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

Lecture – 66
Basal Ganglia – Inputs

Welcome to this class on Neuroscience of Human Movement. In this class we will be discussing Basal Ganglia and in particular Inputs to the Basal Ganglia.

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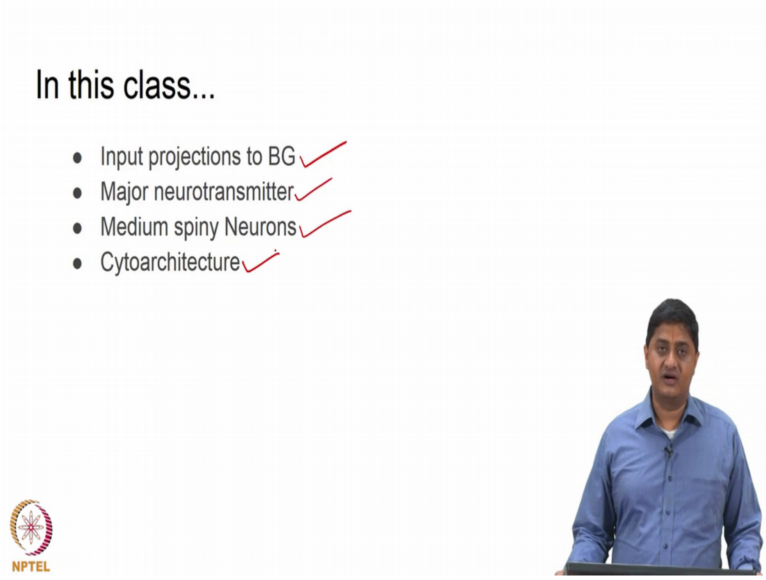

So, today's class we will be talking about input projections to the basal ganglia the major neurotransmitters within basal ganglia and the special nature of one type of neurons in the striatum called as Medium spiny Neurons and cytoarchitecture of different structures within the basal ganglia.

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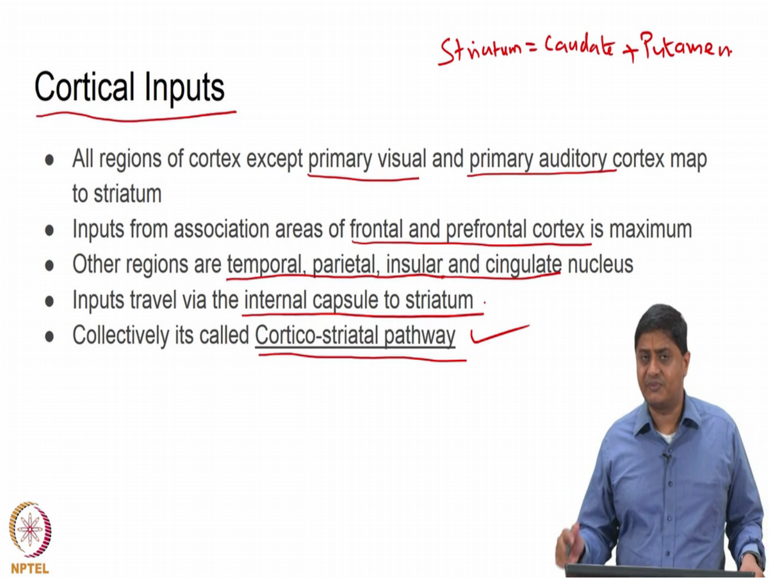

Let us remember that striatum is the major input structure of the basal ganglia. So, striatum refers to caudate and putamen. These are the two nuclei that are collectively referred to as striatum these two nuclei serve as the major input structures of the basal ganglia.

But where do they receive their input from actually they receive their inputs from multiple places. First they receive inputs from cerebral cortex also called as cortical inputs through a pathway called as Cortico-striatal pathway. So, that is given here the cortico-striatal pathway. So, which areas of the cortex project to the striatum? Almost all regions of the cerebral cortex except primary visual and the primary auditory cortex except these two practically all the regions of the cortex project to the striatum although they do not project to the same area within the striatum.

