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

Lecture - 65
Basal ganglia – Pathways

Welcome to this class on Neuroscience of Human Movement. In this class will be talking about pathways within the Basal Ganglia.

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So, essentially there are three pathways in the basal ganglia. So, in this class we will be seeing direct pathway, the indirect pathway and the hyper direct pathway. Before we discuss the details of this I think it is important to realise that these present some model of basal ganglia, this is not a complete description of basal ganglia.

So, a lot of function of basal ganglia can be explained with the help of these pathways or the direct indirect pathway; however, there are exceptions to this rule. So, one has to be careful while discussing or interpreting data from actual experimentation or from actual disease conditions alright. However, in spite of the limitations, the direct and indirect pathway and the models associated with these continue to be relatively dominant.

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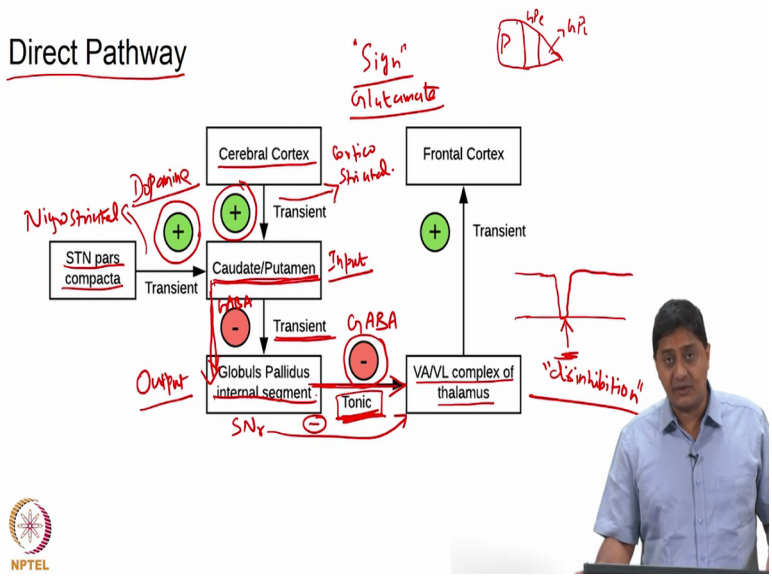

Let us remember that the straight is the major input structure of the Basal Ganglia and the substantia nigra pars reticulata and the globus pallidus internal are the major output structures. Here we have taken only the GPi as the output structure and here striatum is call together separately as caudate and putamen. Important to realise is the fact that the thalamo or cortical neurones in the thalamus are excited and they excite the cortex these thaloamo cortical neurons themselves are inhibited by the output from the GPi, by the output from the GPi from here there is very strong and tonic inhibition.

That means there is going to be a constant inhibition of the thalamo cortical neurons from the globus pallidus internal or you can say that substantia nigra, Pars reticulate. For other neurons substantia nigra pars reticulata also sends tonic inhibition to the thalamus or maybe to other output structures. So, basical essentially this defines an important function and an important aspect of basal ganglia function that is the globus pallidus internal and the substantia nigra pars reticulata contain neurons that are tonically inhibiting the thalamo cortical or the output neurones.

So, because of this reason so, there tonically means what? Tonically means constant inhibition. So, it is always present except when that neuron itself is inhibitor. So, there are these neurones. So, these are GABAergic these neurones in globus pallidus internal are GABAergic. globus pallidus internal from there this GABAergic neurons project to the thalamus and constantly inhibit. We could start explaining this by starting with

Cortex are substantia nigra Pars compacta. But I think it is better to start from this point because once we catch this aspect everything else becomes clear.

So, important to notice that the GPi neurons are constantly inhibiting or tonically inhibiting the thalamo cortical neurons now, it turns out from the striatum there are so, striatum means. So, when we discuss a striatum we discuss that is say that is putamen that is GPe and that is GPi that is remember the GPe forms part of the intrinsic circuitry GPi is the output structure whereas, putamen is the input structure of the basal ganglia.

