Cognition and its Computation
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Lecture - 45
Examples of Disorders in Plasticity

Welcome to our lectures on learning and memory and neural basis for learning or how learning is happens in biological neural networks and the different forms of Plasticity and particularly the critical period of plasticity which occurs during development. So, that is a period of heightened plasticity so to speak as we have learnt which actually enables children to be far more receptive to learning extra languages unlike adults and so on.

There are many such learning methods and the ways people acquire different skills it is much better in children as the brain is much more plastic during this critical period which varies from system to system. And this period also makes the brain more vulnerable to many disorders particularly the different neuro developmental disorders similarly as with aging there are there is degradation or neuro degeneration in the brain and that can also lead to many disorders that are neuro degenerative in nature are associated with the process of aging.

And what we will see is that most of these mental health disorders and addiction disorders are associated with the synapse and synaptic plasticity. And this we are gradually coming to realize that the manifestation of almost I mean a huge number of diseases; neuro psychiatric diseases actually occurs at the level of the synapse and hence also in synaptic plasticity. And so, in this lecture we will briefly cover a few aspects of such disorders in synaptic plasticity.

Remember, that most of the mental health disorders or addiction disorders are manifested in a distributed manner or it has a distributed pathology. And these are true for most of the neuro developmental disorders or in fact, all of the neuro developmental disorders like autism spectrum disorder, intellectual disability, learning disabilities, some cognitive disabilities and so on and even schizophrenia.

So, these are these cannot be targeted in a particular location in the brain and is manifested throughout in many systems across the brain regions. And that causes a problem in terms of therapy and unlike stroke or trauma related disorders of the mental of the brain which is localized where we can have a targeted problem alleviation methods applicable.

In this case we have to target in different regions and especially with the synapse being involved in these diseases it becomes an attractive point of target where we can target all synapses of a particular kind that are involved in a disease or a particular element of the synapse that is dysfunctional for a particular disease and so on. So, it is not true that we know all the aspects or all the elements involved in most of these diseases.

However, it is more or less an overarching theme that is appearing in the latest studies that it is synaptic pathology or synaptic plasticity disorder and disorders at the level of even the synaptic structure that is playing a role in such disorders and so, there can be many therapeutic targets that can be developed. Related overarching theme that has appeared in neuro psychiatric disorders is excitatory inhibitory balance. And if you think about it what we mean is the amount of excitation and the amount of inhibition in an overall network has to be maintained at a at a particular ratio.

So, to speak or at a almost a balanced level throughout the long time intervals. So, it may be that there is a lot of excitation for a period of time, but it has to be balanced with an equal amount or an equivalent amount of inhibition, so that there is no extra or runaway excitation occurring in the system which can lead to toxicity and hence damage to cells or neurons.

So, this excitatory inhibitory balance is also related to synaptic function as you can imagine because it is the excitatory and inhibitory synapses that ultimately cause a neuron to be excited or inhibited. And ultimately cause a network to have excitation overall excitation and overall inhibition and hence its balance is critically controlled by synapses. So, it is the inhibitory synopsis and excitatory synapses. So, it becomes imperative for us, in this course to actually look into some of the aspects of disorders in synaptic plasticity.

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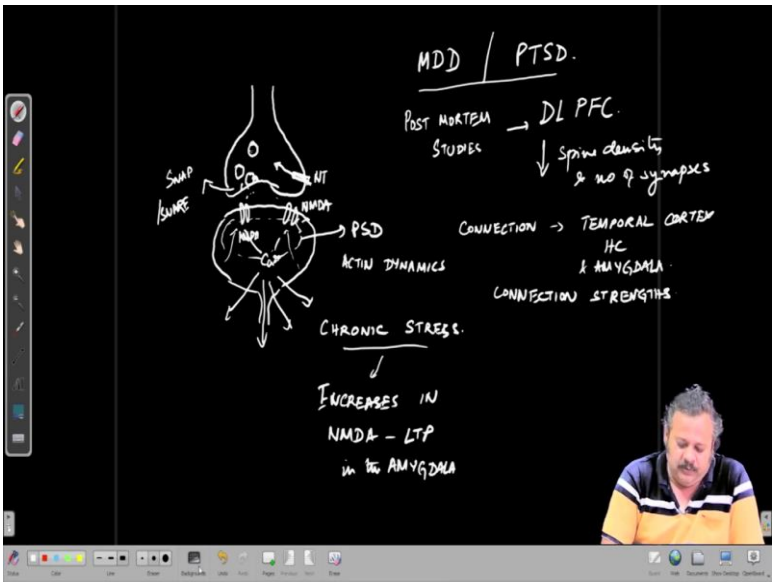

