Neuroscience of Human Movement
Department of Multidisciplinary
Indian Institute of Technology, Madras

Lecture-71
Basal Ganglia Dopamine & Acetylcholine

Welcome to this class on Neuroscience of Human Movement. In this class, we will be talking about basal ganglia. We will continue our discussion on basal ganglia, specifically on the topic of dopamine and acetylcholine and their role in basal ganglia function.

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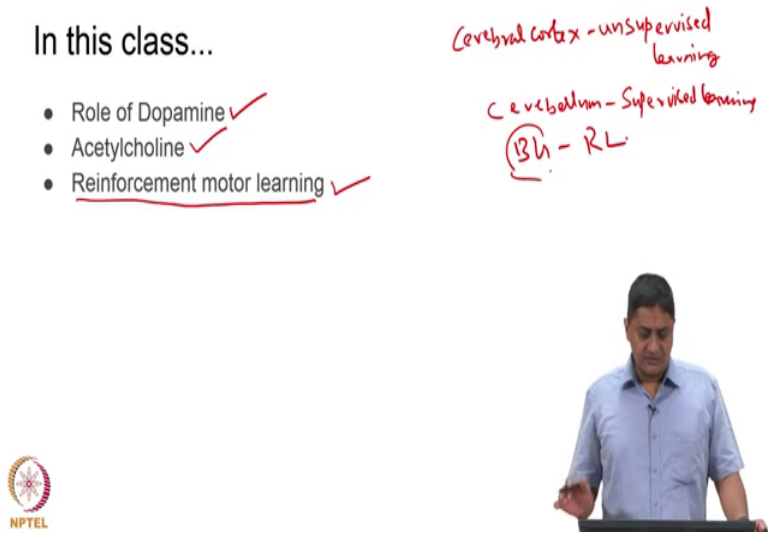

So, in this class we will be talking about the role of dopamine and the role of acetylcholine specifically cholinergic inter neurons of the striatum, right and how these two neuro modulators contribute to reward related movement learning or essentially reinforcement motor learning.

So, essentially learning or specifically motor learning seems to happen in multiple regions of the break these include the cerebral cortex or the motor cortex. So, it essentially performs some sort of unsupervised learning what the computer scientists would call as unsupervised learning, cerebellum of course performs what the computer scientist would call as supervised learning and basal ganglia responsible for reinforcement learning.

This is a theory, this is these are interesting hypothesis developed regarding different forms of learning being specialized in different regions of the brain. So, there is substantial evidence to support this notion, but this is not completely true either. So, much of this is speculative, but still a lot of evidence to support this notion, right. So, that means basal ganglia responsible for reinforcement motor learning what is that do. So, that is what we will see in today's class.

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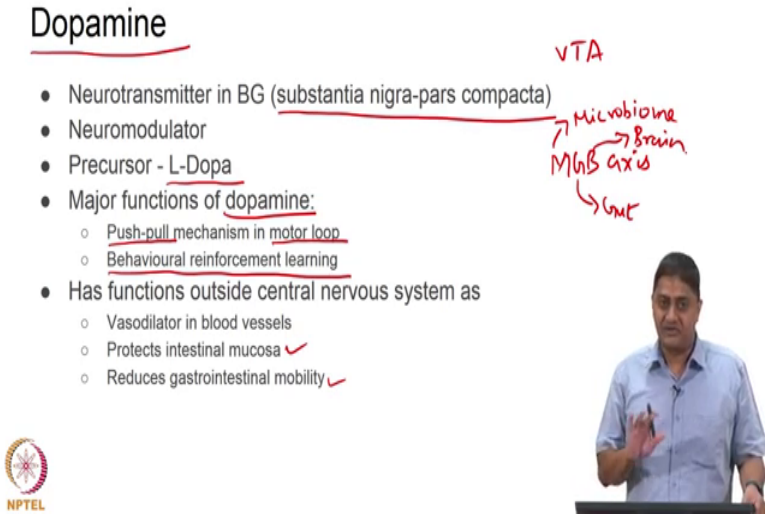

So, dopamine is a major neurotransmitter or neuromodulator in the basal ganglia. Specifically it is produced by neurons from the substantia nigra-pars compacta, but it is also produced by other regions, right. So, tegmental area, the ventral tegmental area, so it is a modulator in the sense that it modulates the inputs coming in from the cortex or in other words, influences affects or access a gain function it turns out that its precaution is a chemical called L-Dopa. Removal of a carboxyl group from L-Dopa results in the amine that is called as dopamine.

