Neural Science for Engineers
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Lecture - 49
Memory and Learning - II

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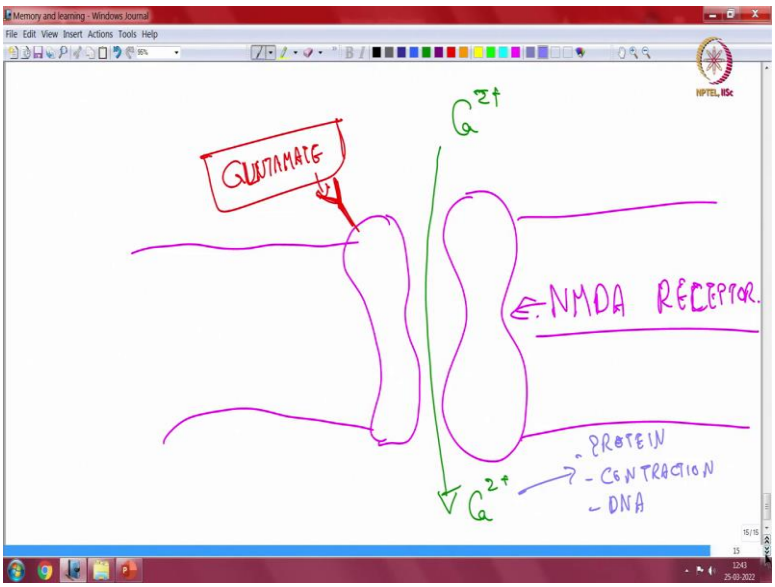

Now, NMDA receptor is again present within the cell membrane and like sodium and potassium and the key thing is it has got it gets stimulated sort of by glutamate. So, glutamate gets associated with that and that is how the NMDA receptor gets activated. What actually does it do? It allows calcium to flow in. So, we are now understanding why there was a discussion on sodium, potassium and calcium as in part of the introduction.

So, NMDA receptors normally are stimulated by glutamate and then that causes influx of calcium. And I spent a lot of time highlighting the calcium which binds to proteins, then it can cause contraction in muscle, it can cause DNA effects which produce further proteins and things like that. So, this is about glutamate and the NMDA receptor, but the NMDA receptor is another very interesting property which is the point of this discussion.

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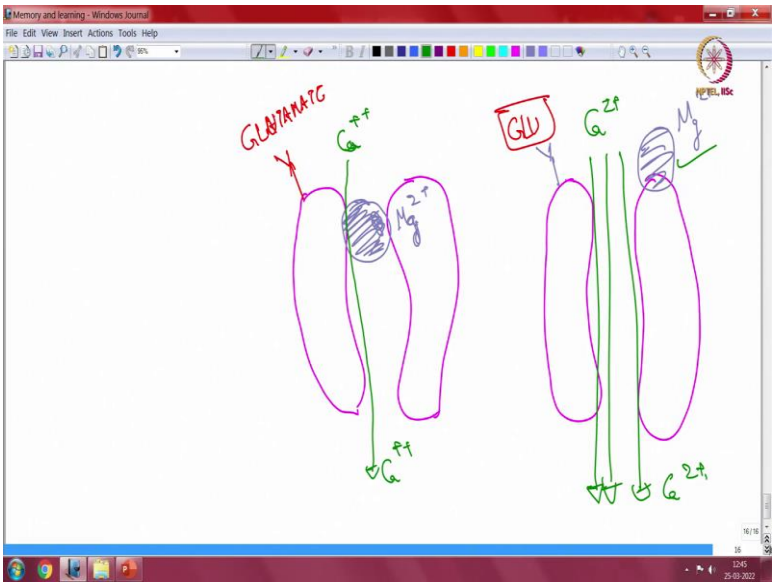

So, the NMDA is partly blocked by magnesium; magnesium is 2 plus. So, what happens is when there is a magnesium block it still conducts. So, glutamate allows some amount of calcium to go through. Now if you remember, remove this magnesium block; magnesium comes out then along with glutamate of course.

The amount of calcium which goes inside is exponentially increased. So, what is the difference between the mechanism? So, difference in this mechanism is that once magnesium is taken out from the channel the amount of calcium which goes into the cell is increased. So, that is the fundamental property of the NMDA receptor and what actually happens is how does the magnesium block gets removed?

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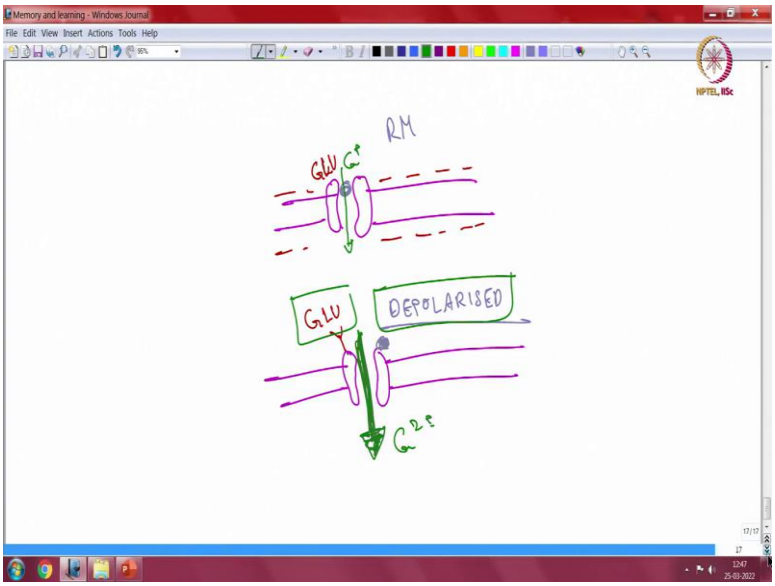

So, magnesium block gets removed with a very interesting property. So, you have a cell membrane and then you have glutamate, and this is a normal cell, negative on the outside and then you have the block. But if it is depolarized resting membrane, the magnesium block gets removed. So, along with the glutamate, what has changed is a small amount of calcium to large amount of calcium. So, what is the change? Draw it reverse or draw it in a different fashion.