So, for example, if we take the take our stereotypical synapse as we have drawn multiple times in this course with the pre synaptic terminal represented in this manner. We have vesicles with the neurotransmitter in the pre synaptic side and there is SAR proteins or SNAP SAR proteins SNAPs complex that are involved in release of the neurotransmitter in the synaptic cleft.

Then on the postsynaptic side on the dendrite there are receptors that are AMPA receptors, NMDA receptors and there are their flow of calcium into the dendrite and then affecting many different secondary pathways that are involved in synaptic plasticity from the calcium that is generated from the NMDA. So, there are also other elements here like in the pre synaptic the SNAP SAR protein the re uptake mechanism of neurotransmitter in this synaptic cleft that is recycled into the pre synaptic terminal there are proteins in the post synaptic density or PSD.

The post synaptic density that is the hallmark of making it a post synapse and serves as a scaffold region for all the elements in the synapse and also has act in dynamics that is involved in shaping the synapse or increasing the size of the spine then there are scaffolding proteins that hold the NMDA and AMPA receptors to the surface and those that transport these receptors to that particular location.

So, all of these elements can potentially be dysfunctional unless it is compensated by some secondary mechanism that can lead to disorders of synaptic plasticity. And it is

also true that it is not just a single element that is often dysfunctional often even at this level at the level of the synapse just like many different regions are involved it is true that many different elements are also involved in a particular disease.

So, if we think of the overall manifestation if this formation of synapse is hampered or dysfunctional the entire network or the circuitry that forms will be or the function of the circuitry will be in geobody.

So, let us take a brief look at some of these diseases when we talk of synaptic plasticity disorders. So, if we think of the major depressive disorder; major depressive disorder and PTSD post-traumatic stress disorder both of these we get to know from post mortem studies from post mortem studies we know have decrease in the spine density and number of synapses in the dorsolateral prefrontal cortex.

So, in the DLPFC it is decrease in spine density and the number of synapses compared to age matched and sex matched control subjects in the post mortem brings which shows that this particular structure is involved in the medio dorsal in the major depressive disorders and PTSD.

Along with this what is involved is the connections between the DLPFC or connections with the other regions like the temporal cortex the hippocampus and the amygdala that are heavily reduced the connections connection strengths the functional connection strengths are reduced in these disorders.

So, this can be seen as a way that the diseases commonly manifest in terms of how the synapses are targeted in particular disease. So, similar to PTSD we also know the case of chronic stress which was studied both in vivo and x vivo and it showed that chronic stress leads to increases in NMDA mediated long term plasticity in the amygdala in the excitatory synopsis of the amygdala.

So, what we want to say is that with long term potentiation being increased it means that the synaptic strengths are increasing whereas. So, that is what happens in the amygdala in case of chronic stress whereas, on the other hand there is a reduction in the number of synapses and hence lesser activity that also is the cause of disease. So, it is not necessary that it has to be an increase in excitation as opposed to inhibition or rather a reduction in

the number of synapses can also play a role in terms of dysfunction. So, both have to be balanced in order for the system to function normally.