So; that means, neurons that originate from a particular location or from a particular functional area of the cortex is separated from neurons that originate from a different area and for a different function of the cortex. So, this is what we saw in one of the earlier classes as maintenance of skeletomotor, oculomotor, executive association and limbic functions of the basal ganglia. These are the four different functions or at least these are the four ways in which we could classify basal ganglia functions. A lot of information about basal ganglia function of course, comes from the motor lobes of the basal ganglia.

So; that means, the well studied lop among these four is the motor lobe and this offers us clue as to how the other lobe function. So, by understanding how the motor lobe function we may be in a position to get an idea of how the other lobe such as the limbic lobe or the executive or association lobes function and disfunction. So, what are the other areas from which the striatum receives inputs? Mainly from frontal and prefrontal cortex although striatum receives inputs from multiple areas in the cortex except the primary visual in the primary auditory cortex, a lot of projections, a large majority of the projections actually come from the frontal and prefrontal areas both precentral postcentral areas project to the striatum right.

However the basal ganglia itself always outputs to the frontal areas associated with the function. So that means, the basal ganglia may be receiving input from other cortical areas, but it will always protect its output to the frontal cortex. The basal ganglia also of course, receives major inputs from the frontal cortex right and what are the other regions from which it receives its inputs? Temporal lobe and parietal lobe and insular and cingulate cortex right and all these inputs travel to the striatum via the internal capsule right.

So, we referred what this is the internal capsule is the collection of cortical white matter right. So, the inputs to the striatum travel via the internal capsule and reach the striatum and collectively this is pathway is called as corticostriatal pathway.

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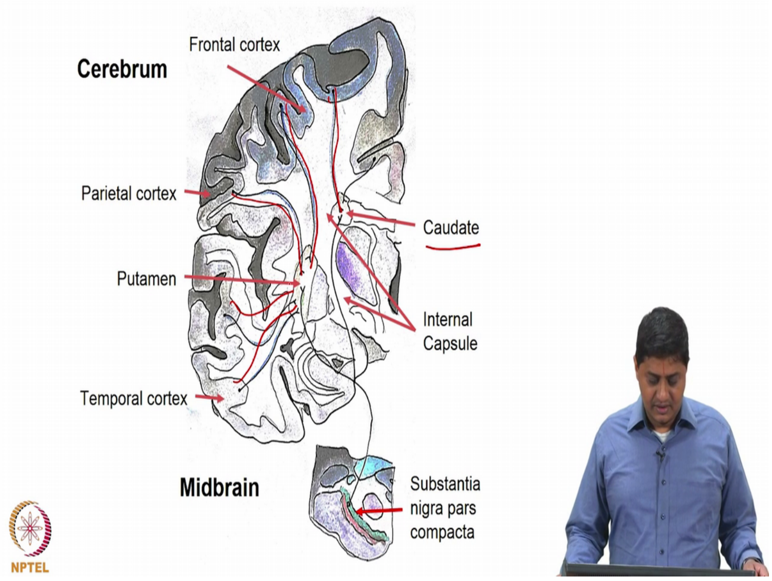

From the frontal cortex for example, input comes to say in this case the caudate nucleus, and here in this case from a different region of the frontal cortex input comes to the putamen and from the parietal cortex input comes to the putamen, and from the temporal cortex input comes to the putamen, from various areas like that let us remember that the striatum also receives inputs from areas other than the cortex. So, here we have only discussed what are the various cortical inputs.