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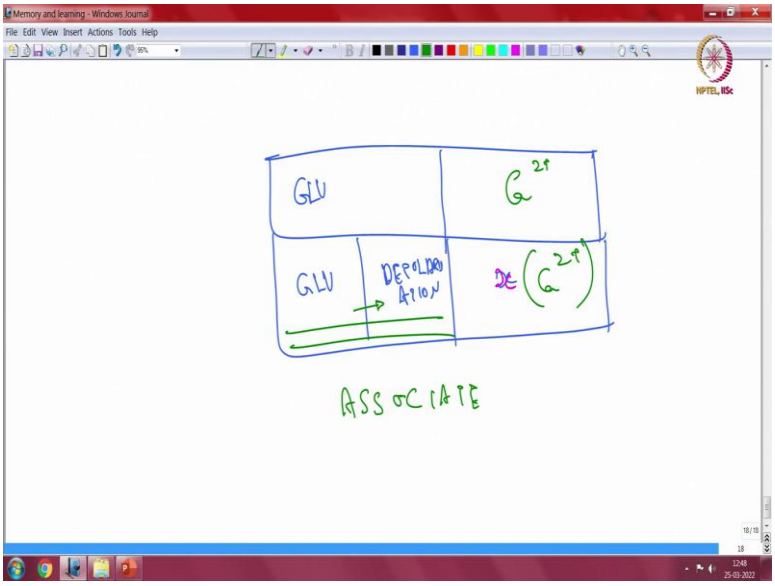

So, we will draw it exactly like we did that. Glutamate results in calcium. Glutamate depolarization x times of. So, you associate glutamate and depolarization you are moving the magnesium block and then you are releasing calcium, it is a very important ion. So, that is why I was building up this story. So, I was building up this story because unlike sodium and potassium calcium is a very different mechanism of action.

And it not only you know it changes things in the short term, but it also changes in the medium term and in the long term. So, this is an important thing. Now there is also an interesting thing which happens, can glutamate itself promote depolarization? Yes of course.

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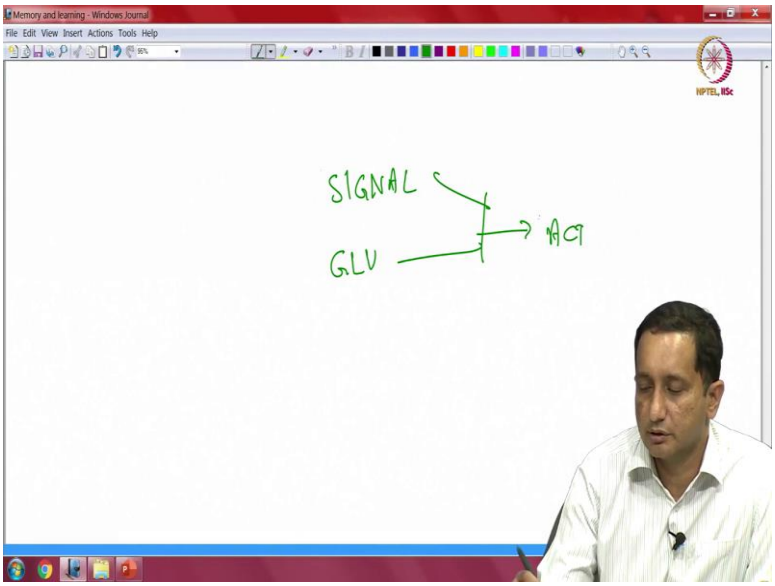

Because glutamate is one of those other things which come along with signal. So, you have a signal and then you have glutamate. So, that in turn would summate and produce an action potential.

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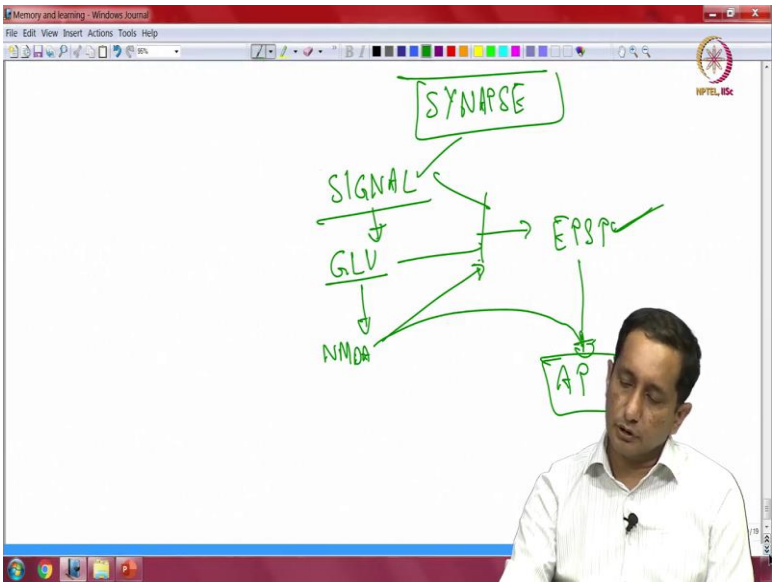

So, you have an EPSP. So, this in turn if you add one more stimulus in terms of the NMDA opening, EPSP results in an action potential. So, you are associating different kinds of signals. So, you have a parent signal which is an electrical signal which is coming at a synapse. So, you have a parent signal coming from the axon of the prior cell and then it comes and then it releases not only glutamate, but also it produces an EPSP. The signal just produces the EPSP.

But the signal also causes glutamate release which in turn attaches to the NMDA and it in turn submits and forms an action potential. So, that is a mechanism. So, how does that work?