So, dopamine is considered as a brain cell pressure chemical. It is very important chemical which controls a whole bunch of functions, affects the whole bunch of functions, not just movements. Of course, here we will be focusing on movement related function, but let us remember that dopamine function is not restricted to movement alone. It actually controls a whole range of behavior including and predominantly including movements.

Importantly dopamine acts as the push-pull mechanism in the motor loop and acts as the signal for behavioral reinforcement learning. What does it also note dopamine is produced not only in the brain, but also is produced elsewhere outside the central nervous system, right. So, essentially a lot of dopamine is found in the digestive tract. So, it protects intestinal mucosa, reduces gastrointestinal mobility and also acts as vasodilator in blood vessels or whole bunch of functions.

So, a lot of dopamine is found in the gut or in the digestive tract also, but then the immediate question would be well if there are diseases that happen due to dopamine disfunction in the brain, maybe we can relocate the digestive tract to dopamine to the brain that could be easy solution. Unfortunately dopamine is a relatively large molecule that cannot cross the blood brain barrier. Hence, the dopamine in the gut cannot be used to influence brain function although there is a very deep interplay between gut activity and neural activity and mood and reward related behavior.

This is of course well known and well studied. This is a heart area of research called as the MGB axis, right. What is this? This is the microbiome or the gut microbiota. The good bacteria or whatever kind of bacteria that is found in the gut, right essentially billions of bacteria are found in the gut, right. So, how they affect our behavior, how they affect our movement, how they affect our general life, right so, that is one. The second one is of course gut, G means gut and this is of course a brain.

So, there is deep interplay and relationship between these three. These things continue to be studied and they are heart area of research. So, you see about 2 to 3 papers every week getting published on this topic and one paper in one of the luxury or the fancy journal, such as nature science etcetera PNAS etcetera, right. So, what is known is a dopamine in the in the stomach cannot be easily transported to the brain. That is known, ok. We will discuss this in much greater detail in future classes or in future slides.

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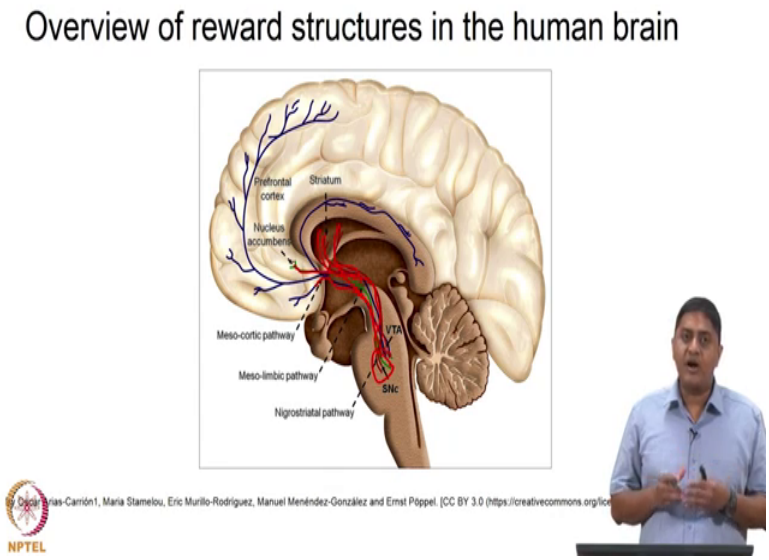

So, let us remember, so what happens. So, this is the ventral tegmental area in the mid-brain and this is a substantia nigra-pars compacta, you know. Let us remember the basal ganglia includes telencephlic, diencephlic and mesencephlic nuclei, right. So, essentially many parts from different areas of the brain constitutes the basal ganglia together, right. So, here are the dopaminergic neurons that project to these striatum right, but from the ventral tegmental area, projections are going to multiple regions, especially the nucleus accumbens, right.

So, what is the importance of this, we will see in one of the future slides, right. So, these regions, the ventral tegmental area and the substantia nigra-pars compacta contains important dopaminergic neurons, right. What is their function, we will have to see.