The direct pathway involves projections from the striatum directly to the GP i. So, here you have direct projections from the caudate and putamen to the GPi this means what? This is the input structure this is the major input structure and this is the major output structure and the connection from the input to the output structure is GABAergic mediated by the output of the medium fine neurons and uses GABA as the neurotransmitter. But let us remember that already GPi is tonically inhibiting the thalamocortical neurons. So, if these neurones in the GPi themselves are transiently inhibited by the input from the striatum, then what happens for a brief period of time the inhibition provided by the GPi neurons is halted. So, let us consider that that is the inhibition level.

That is the level of inhibition that is provided by the GPi neurons. Let us suppose at the particular point in time at that point the striatum sense input directly to GPi and inhibits the GPi activity, then what happens is it at that point the inhibition for the thalamocortical neurons comes down and then it continues again. So, during this brief period the thalamocortical neurons are the excitation levels of the thalamocortical neurons increases or the probability that they will get excited is higher because they are not getting tonically inhibited.

So, essentially what you are having is, an inhibition that is tonic and that in that tonic inhibition itself is transiently inhibited essentially this is the activity this is the most important function of the Basal Ganglia, that is disinhibition. Inhibition is provided by the globus pallidus pallidus internal segments and that inhibition by itself is inhibited by the input, direct input coming from caudate and putamen from the striatum.

Now, that essentially disinhibits transiently why because striatal inputs to the globus pallidus internal is transient whereas globus pallidus pallidus input to the

thalamocortical neurons is tonic right. So, this inhibition is tonic, very important to remember the inhibition from GPi is tonic. So, whenever striatum sense in input for a brief amount of time the thalamocortical neurons are disinhibited because the in input the connection to the globus pallidus pallidus internal comes directly from the striatum.

Because of this reason this is called as the direct pathway is there any other way in which it can happen? The answer is yes there is another way in which it can happen will also discuss that so, but what makes the caudate and putamen to disinhibitor to provided trans inhibitory input to the globus pallidus pallidus internal that is the question. That is because cerebral cortex actually through several pathways not just the motor pathway, there are multiple pathways association pathway etcetera through multiple pathways cerebral cortex sense glutamatergic inputs.

That means excitatory inputs very important note of signs here signs mean s i g n sign whether a connection is excitatory and inhibitory cerebral Cortex sense excitatory are glutamatergic inputs to the striatum. Note the striatum neurons themselves are inhibitory they are gabaergic. So, when they are activated they are going to produce GABA or their output. So, when they are excited they are going to inhibit somebody, but they are inhibiting neurons in the globus pallidus pallidus internal which by itself is already inhibiting the thalamocortical neurons.

So, the cerebral Cortex sense excitatory inputs these are glutamatergic right. So, are they use glutamate as the neurotransmitter in many cases with some exceptions. So, and the other strong input the source of other very strong input received by the striatum is from the substantia nigra pars compacta which sense a very strong excitatory input to the direct path way through the neurotransmitter dopamine is the brain special chemicals from the most important neurotransmitters the function of basal ganglia right..

So, we will discuss its function in much greater detail in future classes. So, dopamine excides the neurones in the striatum. Once again these striatum neurons themselves are inhibitory and so that means, they are going to inhibit the GPi neurons which themselves are already inhibiting the thalamocortical neurones. So, essentially whenever the Cortex once excitation it excites a striatum, thus causing disinhibition of a thalamocortical neurones. This is one important nice model or hypothesis of basal ganglia function it is able to explain basal ganglia function and disfunction ok.

So, once again let us go through this. So, this is the reason we started by explaining from the tonic inhibition of the GPi neurons. So, GPi neurones providing tonic inhibition to the thalamocortical neurons is the most crucial element that you should remember. If this tonic inhibition is halted briefly; that means, there is going to be disinhibition right. So, like here for example, like it has been shown here right. So, and this inhibition is caused by inputs coming from the striatum directly coming from the striatum to GP i.