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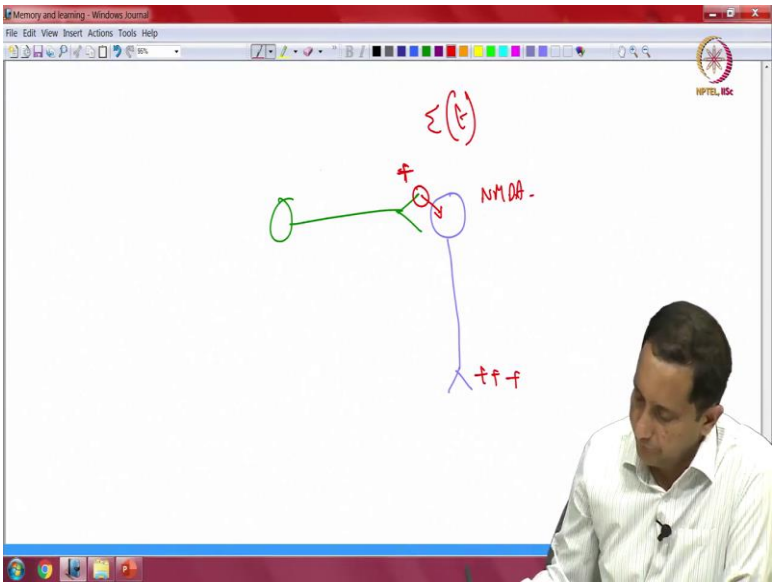

So, a lot of work actually happens within the synapse. So, when a neuron presynaptic neuron, produces increased signal over a period of time the signal strength increases. And that in turn if you have an NMDA receptor over here the signal strength gets chronically changed.

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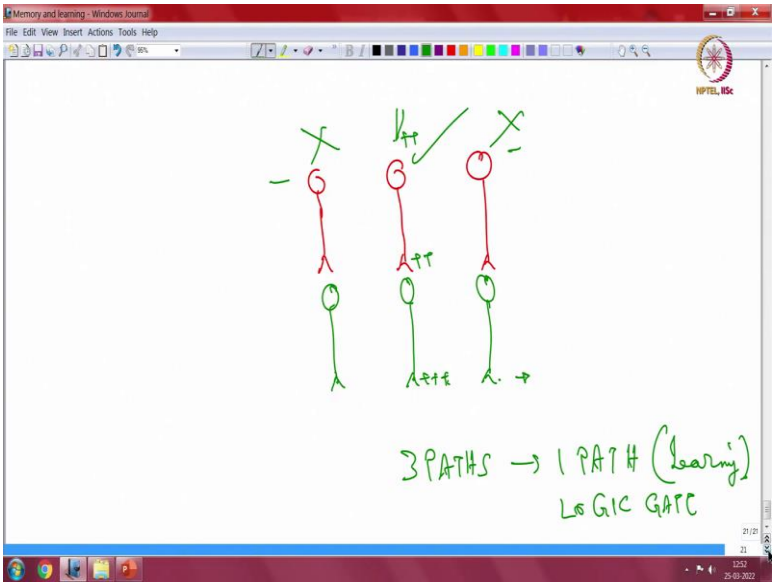

Now if you look at network pathway, consider three sets of pathways which exists. So, each time a signal comes. So, you stimulate the signals. So, that causes a plus, that causes a plus and that in turn causes a plus whereas, there is no signal here, there is no

signal over here. The amount of signal which is generated gradually comes down. So, you are choosing something against not choosing something else. So, there are three paths; one path which is basically learning or a logic gate.

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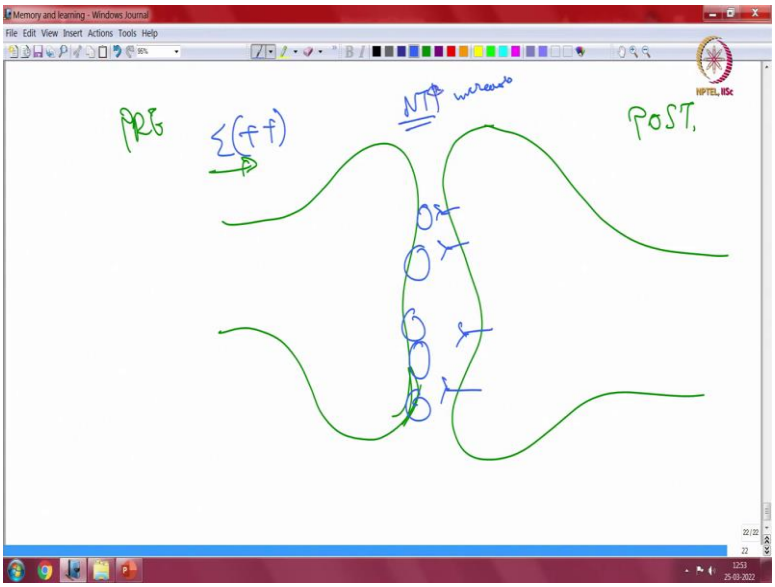

Now what kinds of mechanisms are present within the synapses to produce these kinds of activities is something which needs to be discussed a little more. So, you have the presynaptic membrane and the postsynaptic. So, pre and the post, so you have signal which is coming downstream and that causes release of neurotransmitters and that in turn causes stimulation over here. But when increased number of stimuli happen the amount of neurotransmitter released increases.

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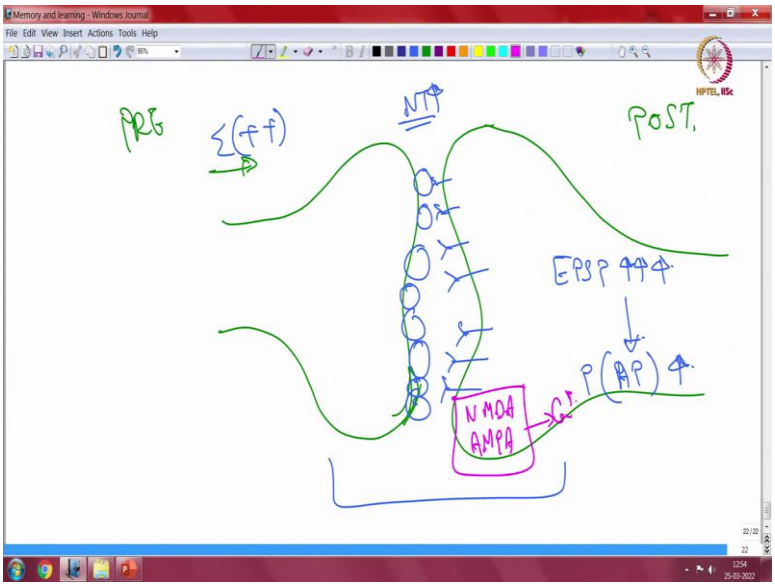

So, neurotransmitters would get more, you know when you increase the amount of stimuli which is coming at this one and correspondingly the amount of receptors also increase. So, what actually happens is you are strengthening the synapse. So, EPSP's keep on increasing and that EPSP contribution to producing an action potential, production of an EPSP which may result in an action potential increase.