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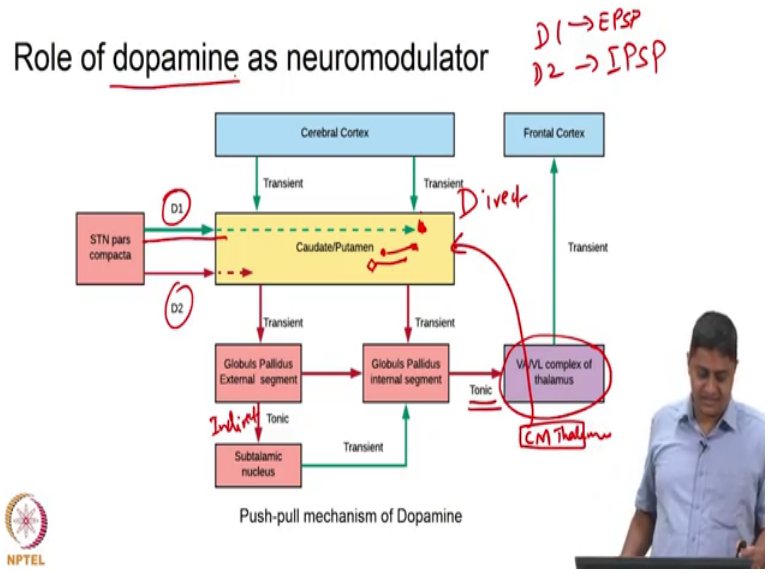

Important role of dopamine as a neuro modulator let us remember one thing. This picture or this diagram represents a cartoon of the basal ganglia function. Here is the direct pathway. So, from the striatum, so this is cortec, this is a corticostriatal pathway. That is a corticostriatal pathway, that is the pathway straight from the striatum to the GPI which is the output nucleus and from the output nucleus to the thalamus and from the thalamus to the cortex. So, that is the direct pathway, right because it does not involve the subtalamic nucleus right.

So, this is the direct pathway, right and this is the pathway that involves the subtalamic nucleus is of course the indirect pathway. So, essentially what happens is that the dopaminergic neurons from the substantia nigra-pars compacta activate or excide the direct pathway.

Suppose there is dopamine secreted from the substantia nigra-pars compacta, what does it do to a given input from the cortico striatal neutron, right. So, there is input coming in from the corticostriatal neuron here, right. So, that is happening in the striatum say in the putamen, right. So, medium spiny neurons in the putamen receiving inputs from some region in the cortex, right. Let us say at that time dopamine is secreted, right. So, then what happens if this particular medium spiny neuron is in the direct pathway, it excites that medium spiny neurons. So, essentially what happens is that it increases the probability that this medium spiny neuron is going to respond to the cortical input.

Note, medium spiny neurons are gabaergic and they essentially converge onto smaller regions of the pallidum. This is what we saw in the previous classes. So, essentially what happens in the pallidum, there is a smaller region that hosts the medium spiny neurons outputs is it not. So, then what happens, that means those pallidum neurons are going to be inhibited, but note this is GPI in the direct pathway is it not. When it is a pallidum, I am referring to the globus pallidus internal segment which is the output nucleus of the basal ganglia.

So, directly the output nuclei of the basal ganglia are inhibited, but since the output nuclei are always providing tonic inhibition to the thalamocortical neurons, there is a transient release of excitation, right. So, whenever dopamine is secreted, it is going to increase excitability of the medium spiny neurons in the direct pathway, right. In the indirect pathway though it is going to decrease, not increase, it is going to reduce the excitability of the medium spiny neurons in the indirect pathway.

But since essentially indirect pathway is in inhibitory pathway, you are going to have a net excitation where not at the medium spiny neuron, but at the thalamocortical neuron. So, essentially whenever dopamine is secreted regardless of whether dopamine is received by the direct pathway or by the indirect pathway, it always has net excitatory influence on the thalamocortical neurons. This is what we have been saying for the past few classes. I am repeating just so you remember. So, you realize that this is indeed a very important principle that. So, why how is this happening we saw D1 and D2 receptors have opposite functions that D1 receptor excides the medium spiny neurons whereas, the D2 receptor inhibits the medium spiny neuron.

In other words, the D1 receptor causes EPSP whereas the D2 receptor causes an IPSP or the inhibitory post synaptic potential. So, this is how dopamine influences the cortical input that is getting received. So, let us remember that these are not the only inputs. What is also happening is from the centre median nucleus of the thalamus not from the VA VL nucleus, but from the CM nucleus of the thalamus, the striatum is receiving inputs and they are called energic inter neurons, right.