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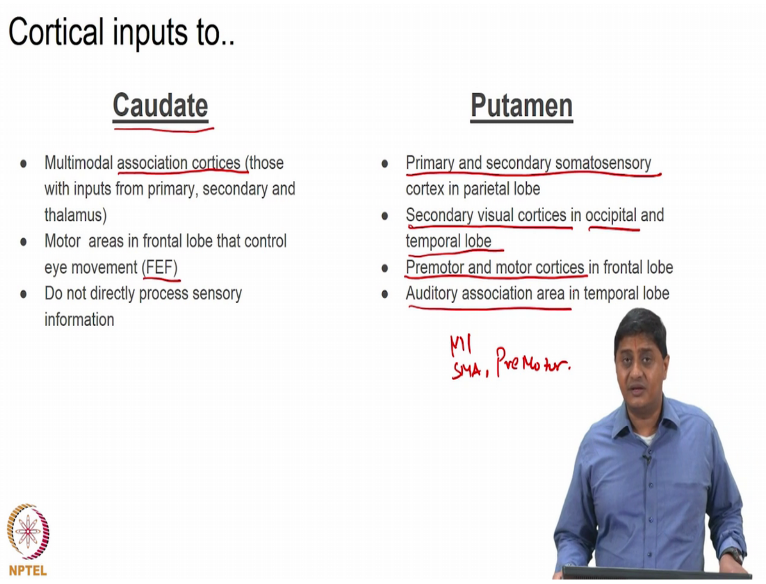

Let us continue the discussion. So, the cortical inputs to caudate and putamen are also different. As I mentioned earlier inputs from different regions of the cortex are kept separate in some sense there is some amount of topography that is maintained throughout the striatum, actually throughout the basal ganglia. So, inputs that come from one region of the cortex are kept separate from input that come from a different region of the cortex and that is very well seen in the difference between caudate and putamen let us remember caudate and putamen are actually similar structures that are separated by the internal capsule right.

So, yet the kind of inputs that they receive are different right caudate receives inputs from multimodal association cortices. So, multimodal association cortices means those areas of the cortex that receive inputs from primary and secondary sensory cortices and thalamus right. And motor areas in the frontal lobe that control eye movement such as frontal eye field right. Importantly they do not directly process sensory information in other words they receive inputs from association cortices, but they do not directly receive inputs from the sensory cortices. So, this is the special feature of caudate. Caudate receives inputs from association cortex, but not necessarily from the sensory cortex right

Whereas putamen receives inputs from primary and secondary somatosensory cortex in the parietal lobe and secondary visual cortex in the occipital lobe. Let us remember that striatum and does not receive input from the primary visual cortex, but it does receive inputs from secondary visual regions in the occipital and the temporal lobe most importantly putamen receives inputs from premoter and motor areas of the cortex, we know what is these are. These are primary motor cortex M 1 and supplementary motor area and premotor cortex, then we also know that pre dorsal premotor cortex ventral premotor cortex etcetera right. And putamen also receives inputs from the auditory association area in the temporal lobe.

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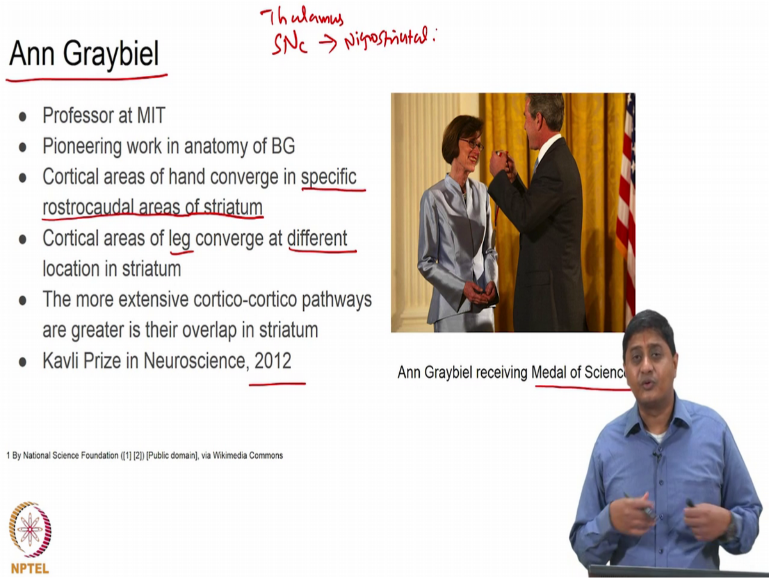

And important contributor to understanding of basal ganglia function is Professor Ann Graybiel. She is the institute professor at National Research Institute of Technology. Her work spanning about 40 45 years has been on the Anatomy of basal ganglia especially striatal functions. So, those areas of the hand that are represented in the motor cortex converge into specific regions within the striatum whereas, cortical areas of the leg converge at different striatal areas.