So, selectively at synapse when signals are coming from a presynaptic cell into the postsynaptic cell, the EPSP's which are generated keeps on increasing and that in turn results in an increased probability of an action potential. So, that is what actually happens within that. Now if we include interesting things like the NMDA and AMPA receptors we are looking at an amplification. So, you are looking at this not only produces EPSP's, but also activates the calcium mechanism. So, calcium within the place has other kinds of roles.

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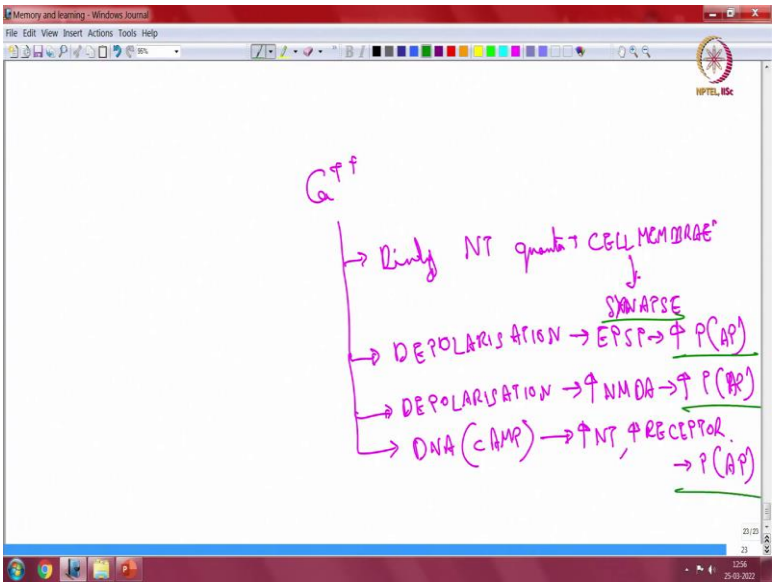

So, what is the role of calcium in the presynaptic membrane? So, calcium is responsible for binding neurotransmitter quanta to the cell membrane that in turn goes into the synapse. So, this calcium also causes depolarization. So, that cardio improves the EPSP, that increases the probability of an action potential. This also causes depolarization. Now a depolarization which in turn say accentuates, so you have increased NMDA recruitment.

So, which in turn sort of increases the probability of action potential, this also goes to the DNA through second messenger proteins say CAMP and that in turns increases neurotransmitter release, increase receptor release and receptor synthesis say more NMDA gets synthesized and that in turn increases overall probability of action potential generation. So, by several mechanisms you know you have an increase in the probability of an action potential coming out through one single synapse. So, this is for one synapse.

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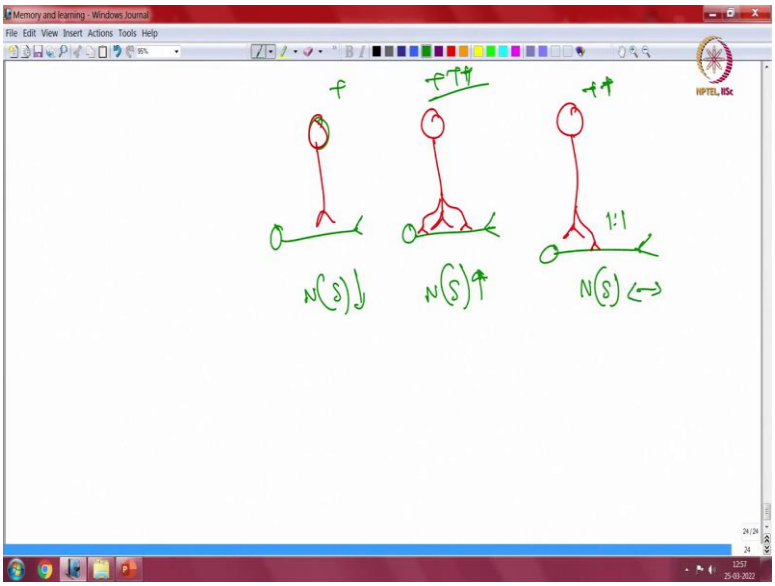

Now we go back to the same pathway. So, pathway earlier was drawn in red. Then you have a cell which is like this. So, when you repeat increase the amount of signal. So, we will start with normal. So, normal there is a 1:1 ratio, it is an assumption of course. But you understand the logic that there is some baseline stimulation which is happening and then when there is 1:1 stimulation of the postsynaptic neuron.

Now, if there is increase in the signal what actually happens is the number of synapses increase. So, for that there is another thing. So, it is 1:1 in the sense that you know this is the normal and this gets increased. Now suppose the amount of stimulus actually decreases you would find that the number of synapses comes down, number of synapses increases, number of synapses remains stable. So, this is in terms of see what I explained earlier was within a synapse.