That means it does not go through the internal circuitry that GPe, it directly goes to the output structure GPi right. So, whereas that striatum neurones themselves are excited by two possible sources from the cortex the glutamatergic projections from the cortex excite the striatum, and the dopaminergic projections from the substantia nigra pars compacta except the striatum. This pathway from the cortex to the striatum of course, called as cortico striatal pathway.

And this pathway from the substantia nigra pars compacta to the striatum of course, called as nigro striatal pathway this pathway that is the nigro striatal pathway and that is the cortical striatal pathway why is this called as a direct pathway? Because the input from the striatum directly goes to the output structure which is the GPi or the substantia nigra nigra pars reticulata.

This is the reason why it is called as a direct pathway then what about the indirect path.

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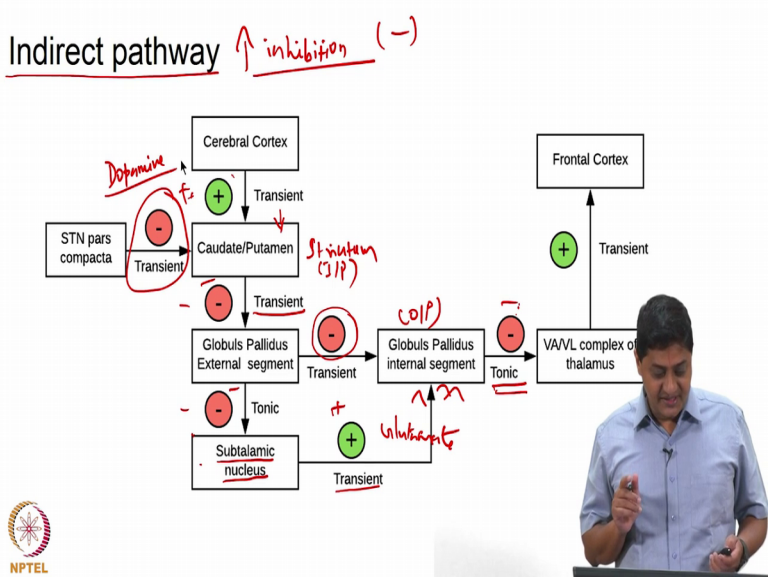

Another structure the subtalamic nucleus is involved it this. It turns out that the subtalamic nucleus provides excitatory inputs glutamatergic inputs to the GPi. Whereas, it is tonically inhibited by the input coming in from the globus pallidus external segment and a globus pallidus external segment itself is inhibited transiently by the input structure are the Striatum.

So, in this case Striatum which is the input structure is connected to GPi which is the output structure through two possible intermediate connections this is in a direct, but rather through the globus pallidus external segment which is part of the internal circuitry and the subtalamic nucleus which is part of the internal circuitry. So, these two things together make up the internal circuitry in this particular case and. So, since the input is connected to the output not directly this is called as the indirect pathway. The tonic input from the GPi to the thalamocortical neurons that is transiently inhibited by the GPe.

But the most important explanation actually comes through the pathway that involves the subtalamic nucleus through that pathway. So, the GPi neurons are transiently excited, not inhibited transiently excited by the subtalamic nucleus whenever the subtalamic nucleus is activated, whenever it is excited it is going to increase the inhibition level provided by the GPi to the thalamocortical neurons. So, that means, whenever this block is active the level of the information provided is going to actually go up right.

But then this activity is inhibited tonically by the GPe, the activity of the subtalamic nucleus neurons are inhibited tonically not transiently, tonically by the globus pallidus external segment neurons which themselves are transiently inhibited by the caudate and putamen by the striatal neurons. So, inputs coming in from the striatum briefly transiently halt the activity or the tonic inhibition provided by the globus pallidus external.

So; that means, what? Essentially inhibition provided to the subtalamic nucleus is reduced whenever there is a positive input that is coming. Essentially that causes an inhibition of the globus pallidus external and; that means, the level of inhibition provided by the globus pallidus external segment to the subtalamic nucleus here reduces. That means, the probability or the excitation level of the subtalamic nucleus increases essentially then increasing the input to the globus pallidus internal and that is not an

inhibitor input that is and excited to input to the globus pallidus internal and that is not an inhibitory input that is an excitatory input.

