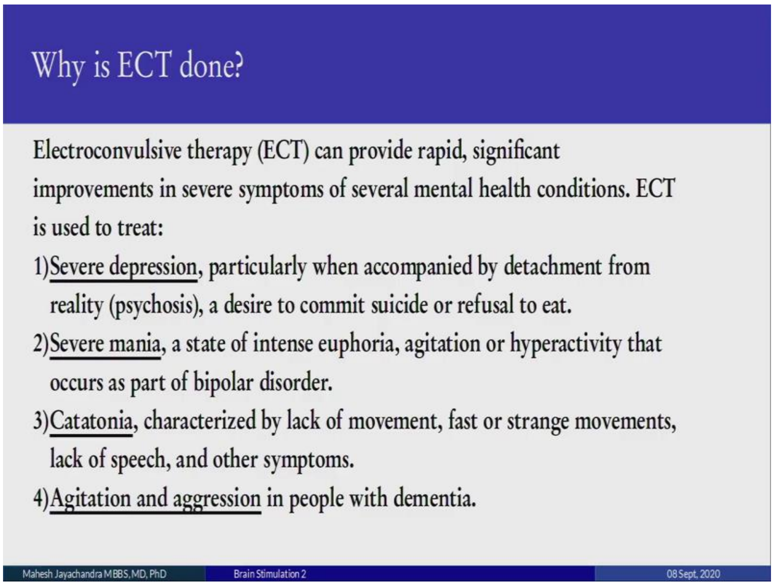
(Refer Slide Time: 23:12)



That was TMS. Now ECT. Now some of you all might have seen this classic movie, One Flew Over the Cuckoo's Nest with Jack Nicholson, where he gets on the wrong side of the nerves and he keeps getting shocked. And movies like that and a lot of rumors and superstitions, superstitions, beliefs have given ECT a bad name. This is electroconvulsive therapy. Now typically, it is a procedure done under general anesthesia, where electrical currents are passed through the brain and it triggers the seizure, you have epilepsy briefly.

Now, ECT causes changes in brain chemistry that can quickly reverse the symptoms of certain health conditions. So, it is a therapy of last resort. It often works when other treatments are unsuccessful and when the full course of treatment is completed. However, it may not work for everybody. And as I said, much of the stigma attached to ECT is based on early therapies and treatments, where high doses of electricity were administered without anesthesia leading to memory loss and other serious side effects.

(Refer Slide Time: 24:27)



So, when it is used properly, it can provide rapid significant improvements in severe symptoms of mental dysfunction. So it is severe depression. Particularly, when depression is accompanied by detachment from reality psychosis, a desire to commit suicide, or a refusal to eat. Severe mania, where you are very euphoric and agitated and hyperactive and it is a part of bipolar disorder, manic depressive illness.

Catatonia, where a person is like a board and there is no movement, no expression or there may be fast unusual strange movements, lack of speech, and similar symptoms. And finally, agitation or aggression in people with dementia. So in all these conditions, where the patient cannot be controlled with standard therapy drugs, we use ECT.

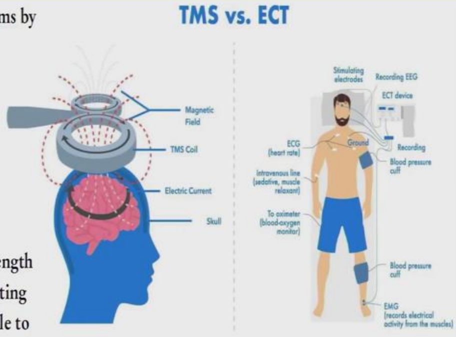
(Refer Slide Time: 25:21)

Comparing TMS and ECT for Depression

TMS alleviates major depression symptoms by sending electromagnetic pulses into the prefrontal cortex.

ECT "resets" neurological pathways through electroshock seizures.

Transcranial magnetic stimulation uses electromagnetic pulses similar to the strength of an MRI machine. By specifically targeting the prefrontal cortex, these pulses are able to reactivate the neurotransmitters believed to be responsible for depressive symptoms.



Comparing TMS and ECT for Depression (contd.)

1) TMS is best for major depressive disorder sufferers who have found no relief from the first and second lines of treatment prescribed for their symptoms.

2) TMS patients undergo sessions over the course of four to six weeks. A metal coil is painlessly attached to the front region of the head, and is measured and calibrated in the first session.

3) Other than a tapping sound and sensation on the scalp, patients feel nothing and relax during the session. Upto 70% of patients show a positive response in a few weeks. TMS sessions are painless and non-disruptive to daily life, with minimal short-lived side effects.

Comparing TMS and ECT for Depression (contd.)

1) ECT, on the other hand, is reserved for severe cases of psychosis, catatonia, or bipolar disorder, and is indicated for those who have life-threatening symptoms.

2) ECT requires the anesthetization of patients before triggering a seizure with the use of a low electrical current.

3) With ECT, patients may wake from their anesthesia feeling confused, unable to pinpoint where they are or how to manage their surroundings. This confusion usually lasts a few hours, but in some elderly cases it can last for several days.

So they are slightly different. For example, you can use TMS and ECT for depression. So TMS alleviates major depression, depressive symptoms by sending electromagnetic pulses to the prefrontal cortex. ECT you cause seizure and reset the whole brain. And TMS uses electromagnetic pulses which are similar to that of an MRI machine. And these, the theory is that when you stimulate the prefrontal cortex, these pulses reactivate the neurotransmitters believed to be responsible for depressive symptoms.

If you see the figure over here, this is TMS, we have gone through it. ECT, is only done in the hospital and under general anesthesia, and a lot of things are monitored, ECG, there is an intravenous line for sedation, the blood pressure, EMG activity, stimulating electrodes, and the ECG device. So TMS is best for major depressive illness who found no relief from the first and second lines of treatment prescribed for their symptoms. And this TMS usually is given over a prescribed period of 4 to 6 weeks, about a month.

And a coil is attached, a person goes and switched on and gets zapped on the left prefrontal cortex. And that is how it goes. So what are the side effects? Well, you have this tapping noise and then there is a weird sensation on the scalp. But otherwise, there are no, you do not feel anything. I speak from personal experience because in my lab I tried stimulating my brains with TMS, motor cortex and I could not feel it at all, but my hand, my leg all moved by themselves.

The nice thing about TMS is it is non-invasive and about 70 percent of patients they have some kind of familiarization of symptoms, they feel much better. And it is painless and non-disruptive to daily life and does not have very few side effects. ECT on the other hand is reserved for severe cases of psychosis, catatonia, or bipolar disorder. So you need (anes), the patient has to be anesthetized, which means it has to be a cardiac treat, it cannot be done even in the clinic, it has to be done in a place where you have appropriately trained mental health professionals.

This is another problem with ECT. Most psychiatrists are not trained in it. I mean, they learn it during their training, but they do not know how to do it. So you have to go to a center that is certified for ECT. For example, in Bangalore, you go to NIMHAS. So with ECT, the patient may wake up completely disoriented and this confusion may last for hours, in the elderly it may last for days. So the person cannot be, it is not like TMS, but after TMS it is fine, it goes on. Somebody has to be around. So that, in brief, is an introduction to electrical stimulation of the brain. Thank you very much.