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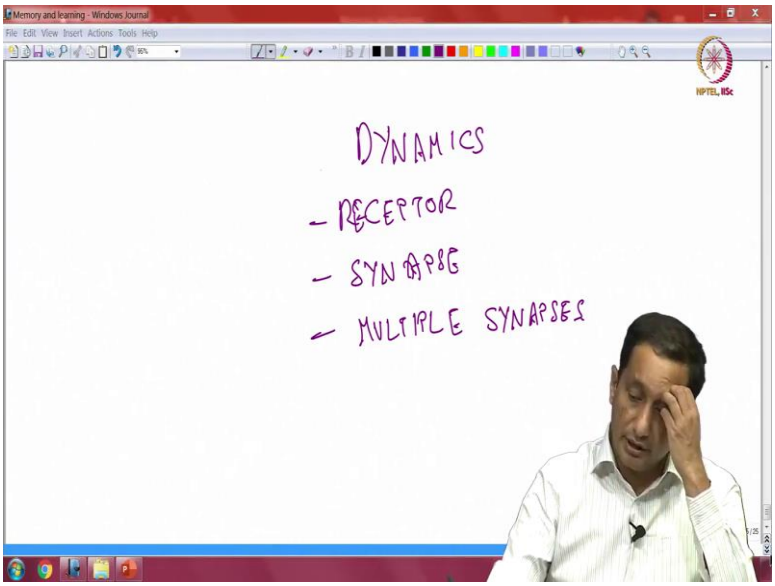

So, we started with dynamics of receptor, then synapse. So, the learning sort of happens at these multiple layers. So, within a molecule you can have this gradation of response. So, the more the stimulus, the more the output and over a period of time ensures that it is memorized when the magnesium is coming out of the receptor it is a sort of memory which is created.

You have created 1 bit of memory because after the magnesium has come out, the amount of calcium which is going through that channel has increased and that is because the particular signal which is responsible has made this to happen. So, that is within a receptor. Within a synapse the number of channels which open, the number of neurotransmitters which are generated, the number of receptors which are generated.

Everything is a dynamic process, number of synapses increases, number of receptors increases, and it is that there is a cycling. So, the number of neurotransmitters which are produced, consumed is a cyclic process. Number of receptors which are produced, occupied, stimulating as a cyclic process you know it is a process which keeps on changing.

So, what happens with increased stimulation is the gain changes. So, with the positive gain the number of all of these things increases with a negative bias lesser amount of stimulation happens. Now here is where the key point of association which is happening. So, you have a baseline stuff which is happening you know some kind of baseline

activity which is happening. So, there is something positive added on to that in terms of an association. So, there is something new which has happened, and that newness of the stimulus is captured by these various mechanisms.

So, I started with NMDA then explained as to what happens within a synapse and that multiplied by number of synapses. So, that is how you know in graded fashion I have tried to explain how memory is encapsulated. So, encapsulated in the sense it is stored. So, learning happens in the same fashion. So, learning is you are repeating a procedure.

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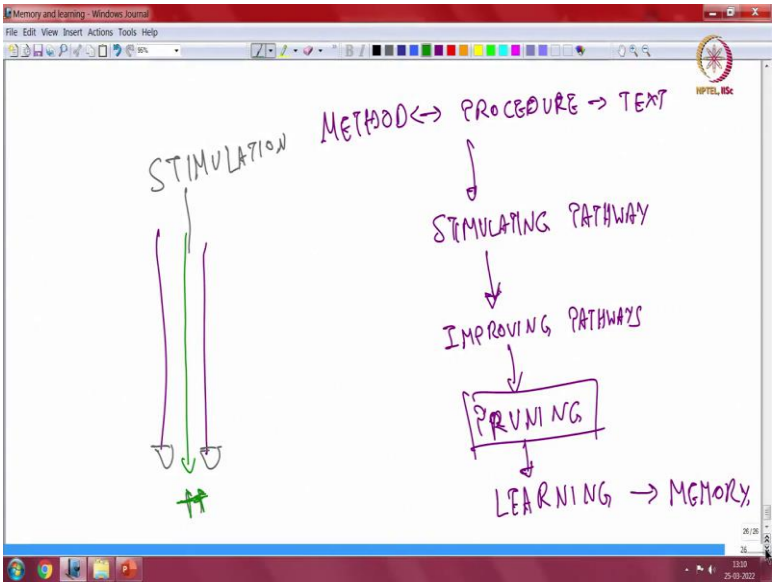

So, when you are repeating method or procedure or a text, you are stimulating pathways. So, that stimulation in turn you are improving the pathways, it is sort of pruning and I hope you the people from ML would know pruning in ML terms. So, it is somewhat like that. So, it is not mechanical pruning in which you cut the network out it is a dynamic process of pruning in which signals passing through a particular pathway gets facilitated internally.

So, there is a positive feedback loop and that gets reflected on and that in turn is responsible for learning and also for memory. So, you have three pathways and one of them is the facilitated pathway. When there is a stimulation, the facilitated pathway gets stimulated more, so giving you an output so that is retrieval. So, you have three paths, and you are able to put out information.

Because that pathway is the fastest or the strongest pathway within the network. So, you have competing networks all of these remember are interconnected. Because all of them are structurally built unlike any kind of software mechanism in which you build entire networks out of code and you can cut, prune what happens in the head is you know all these are fixed stuff.

The only thing which can actually change is the number of synapses and the strength of synaptic linkage. So, these are the tolerable limits of mechanical activity all the rest of it is dynamics. So, you would increase signal strength based on these biochemical pathways, you can decrease strength based upon biochemical pathways and that is how you know this learning mechanisms are expressed, and memory is expressed.

So, I have taken lot of creative liberty in putting forth this topic. Because if you go through the textbook you would go across this material without finding any connection between many of these things. It is a bit dense stuff to comprehend and understand I made an effort to link up you know each of these factoids is true. But whether they are actually linked in biology between the NMDA to learning to not NMDA to the number of synapses to extra synapses and the bulking of synapses they are all individually true things.

But I have presented it in such a fashion, so that you have an understanding that very different scales of activity are responsible for encoding, producing, memory learning and things like that.