What she has also found is that, the more expensive the cortico cortical projections not the corticostriatal projections. If cortical areas are network within the cortex is well developed or more expensive, than their overlap if two areas in the cortex are well connected then the regions or their representations in the striatum are also overlapping to a greater extent. So that means a lesser amount of cortico cortical network will lead to a lesser overlap in the striatum. She of course, has received several honours including the highest award in the United States for science, medal of science and the Kavli prize in neuroscience in 2012. Before we move on let us discuss what are the other inputs received by the striatum these are inputs coming from thalamus and substantia nigra pars compacta right.

So, this is also called as the nigrostriatal pathway right after all this is a very important network, a very important pathway for basal ganglia function alright other than the cortical inputs there are also inputs received by the striatum from the substantia nigra pars compacta that have a profound influence on basal ganglia function; also striatal neurons receive inputs from several interneurons within the striatum. So, and these are in great variety under beyond the scope of this course.

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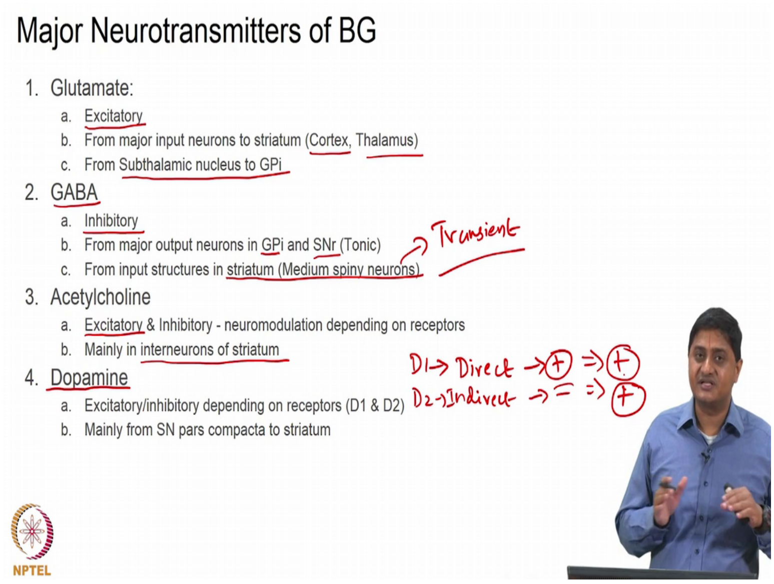

What are the major neurotransmitters within the basal ganglia? Importantly glutamate; glutamate is an excitatory neurotransmitter and glutamate is released by major input neurons to the striatum from where? Basically from cortex and from thalamus.

And also importantly within the basal ganglia, glutamate is used by the excitatory neurons of the subthalamic nucleus right. From the neurons that project from the subthalamic nucleus to the globus pallidus interna, which is the major output structure of the basal ganglia it is an excitatory pathway which we discussed in the previous class. The pathway from the subthalamic nucleus to the globus pallidus internal is actually an excitatory pathway thus increasing the level of tonic activation, the level of tonic inhibition provided by the globus pallidus internal right. And another major neurotransmitter is of course, GABA this is an inhibitory neurotransmitter of course. And importantly GABA is used by GPi and SNR neurons by the globus pallidus internal and substantia nigra pars reticulata which are the major output structures of the basal ganglia.