So, there are inter neurons within the striatum that also affect striatum function. So, there is a whole bunch of interplane that is going on. So, again this is a cartoon that represents one particular feature, but here we are only interested in discussing dopamine. So, this is

the role of the dopamine. Dopamine essentially has a net excitatory influence not on its target, dopamine has a net excitatory influence on the thalamocortical neurons or the major output of the basal ganglia.

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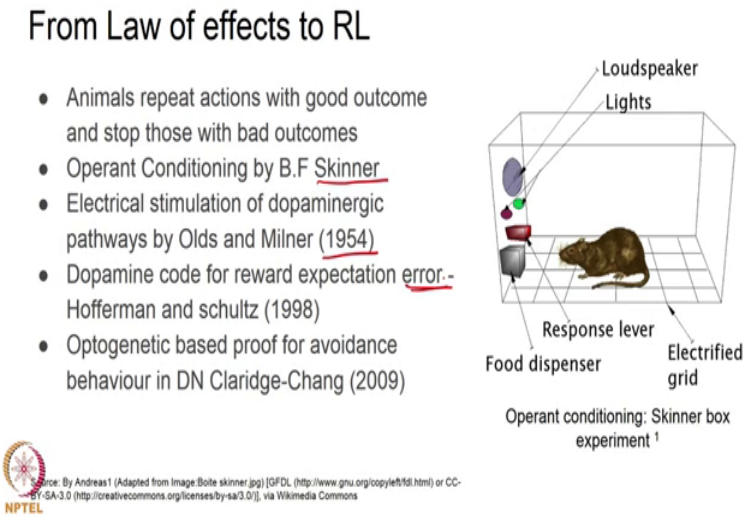

Then, what happens right what is the other function of dopamine that is the question. So, essentially something that we have known for long time for example, close to a century is that animals in general repeat actions that are beneficial to them, right. Whatever they think is beneficial to them is going to get repeated and those that are not beneficial are punitive, those that cause pain or cause some sort of you know discomfort are avoided by the animals. These has these have been studied quite well by you know the people who have proposed these kind of theory such as you know Skinner's theory and Osther, such theories right.

What people have also done is they have electrically stimulate the dopaminergic pathways in animals, right and they have found that you know it excides the animals in a very big way and the responses are completely new and unexpected and the at that time some of this is 1954. And what has also been learnt crucially very importantly is at the dopaminergic neurons do not actually code the reward itself, but rather at different function, at different quantity, it is important to note the other thing that has also been.

So, what is also known is that the dopaminergic neurons code not the reward itself, but rather a different quantity called as the error from the reward expectation. So, this is

work from Doctor Schultz and his group, right and more recently there is evidence to suggest that optogenetic modification of these neurons will change avoidance relative behavior etcetera, right. So, essentially what are these things? So, at least we will need to study what is this error related function, right.

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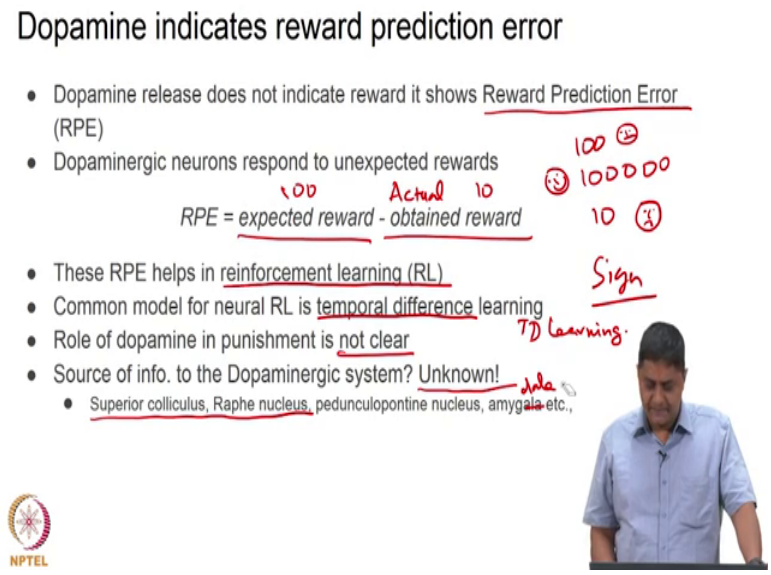

Importantly dopamine release does not indicate the amount of reward. It actually indicates what is called as a reward prediction error. What is this reward prediction error?