Essentially increasing the tonic inhibitory level provided by the GPi to the VA VL complex when was this happen? This happens in situations when different from that discuss the direct pathway. So, these are not the same cartico striatum neurons these are a different set of neurons that are used conveniently when we do not want to do something right. There is a need for a greater exhibition right, in such occasions there is an excitation provided by the Cortex that increases that increases the activity of the striatal neurons the striatal neurons themselves are inhibiting the GPe neurons.

And the GPe neurons themselves are tonically inhibiting the subtalamic nucleus neurons right. So, essentially this there is two minus. So, there is one minus here and there is one minus here that becomes plus there is a plus here, there is a minus here there is a minus here. So, the output at that point is going to be plus and that is multiplied by one more plus. So, that is that is an increase excitation level and that is multiplied by a minus. Essentially increased inhibition is the output of the indirect pathway right why. So, the increase excitation level provided by the cerebral Cortex increases the probability that striatum is going to inhibit the GPe neurones and the GPe neurons themselves are already inhibiting the subtalamic neucleus neurons.

So, that is one plus and two minus essentially making the situation here the probability that the subtalamic nucleus is going to get excited to go higher right and the subthalamic nucleus is actually having glutamatergic outputs to the globus pallidus internal segment and the globus pallidus internal segment is tonically inhibting the thalamocortical neurons. Essentially there are three minuses right and two pluses; that means, that net output is actually a minus something else is also there that is what happens here? Here you have a different situation dopamine which I said is usually an excitatory neurotransmitter in this case as the inhibitory neurotransmitter for the indirect pathway.

The details of this we will discuss in a future class, but please see the direct pathway here I said dopamine has a plus sign, but in the next slide I said in the indirect pathway dopamine has a minus sign why as this we will discuss in a future class, but essentially dopamine are the substation a graph parts compact a input is always excitatory the net

output of dopamine on the thalamocortical neurons is always excitatory, that is why it is having an inhibitory effect on the increased inhibition producing in direct pathway.

So, if indirect pathway is inhibited; that means, the net excitation level goes up. So, Dopamine always has a excitatory influence on the thalamocortical neurons, something that we must discuss in future classes.

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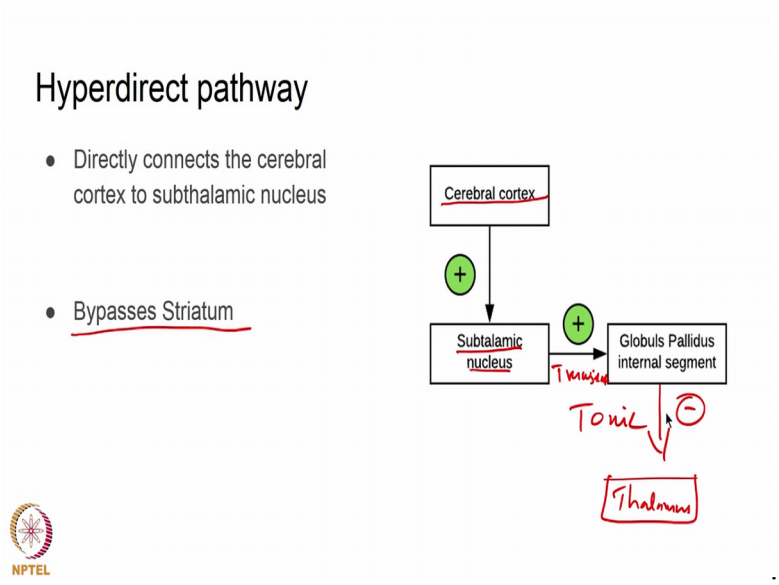

Then there is the hyper direct pathway in this case the subtalamic nucleus is directly excited by projections from the cortex right. So, there is direct connections from the cortex bypassing the striatum to the subthalamic nucleus and let us remember what the subthalamic nucleus is the subthalamic nucleus is providing transient excitatory input to the globus pallidus internal segment which provides the tonic inhibition to the thalamus is it not.