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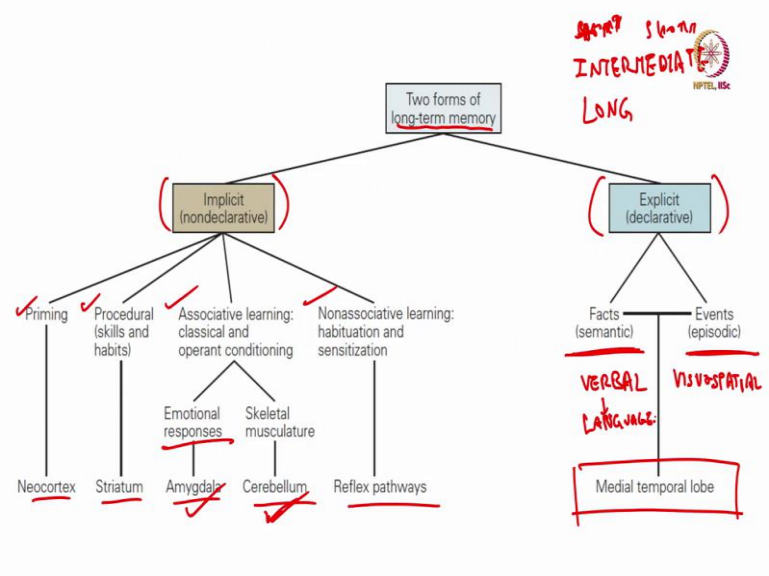

So, we started out here, long term memory. The implicit is you need to have a huge network which gets built with the individual components, which are unconscious. So unconscious in the sense that, say when you start to learn to drive a car you need to be conscious that your right foot on accelerator, right foot on brake, left foot on clutch. If you are driving the older style vehicles not for Tesla people, and electric vehicles and automatic vehicles.

So, then you need to know how to turn the steering, change gears, change clutch, use the clutch and things like that. So, you cannot declare these things and you do not learn steering separate from the clutch and the accelerator, you learn everything together. All of them are in different parts of your visual space.

And you need to associate all of these things. Amygdala is something which is responsible for emotional responses. Cerebellum I have explained in great detail as to how it is connected with control of skeletal musculature. The explicit declarative is on the other hand based on events.

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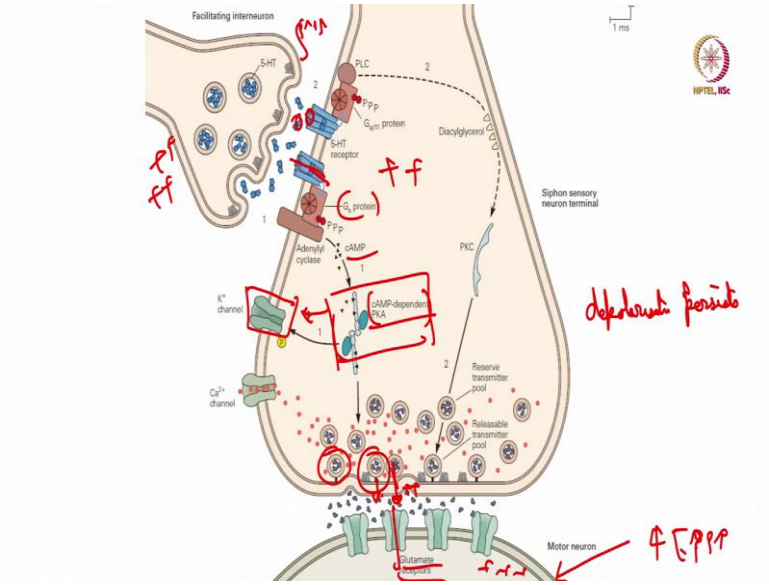

You know you have events which are encoded within your head and that encoding is in two parts. So, you have visuospatial, and I think it is verbal, I may have to check that, so verbal in the sense language. So, you would have text and it can be any kind, you can have auditory visual etcetera.

And visual especially in terms of related this one. So, this is what the picture is about. So, when there is you know repeated stimulation what actually happens within the synapse? So, this is the synapse.

So, within the synapse you have the proteins which interact with these neurotransmitters and that in turn produces this G protein, cyclic AMP and that in turn facilitates these molecules. With one of the mechanisms by which you enhance synaptic activity. So, what it does is, it closes the potassium channel.

So, you exclude this out of your network by which you ensure that depolarization persists. So, when depolarization persists, increase in the EPSP in the output neuron. So, blocking potassium through a protein mediated mechanism. Protein would cause the depolarization to persist because the membrane potential is not allowed to come back to its native state for a longer duration of time. So, that is the mechanism. So, this is the calcium channel.

So, calcium channel in turn allows the calcium ions to interact with this one. So, increase in the amount of neurotransmitters which are released, which is increased and that in turn stimulates this one. So, on top of that you have glutamate receptors, you are amplifying signals. So, you stimulate in the presynaptic neuron that produces stimulation downstream.

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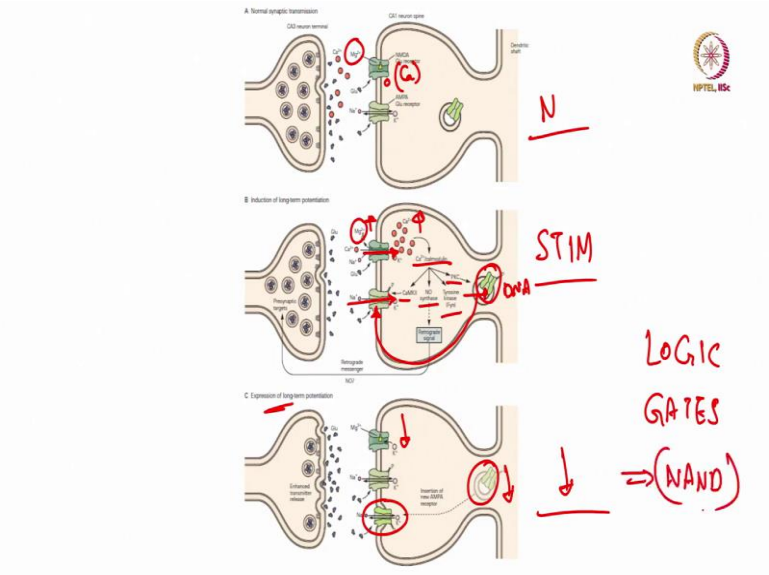

So, that is the method by which you associate stuff and then produce signals downstream. So, this is the explanation the magnesium block, which is here, this is normal and then this is the stimulation. So, when there is stimulation, magnesium comes out, calcium goes in, no calcium here.