It is the difference between the expected reward and the actual obtained reward or the actual reward. So, let us look at this and understand what this means, right. Let us say that you know someone has promised to give me say 100 rupees if I finish teaching this class. So, I finished teaching this class. At the end of the class, the cameraman or the NPTEL team is going to give me 100 rupees. This is what have been told. So, I am expecting 100 rupees and let us say what happens actually.

So, this is my expectation. My expectation is I finish this dopamine class and then, I go. When I go out, they are going to give me 100 rupees say for example, this is my expectation. Then, I finish this class and go and they give there are multiple possibilities. They could give 100 as they said, they will give let us say they could give 10,000 100 times as much or they could give 10. Let us consider these 3 possibilities, right.

So, I am expecting 100 and I get 100. So, essentially the expected reward is 100 and the actual reward is also 100. So, the reward prediction error is 0. So, that means I am expecting that I am not going to be super happy when I get it. This is what they said they will give and I got what they said they will give, ok. So, I am not going to be unhappy, but at least I am not going to be very happy jumping and enjoy or something of that sort, right. So, this is the situation when the difference between the expected reward and actual reward is close to 0 you are not particularly unhappy, but you are also not particularly happy.

But suppose they have told me that they going to give 100 rupees when I go. They are giving me say 10,000 or 1 lakh rupees say for example. Immediately anybody can guess what will happen, right. So, here I have 100, but what I am getting is 100,000. The actual reward is way higher than the expected reward. I am going to be of course super happy. I am going to be jumping enjoy. Of course, I am going to be jumping enjoy this is. So, here with this I am going to be you know happy, right. With this I am going to be neither happy nor sad, but then there is another case also in life these things happen more often. Is it not?

So, I am expecting 100 rupees. They are not giving me anything or they are giving only 10 rupees. Well anybody can guess what would then happen, right. So, what will happen essentially that is it not I am sad I am unhappy about that. Why is that because then what happens is that the expected reward is 100, but the actual reward is 10. The error is big, the error is big. Is it not? So, note the direction of this error matters or in other words the sign s i g n of this number matters whether it is positive or negative, this matters as you will soon see.

So, this helps in conditioning the outputs of the system and hence, is start hypothesis to help in reinforcement learning. How exactly this does that continues to be a mystery, but this is the dominant hypothesis in this field, right. One common model for studying reinforcement learning in neural systems is what is also called as temporal different learning or popularly called in reinforcement learning literature as TD learning. Importantly the exact role of dopamine in punishment is not clear, whether dopamine affects it in a negative way or how exactly it works is unclear for us.

By the way how does the dopaminergic system even known, what the expected reward is, actually once again that continues to be a mystery. That is not exactly known. There are speculations that the source of this information about what is the value of this, what is the value of the reward, right the source of that information is probably from multiple region such as raphe nucleus, pedunculopontine nucleus, amygdala. This is a amygdala of course amygdala superior colliculus etcetera, right. So, essentially the dopaminergic system response to unexpected rewards, right.

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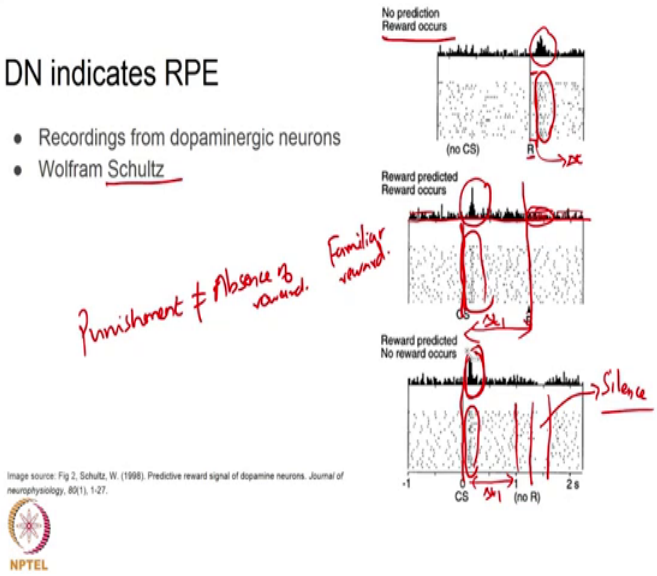

Here is the beautiful classic experiments from the group of Doctor Schultz, right. These are recordings from dopaminergic neurons and each dot here represents whether the neuron was active or not. So, each dot here represents one dopaminergic neurons action potential or activity, right. x axis here is time, the y axis represents the number of you know neurons that are activate at given point in time and this is another way, this is the bars above that line right represents the cumulative number, the total number of neurons that were active essentially, right.