So, it is going to inhibit directly or super directly the output of the thalamocortical neurons by increasing the excitation level of the subthalamic nucleus. Note that in this case the major input structure of the basal ganglia which is a striatum is bypassed.

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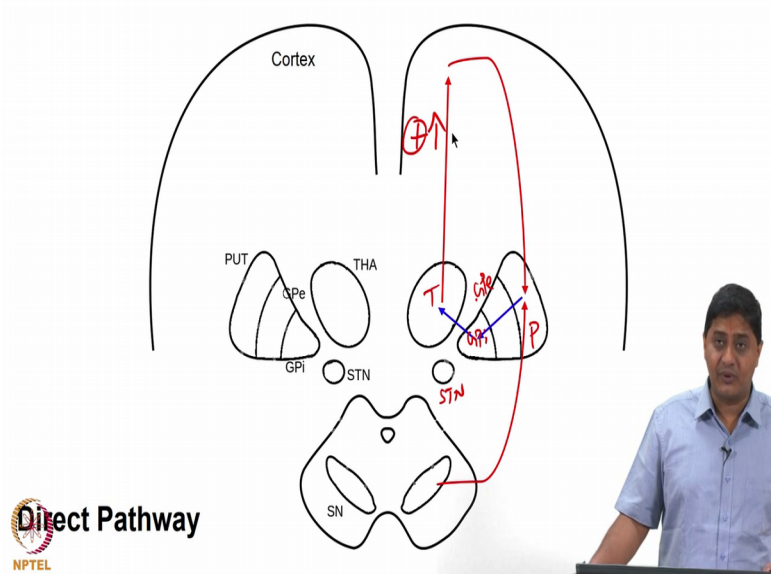

So, here what you have is cortex from the c ortex there are projections to the striatum in this case the putamen is taken as a striatum this is a putamen this is GPe, and this is GPi (Refer Time: 23:10) this is GPi this is thalamus this is subthalamic nucleus right. So, the red connections here refer to excitation and the blue connections here and the blue arrow marks here refer to inhibition alright.

So, there is excitatory inputs from the negotiator pathway and the corticostriatal pathway that causes an inhibition from the stiatum to the GPi and GPi I itself is tonically inhibiting this is tonic very important to remember this aspect. If this aspect is remembered that GPi is to tonically inhibiting the thalamocortical neurons then it is very easy for you to explain and understand basic and basal ganglia function right. GPi is toniacally inhibiting the thalamocortical neurons and that tonic activity is transiently inhibited by the excitatory inputs coming in from the cortex and the negotiator pathway.

So, essentially this direct pathway exides the activity of the thalamocortical neurons are disinhibits the activity at the thalamocortical neurons. So that means, from the thalamus to the Cortex there is an increased level of excitation. So, that happens an increased excitation level happens. So, the possibility that there is going to be excitation at the cortex is increased by the activity of the direct pathway. So, in the indirect pathway what happens if subthalamic nucleus is involved let us remember. So, this is the subthalamic nucleus.

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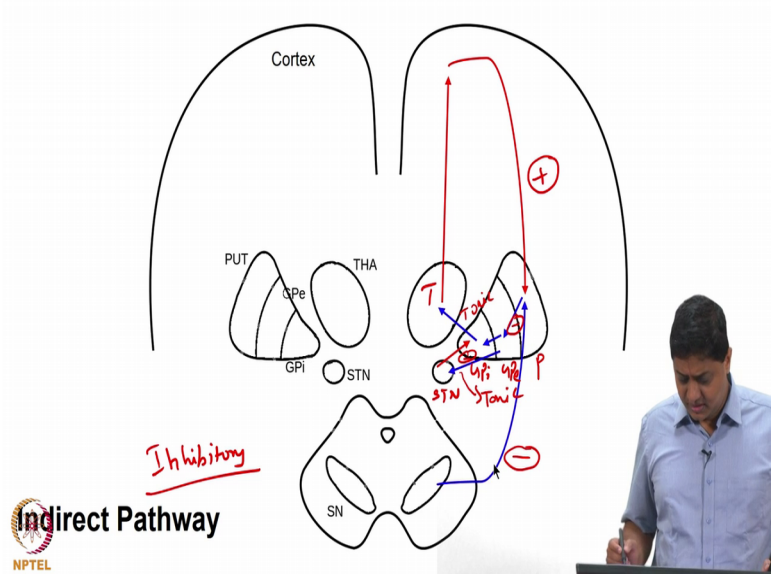