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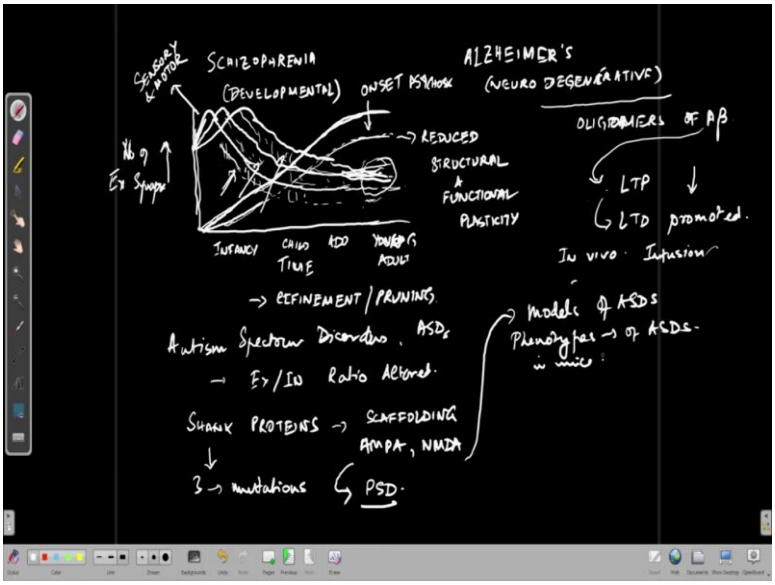

Going forward along these direction we if we consider diseases like the schizophrenia and well known neuro degenerative disease which is Alzheimer's and a large number of sub humans are affected by this disease. And so while schizophrenia is a developmental disorder this is neuro de generative disorder. In both cases we will find that it is the element of the synapse particular elements of the synapse especially NMDA and AMPA receptor related pathology that comes into play and in terms of LTP and LTD we again see similar kind of dysfunction at the synaptic level.

So, in general in the way schizophrenia has been hypothesized to work is that it is a neuro developmental disorder in the sense that if it is the this axis time showing infancy, childhood, adolescents and young adult. It is known that the onset of psychosis in schizophrenia is around the young adult stage and for a long and actually the manifestation of the disease starts long before, but it is very difficult to associate those symptoms or those phenotypes to schizophrenia very easily.

But there are sensory and motor cues and also integration related dysfunctional queues and other cues that are present early on that can warn us about schizophrenia. So, the model that has been hypothesized is that so, as we know the sensory circuits are

developing do develop the earliest and if this axis is the number of excitatory synapses in the system.

Then we know that throughout the development of initially with very high number of synapses gradually with time there is a decrease in the number of synapses until into adulthood where it is stabilized in terms of the number of excitatory synapses. And this we have talked about in the developmental plasticity in terms of structural plasticity so, along edge there is refinement and pruning of synapses.

So, in this is for sensory and motor circuits sensory and motor similarly if we think of the multi sensory or elements in the parietal circuits that has to do with integration of the different aspects different sensory and motor aspects those synapses are also refined and prune throughout age. But actually happens slightly later and similarly if we think of the executive circuits which they have matured the latest they turn out to develop more around adolescent and reach their final levels.

So, throughout this region the amount of synaptic refinement goes on almost at a similar rate until it saturates after young adulthood and this refinement or pruning or the structural plasticity.

So, this is onset of psychosis as we mentioned this refinement if it is hampered this kind of reduces the refinement and pruning to dysfunctional level. And what this actually means that with this reduced structural plasticity reduced structural and functional plasticity that is refinement and pruning in schizophrenia which actually leads to reduced refinement or of the motor circuits.

And so, there are elements of change manifesting early on in development in the motor and sensory circuits that also leads to reduced synapses in the parietal regions and also reduced synapses in the cognitive and limbic regions that are in the PFC and so on. So, there are manifestations of different aspects of the disease early on in the motor circuits, in the parietal circuits, motor and sensory circuits, in the parietal circuits for integration and in certain cognitive circuits, but the overall psychosis manifests.

Finally, in young adulthood where there is a complete dis balance of what the different levels of synaptic activity should be present compared to the normal. So, this hypothesis this kind of hypothesis is supported by a lot of evidence in terms of the expression of

synaptic proteins that have been studied and also from post mortem anatomical studies of patients in with schizophrenia and so on.