So, you are not expecting anything say for example, you are not expecting a reward. So, this animal is not expecting any reward, but reward happens. This is bonanza, this is bonus. You are expecting nothing. Suppose you are expecting say you know a fail grade in a course and you are getting a top grade, then what happens is you are super happy. Why? There is a great difference between your expectation and actual reward. I am not

expecting a reward, but then reward happens that causes this kind of a spike after the occurrence of a reward, right. Here is when the reward is happening soon, it is a very small latency relatively short latency. So, that is the latency that is the delta t, right.

With that delta t, the activity happens. Note the number of neurons that are active here very large number of neurons that are active, immediately or soon after the presentation of the reward, right that is also reflected in the amplitude of this which is the cumulative part. Is it not? So, that is reflected in this. Now, soon the animal learns that you know if this stimulus is presented, soon a reward is going to be presented. Then, what happens this is the situation of a familiar reward. This is like saying I am expecting 100 rupees, I am getting 100 rupees a familiar reward, right.

The conditional stimulus is presented very important to note where the activities happening, the stimulus is presented here. The reward is happening here. The activity of the dopaminergic system does not follow the reward in the case of familiar reward, but rather the conditional stimulus, the maximum activity happens not after the reward, but just after the presentation of the conditional stimulus. Here I am expecting a reward soon after the stimulus for the reward comes, then there is going to be activity, but when the reward comes, there is not that much activity, just base line activity here.

So, note the reward is happening there is it not note the activity. Note the amplitudes here that amplitude is practically like the baseline amplitude. Is it not? There is much difference from the baseline activity. So, that means this is a familiar reward. Yeah whatever they are giving 100 rupees, that is alright. I am only I am getting excited when the stimulus is given. That is here, not when the actual reward is given. This is very important note. Then what happens is punishment or the absence of a reward, note these two things are not the same.

Punishment is actually not the same as absence of reward. These two things are different, ok. I am expecting a reward and the stimulus that signals the presence of a reward is presented at that time and note activity happens following stimulus as one would expect just like the previous case activity happens following the stimulus like here, but then after the same time delay say delta t 1 after the same time delay, no reward is happening. When no reward is happening, what you are observing here is essentially not baseline activity. This is silence, total silence.

So, I am expecting a reward, I am expecting to get 100 rupees. They are giving me 0 rupees, then my response is total silence, right. So, but note that happens just after the expected time for the reward, but the conditions stimulus activities still remains. By the way if this is repeated multiple times, then this will also disappear. If this I mean if you keep saying that you are going to get reward and you did not give that reward, then what will happen the I will learn and this will become baseline activity, this will practically disappear if this is repeated if this kind of behavior is reinforced.

Essentially it seems to essentially what seems to happen is coding of the difference between the actual reward and expected reward which is why it is important at least from one point of view they keep the expectations relatively low. If you keep the expectation like in eastern philosophy, like in eastern philosophy keep the expectations relatively low like in Buddhist philosophy, the desires are to be kept relatively low.

I am not getting into religion here, but if you keep the expectation relatively low, whatever you get you are going to get some amount of dopamine activity, some amount of dopamine that is going to keep you happy. At least it works, at least the eastern philosophy and the science agree in some abstract sense here, right. So, essentially if the reward is predicted and no reward occurs, there is silence, right. This is not baseline. Note here this is flat line, not baseline, right. Baseline activity is that much here you have only flat line. So, that is what happens when you are punished or when the expected reward is not presented, right.