They use GABA to tonically inhibit their targets and their targets are either neurons motor neurons in the brain stem in the case of substantia nigra pars reticulata in many cases or the thalamocortical neurons in the VA and VL thalamus is it not. And GABA is also used by major input structures in the striatum, these are the medium spiny neurons we will see that in the next few slides. So, this usage of GABA is different from the GABA usage by GPi and SNR pay because GPi and SNR use GABA tonically. So, they keep tonically inhibiting their targets whereas, medium spiny neurons and their function and their release of GABA is usually transient right.

So, this is usually transient very important. So, this is what defines basal ganglia function that the transient nature of the GABArgic medium spiny neurons gets or selects the specific function or movement that needs to be performed a detail that we will continue to understand as we discuss right. Acetylcholine is mainly believed to be excitatory right however, depending on the receptors acetylcholine may have either an excitatory or an inhibitory influence on its targets. So, this is important, in one of the earliest classes we mentioned that neurotransmitters by themselves are usually excitatory and are inhibitory, and we say when we say acetylcholine is excitatory this is usually the case, but depending on the receptors it may in some cases be inhibitory.

And mainly acetylcholine is released by interneurons within the striatum. So, what is their function? Is, something that we need to understand and study and among the last, but definitely not the least is dopamine. Dopamine is produced by substantia nigra pars compacta neurons in the substantia nigra pars compacta produce dopamine and they innervate input structures mainly putamen and caudate. So, mainly we are saying when we say input structures we refer to striatum. So, through the nigrostriatal pathway dopamine influences or modulates inputs that are received from the cortex. So, dopamine has this influence that it excites the direct pathway and it inhibits the indirect pathway.

Let us remember this, the direct pathway is by definition an excitatory pathway, the indirect pathway on the other hand is an inhibitory pathway. If you excite an excitatory pathway the level of excitation goes up, but Dopamine selectively inhibits the indirect pathway only inhibition of the indirect pathway means inhibition of inhibition or disinhibition or excitation. So, through the D 1 receptors, D 1 receptors in the medium spiny neurons actually result in the excitation of the output structure at the thalamocortical level, there is an increased excitation whenever Dopamine is released due to the direct pathway.

But not just that Dopamine also inhibits the indirect pathway which by nature is already inhibitory. If inhibition is inhibited; that means, it results in a sort of excitation or disinhibition essentially resulting in excitation at thalamocortical level not at the striatal or the interneuronal level, at the thalamocortical level. So, basically dopamine always has an excitatory influence on the output structures or from the GPi to the thalamocortical neurons, there is an increased amount of excitation or reduced amount of inhibition. This is the most important function of dopamine, which is why when dopamine amount is compromised then there is going to be disfunction that lead to hypokinesia right or reduced movements or an increased amount of inhibition something that we will discuss in great detail in future classes right.

So, dopamine can be excitatory or inhibitory depending on receptors likewise acetylcholine can be excitatory or inhibitory depending on receptors. Importantly these two perform opposite functions within the striatum. So, where dopamine is excitatory acetylcholine is inhibitory right. So, essentially acetylcholine performs the role of inhibiting the net output of the basal ganglia whereas, dopamine performs the function of exciting the level of output of the basal ganglia actually the details are left, but at least for the purpose of this class this much is sufficient.