So, similarly in Alzheimer's disease what we know what the biggest problem that is manifested early on of course, towards the end of the Alzheimer's disease progression it is not that important anymore because there is lot of cell death and nothing can really be done. But the early manifestation start with the oligomers of protein called A beta and there is involvement of another protein tau both of which are associated with synaptic plasticity.

What happens is with A beta in the hippocampus LTP is drastically reduced and it promotes LTD, LTD is promoted instead of LTP. This has been studied by in vivo with infusion models where these oligomers of A beta is infused into the hippocampal region and then the disease the learning and memory test have been done which show that the animal is manifesting dysfunction in learning and memory.

And at the circuit level when we look at the synapses and circuits in x vivo studies with slices what is found is that there is an increased LTP and or rather sorry decreased LTP compared to what is observed normally and a huge increase in long term depression.

So, what we see is that the same activity that was supposed to cause long term potentiation is unable to cause that long term potentiation and hence the synapses are not strengthening that are required in the process of memory formation and so on. Instead with LTD being promoted the activity that did not produce LTD or only produced LTD to a very small extent is actually increasing the amount of LTD happening has an increased amount of LTD corresponding to those stimuli. And; that means, the synapses are getting weakened when they should not be.

And with the weakening of the synapses what eventually happens is the synapse without any activity finally, dies because it is of no use. And that is the ultimate level where this progression of disease takes the synapses to basically the death of the synapses happen. So, along with this if you see that if LTP is reduced and LTD is promoted in the hippocampus you can also easily infer that there is going to be a dis balance of the amount of excitation and the amount of inhibition that was present originally in the hippocampus circuitry.

Because the things that were exciting are not exciting as much and the things that were depressing only to a little amount is now depressing activity to a great degree and so overall the excitation and inhibition is going to levels is going to change and cannot be maintained. Another common neuro developmental disorder that has been studied or has been is been studied extensively because huge number of subjects are suffering from it which is autism spectrum disorders or ASDs.

In this case, as we said very common theme that has emerged across multiple models and even in humans is the excitatory inhibitory ratio being altered. So, this has been seen in multiple forms of the autism spectrum disorder and multiple locations in the spectrum of the disorders and the overarching theme appears to be this excitatory inhibitory ratio alteration which again relies on synaptic plasticity and how the synapses behave. Common model of autism spectrum disorder that has come about is through the shank proteins.

So, these proteins are involved in scaffolding the AMPA and NMDA AMPA and NMDA receptors post synaptically they are they help these proteins mediate the AMPA and NMDA receptors to be stably present and connect with the post synaptic density proteins. And the shank there are three types of shank proteins and these mutations of these proteins all lead to problems in synaptic plasticity.

And in fact, serve as models of ASDs when we have this shank mutations in mice we actually see phenotypes in mice that mimic what is present in ASD patients in mice.

So, there are many such proteins that have been identified and commonly seen in synapses that are associated with these disorders like autism spectrum disorders and schizophrenia and so on. Finally, with we will end with this note is that it is seen that there are transient structures that are present developmentally in the cortical regions that help the formation of circuitry.

And most of the genes and related proteins that are associated with neuro developmental disorders like schizophrenia and autism spectrum disorders they are enriched number of them are enriched in these transient circuits that are involved in cortical development. And so, we can see that if there is a problem in the genetic program for development many of these pathways can get affected which finally, can lead to many different parts

of the spectra many different consequences which can lead to different aspects of autism spectrum disorders or schizophrenia.

The synaptic proteins become important targets for therapy and so, need to be studied further. So, what we have done here is given you only a brief picture of the elements that are involved in disorders of synaptic plasticity and some only some of the synaptic disorders that are associated with synaptic plasticity. With this we end our week on the lectures of learning in biological networks and structural plasticity and Disorders of Plasticity we take up next lectures on speech and language.

Thank you.