This is the thalamus this is the globus pallidus internal this is a globus pallidus external and this is the patomon right. So, in this case what we saw is that the subthalamic nucleus exides the globus pallidus internal right. So, that is what we saw.

So, essentially the input coming from the corticostriatal neurons continues to be excitatory; however, note the colour of the arrow coming in from the substation graph compactor that is actually blue that means it is inhibitory. So, the corticostriatal neurons exide the striatum are in this case the putamen and which excites the the neurons from the putamen to the globus pallidus external and these are inhibitory interneuron right.

So, these are gabaergic so, that is why the line here is blue; and they also further inhibit the neurons in the subtalamic nucleus, note this connection from the globus pallidus external to the subtalamic nucleus is actually tonic just like the connection from the globus pallidus internal to the thalamus is tonic. So, the activity of the subthalamic nucleus is increased for a brief amount of time by the transient input received by the GPe. GP e neurons are inhibited and these neurons are tonically inhibiting the subthalamic nucleus neurons.

Important note is at the subthalamic nucleus itself is having an excitatory influence on the globus pallidus internal so; that means, essentially there is one minus here and another minus here and these two minuses cause an increased probability of excitation of the subthalamic nucleus, increasing the activity of the subthalamic nucleus neurons. So,

these neurons send a higher level of excitation not to the thalamus, it sends higher level of excitation to the globus pallidus internal segment thus increasing the tonic inhibition level provided by the globus pallidus internal.

So, essentially the indirect pathway is an inhibitory pathway. So, whenever the indirect pathway is excited, the level of inhibition provided by the GPi neurons to the thalamocortical neurones actually increases. Note what I have not explained here is the important role of the nigrostriatal pathway in this which is inhibiting the indirect pathway. So, I already mentioned that the effect of dopamine on the thalamocortical neurones is always excitatory, this is something that we will discuss in future classes.

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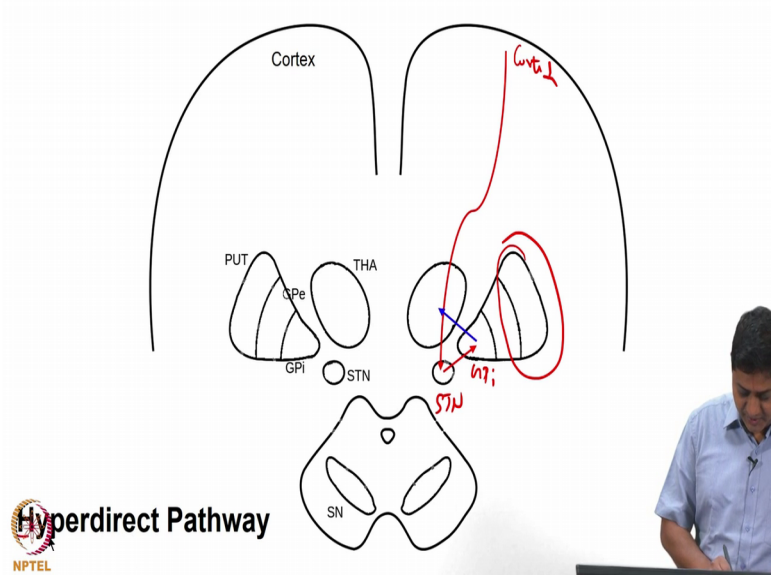

Again in the hyper direct pathway the input directly comes from the cortex to the subthalamic nucleus and from the subthalamic nucleus to the GPi the excitation goes, but from GPi to the thalamus the inhibition level is increase. Suppose for whatever reason there is an important need to inhibit cause an increased inhibition then the cortex directly contacts the subthalamic nucleus bypassing the striatum. So, this pathway is called as the hyper direct pathway.