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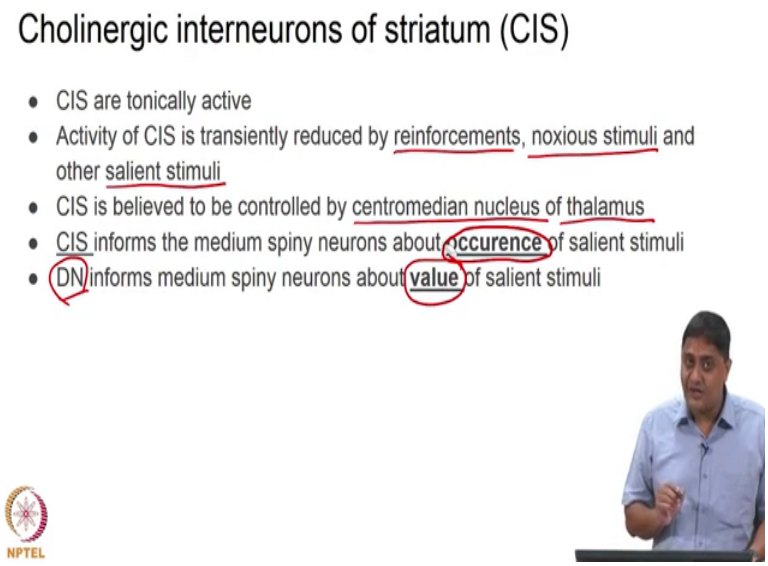

What happens with the cholinergic interneurons? Cholinergic interneurons how the striatum are tonically active, they are actually involved in multiple networks. So, they are well connected. So, to speak and their activity is transiently reduced by reinforcements and noxious stimuli and other such as salient stimuli, right. And it is believed that the activity of the cholinergic interneurons are the striatum are controlled by the centromedian nucleus of the thalamus. Not very clear how, why, what is the purpose or how exactly this happens, it continues to be studied, importantly the cholinergic interneurons of the striatum informs, about the occurrence of the salient stimuli.

Whether the salient stimulus happened or not and when it happened, this is informed by the cholinergic interneurons of the striatum. What is the value of the stimulus that happened is informed not by the cholinergic interneurons of the striatum, but rather by the dopaminergic neurons. So, the dopaminergic neurons encode the value and the cholinergic interneurons of the striatum encode the occurrence of the stimuli.

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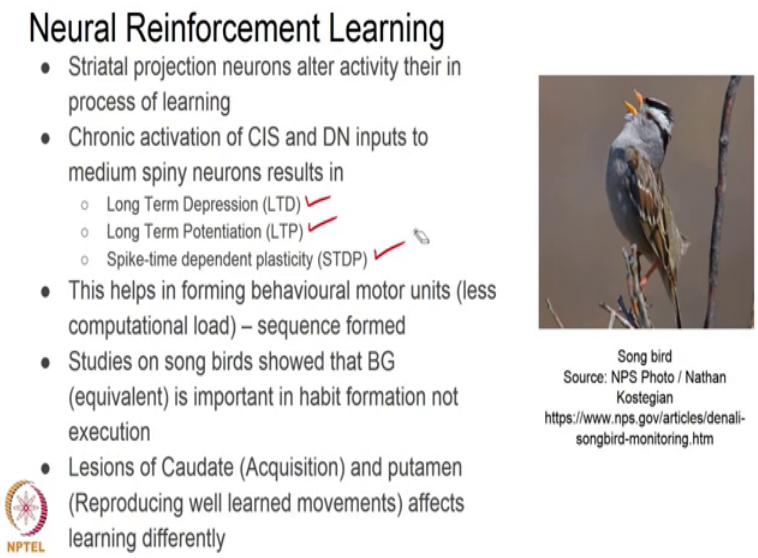

What about learning in animals? It turns out that neurons that project to the striatum and neurons in the striatum alter their activity depending on the stage of learning, right. There is chronic activation of the cholinergic interneurons of the striatum and the dopaminergic neurons from the substantia nigra-pars compacta and this interplay between the cholinergic neurons in the dopaminergic neurons. Note, these two have different functions, right. This interplay between the cholinergic interneurons of the striatum and the dopaminergic neurons results in multiple things, multiple phenomena either long term depression, long term potentiation or what is called as STDP or Spike Time Dependent Plasticity, right.

So, this helps in forming you know sequences like grouping activities together. For example, every day after brushing I drink water say for example, every day after I wake up, I brush my teeth and then, I drink water. Now, brushing the teeth and drinking water are of course performed in two different locations using two different effectors, but somehow these two are grouped to me together. Actually this is a more complex task. For example, even in simpler task also several things that happen in a sequence say task A must happen before task B for example, right.