But calcium is increased here and that goes downstream. See there are so many mechanisms they go all the way to producing new proteins from the DNA, this in turn comes all the way back here into this membrane and that in turn facilitates for the channels.

On the other hand, when there is negative stimulus, the signal here comes down. So, the amount of new transmitters which come down and you can have inhibitory channels which are brought over here and that in turn causes negative gain. So, normal stimulus negative so that is how you have logic gates somewhat representing NAND. So, that is how things are within the memory part of the story.

Now, there are two other properties in relation to memory which are interesting, and which should be known. And I am explaining something about it only to highlight how complex the entire phenomenon is. So, we discussed classical conditioning.

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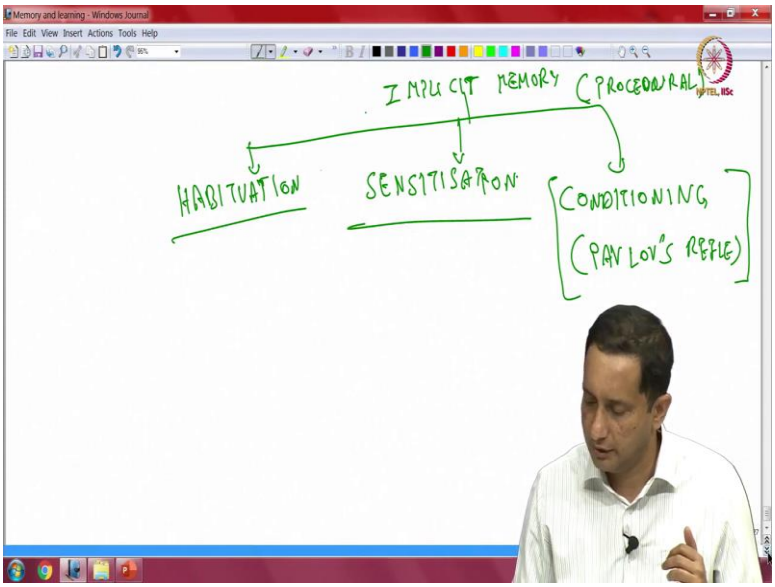

So, by Pavlov's reflex, now there are two other things, habituation and sensitization. So, these are discussions in implicit memory. Implicit and explicit are the two things. This is also called to refresh your thought memory procedural. So, we spoke about how association is responsible for building up a network.

And how you can retrieve, how you can store memory in terms of synaptic information, in terms of receptor information, in terms of numbers of synapses. And how a network gets facilitated across its entire pathway because of repetition, you know repeat something and that gets built up.

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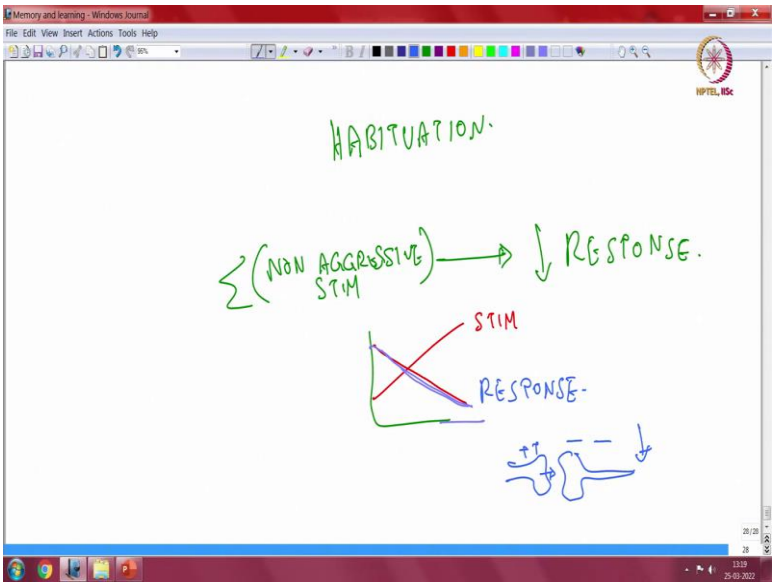

Now there are two funny stuff which happen in very direct opposition so as to say. So, habituation is non aggressive, I have to use the term stimuli, when you repeat causes reduction in response. So, I should use the human part of the experiment, you can try it out on somebody else, it may not be working on you.

So, there is something called as the tap test in which you know tap in this particular area and in normal people if they are tuned to it may not respond. But you know the general reflexes you keep closing your eye blinking. So, you do that 1, 2, 3 sort of blinks happen and then you repeat that nothing happens. So, that is a repetitive STIM and you find that the response which was their initially goes down and goes down. So, you increase stimulus, response comes down.

So, that is habituation you know you get habituated to something. So, interestingly the mechanisms which govern habituation are exactly the same as what I have spoken earlier. It is synapse based, you have synapse which goes on to the output synapse, you keep on increasing the stimulus, the response keeps on decreasing. So, this is actually opposite to that of the Pavlovian response. Because there are mechanisms by which you down regulate the synapse.

Now what actually qualifies for habituation? What actually would qualify for learning? I leave it as a conjecture, I hope I do not get questions on this. But these are facts which exist.

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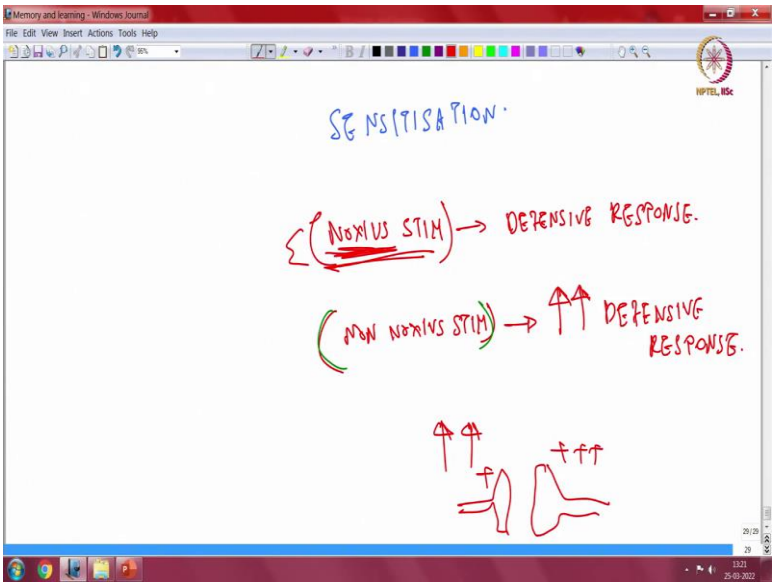

So, the opposite of habituation is sensitization. So, you give noxious stimuli, you have a defensive response. So, you summate that, and you keep on giving noxious stimuli, a non noxious STIM results in an increased defensive response. So, the key is the noxious part of the story because you give repeated. Say for example, it is tested in lower organisms that you keep giving electrical shocks and the organism shows some level of withdrawal response from the noxious stimuli.