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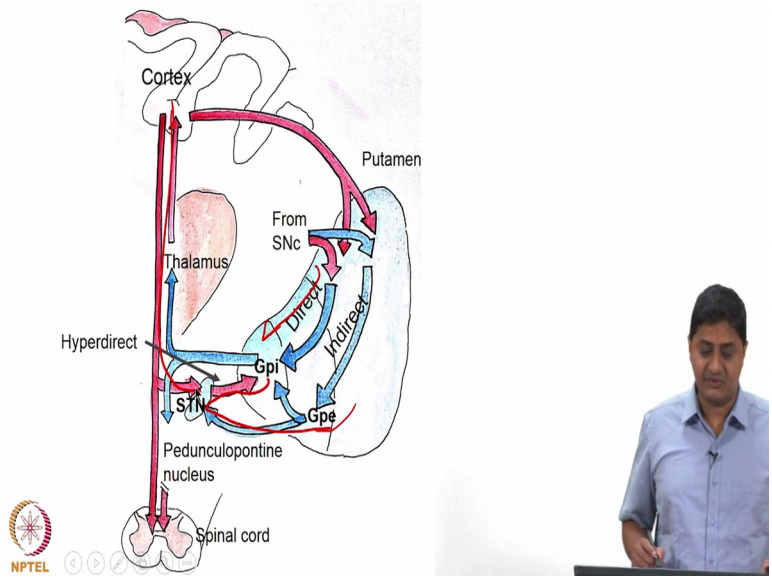

So, once again this is another pictorial representation of the situation. So, you have the direct pathway coming in from the striatum to the GPi, the indirect pathway coming in from the striatum through the subthalamic nucleus to the GPi and thalamus and the hyper direct pathway coming indirectly from the cortex to the subthalamic nucleus.

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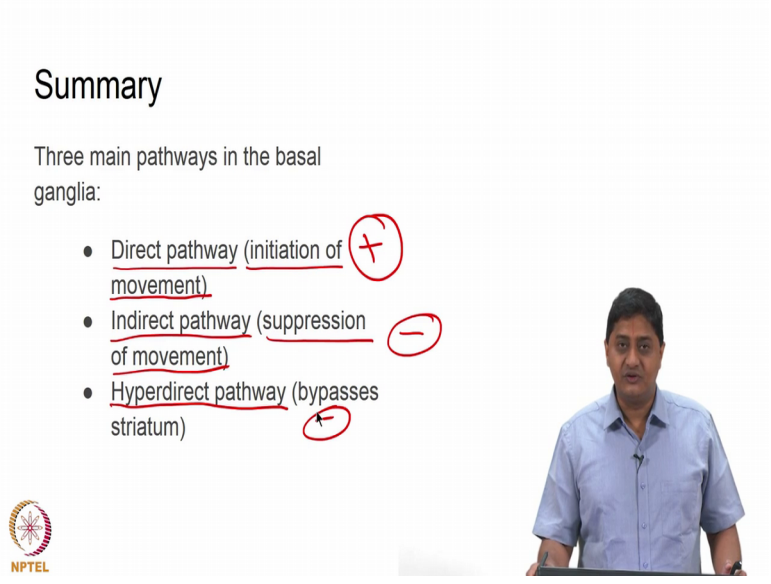

So, in summary we have discussed three pathways the direct pathway which is responsible for initiation of movement, which is an excitatory pathway. The indirect pathway which is important for suppression of movement, which is an inhibitory

pathway and the hyper direct path which bypasses a striatum also an inhibitory pathway. So, with this we come to the end of this lecture we will continue this discussion in future class.

Thank you very much.