Now, in this case these two are grouped together or in some sense, they are part of a given sub program. So, some sort of grouping of this control happens, maybe this is a more efficient approach because it results in less computational load. So, essentially this

isn't a computer program or a motor program more behavioral groups of an activity, right some sort of that also what about animals for example in a song birds, right.

It has been shown for example in song birds that the equivalent of the basal ganglia is crucial for learning of the species specific sounds. So, if that is the song that this species practices during the crucial learning period. If the basal ganglia is listened, then what happens is that this after the crucial learning period is the over, the song bird is no longer able to learn this. In other words, transient or in other words transiently listening the song bird BG equivalent area essentially prevents this bird from learning the song that it is supposed to learn.

So, that means at a crucial period that this animal can only learn only during, so that means this animal can learn only during that crucial period and if during that crucial period BG is disabled, then what happens is that these studies song birds for example have shown that the basal ganglia is crucial in forming the habit or in other words, in learning the task. So, transiently if the basal ganglia equivalent structure is disabled for a brief period of time during which the bird is able to learn maximum amount right, so the crucial learning period during that period if disable the basal ganglia equivalent circuit what happens is that this bird is no longer able to learn, after that even releasing this temporary lesioning, right.

Even after releasing that, then also this bird is not able to learn, right, but suppose the bird has already learnt that, learnt the songs during its crucial learning period is crucial learning period is over, then knocking out these structures does not affect performance. So, that means it seems like the basal ganglia is crucial in acquiring motor skills in forming a habit, but not necessarily in executing that habit. So, for me to learn something new, the basal ganglia or its equivalent structure is crucial, but for me to execute that function it is not as crucial. At least in the case of the song birds right and in other animals, it has been shown for example the lesions of the caudate and putamen have differential effects on movement relative function. Essentially what happens is the lesions of the caudate actually affects acquisition of motor skills whereas, lesions of the putamen affect reproducing already well acquired motor skills.

So, if caudate nucleus is for example compromised, then what happens is that the person is no longer able to learn new things or the animal is no longer able to learn new things.

If the putamen is compromised, then what happens is that whatever was previously learnt, the animal is not able to execute, ok. So, there is differential function between the caudate and putamen, right. So, that is how learning and reproducing learn movement is affected, right.

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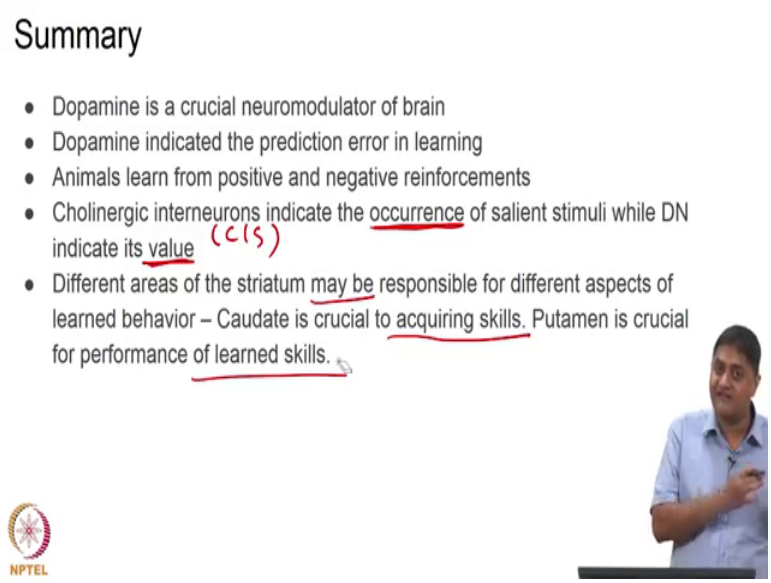

So, in summary dopamine is a crucial neuro chemical, crucial neuromodulator in the brain, right and dopamine actually encodes the prediction error in learning and animals learn both from positive and negative information reinforcements. And the cholinergic interneurons of the striatum indicate occurrence of the salient stimuli whereas, the dopaminergic neurons encode the value fundamentally different functions and different areas of the striatum may be responsible for different aspects again speculation, right.

Different areas of the striatum may be responsible for different aspects of learned behavior or learning caudate is believed to be crucial for acquiring skills. Putamen is believed to be crucial for performance of already acquired, already well learned. So, with this we come to the end of this lecture.

Thank you very much.