So, subsequently if you are able to do a touch stimulation on the organism it still continues to have a defensive response. So, here the synapse gets increased. So, one I started with association which is Pavlovian association between a condition and an unconditioned stimulus producing a particular response. In habituation it is a non noxious stimuli the response keeps on coming down. In a noxious stimuli which is sensitization, it keeps on increasing.

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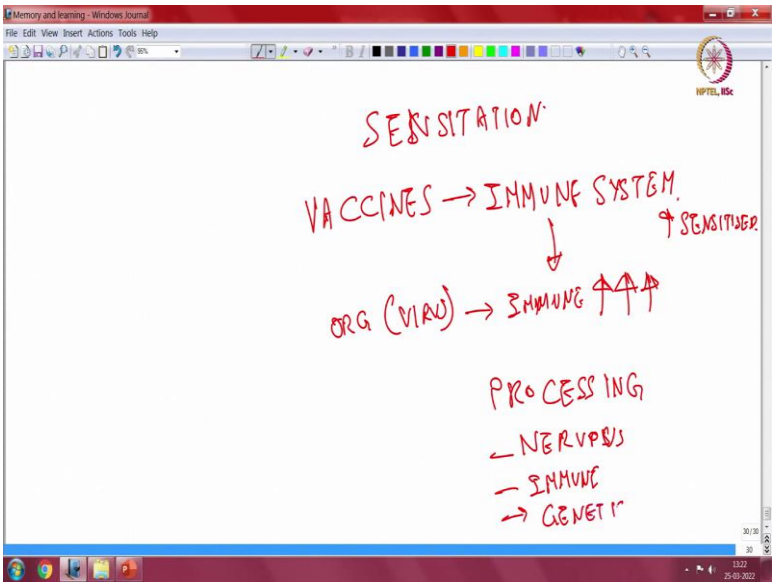

Now to explain a little or more than explain a little, to improve your own sensitization. All of us are now familiar with vaccines. So, the immune system has a similar response. So, you give vaccine, the immune system is sensitized when the organism, virus for example, immune system gives an exaggerated response and attacks.

So, it has its pluses and minuses, but what I wanted to say is sensitization is a concept, habituation as a concept is there within other kinds of processing systems. Remember in my introductory class that we spoke about how nervous system is not the only information processing entity within biological systems. You got immune system and you have genetic systems which are there, and which produce different kinds of processing mechanisms.

They incidentally have memory, they also do have learning to some extent, and this is an example where the immune system responds to something which everybody at present knows so that is why I use that particular example. So, sensitization in nervous system also can happen in similar fashions.

You can look beyond a signal you know you sensitization may happen within psychological levels. So, you have an unpleasant interaction and that gets spread on to other places. So, you know I think you get the drift.

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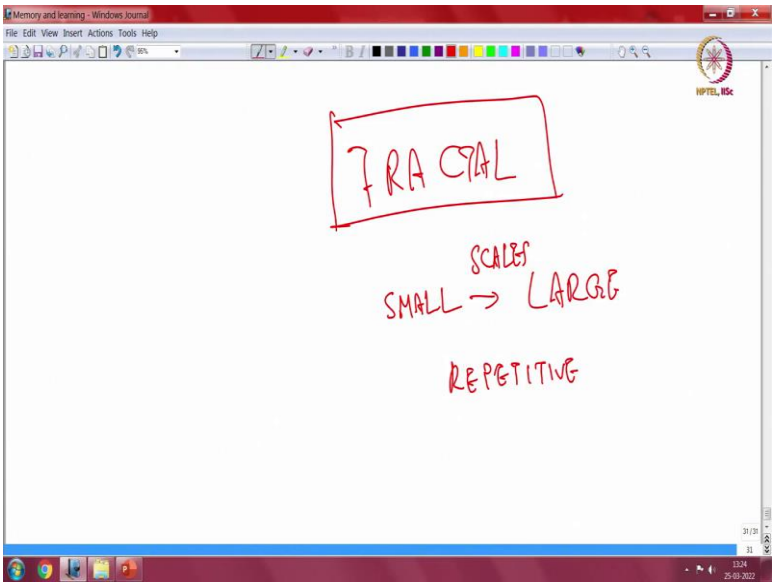

So, these are mechanisms which are there within a nervous system at very low levels in terms of a synapse or in terms of receptor. But they can scale up all the way to psychological and behavioural responses. So, there are repeating patterns, it is like a fractal set. So, dynamics is fractal. So, you have small to large scales which have very repetitive entities which are coded and sort of manifest.

And that all of these manifestations are what governs our behaviour, what governs our biological systems response and our interactions with the with the environment and with other people and organisms in general. So, I think with that discussion on the fractal part of learning memory and biological systems I conclude this part of the story and also conclude this part of this discussion on the neural system in general.

It has been a really interesting time for me, because I have tried to explore several independent concepts. Independent concepts in the sense that you would not find the same material exactly in a text book. So, that is the idea. So, I have taken liberties of mixing and matching stuff from across the book across stuff which I see as a neurosurgeon. And tried to put forth concepts in I hope engineering sense or as a nonmedical sense which should be beneficial to the larger audience. So, with this thank you and comments, suggestions are welcome.

Thank you.