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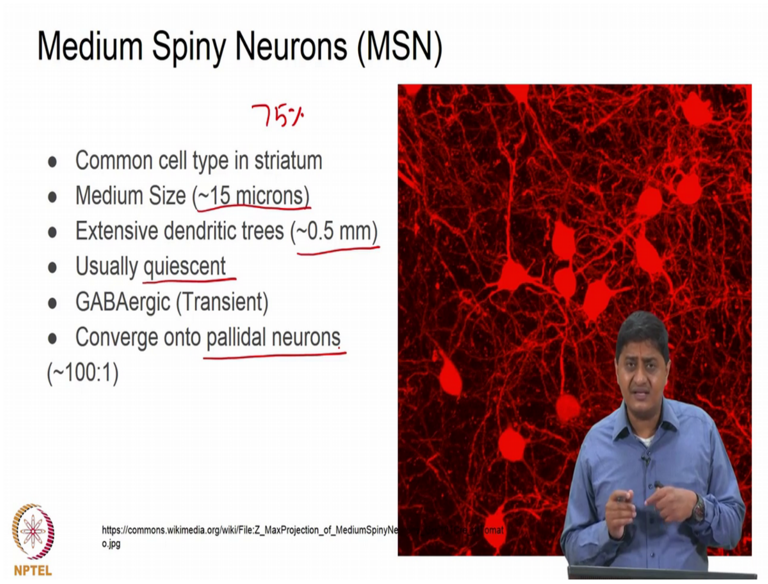

So, now let us discuss medium spiny neurons; medium spiny neurons is have is the most common cell type in the striatum. So, about 75 percent of the striatal neurons are actually medium spiny neurons. They are called medium spiny neurons because their size is medium about 15 microns and they are usually identified by their extensive unique dendritic trees of the order of 0.5 mm, 500 microns.

So, the size of the dendritic trees is 500 microns whereas, the size of the neuron itself is 15 microns right. And important to note is that the medium spiny neurons are usually quiet, they are usually quiescent they are not all the time active this is important because the GABAergic neurons in the GPi which is the output structure of the basal ganglia is always active and they are tonically inhibiting the thalamocortical neurons.

Whereas, the medium spiny neurons in contrast is usually quiet, but when it is active a great change happens right. Importantly they converge onto pallidal neurons in the ratio 100 is to 1. So, 100 medium spiny neurons project to one pallidal neuron right. Note medium spiny neurons project both to the GPe or the globus pallidus external and GPi or the globus pallidus internal. So, they project both to GPe and GPi regardless of which target is being used the medium spiny neurons converge in the ratio 100 is to 1 are approximately 100 on an average 100 medium spiny neurons project 1 pallidal neuron right.

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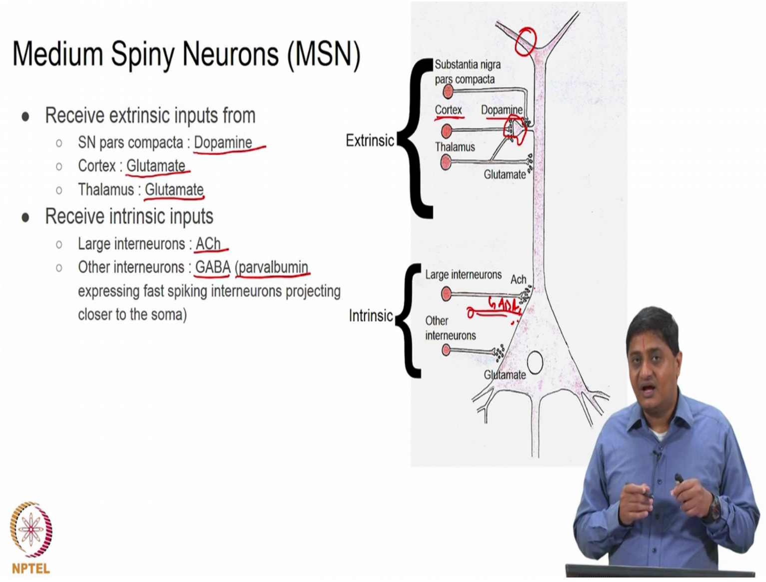

So, what are the various inputs received by the medium spiny neuron why are they called as spiny neurons? Because of the presence of spines in their dendritic trees so, there are several spines like that in their dendritic trees right. They receive external input from multiple sources from substantia nigra pars compacta of course, they receive dopamine, but first they receive inputs from the cortex right. What is the neurotransmitter? Glutamate; so, the cortical neurons or the corticostriatal neurons are glutamatergic. So, and the neurons from the thalamus are also glutamatergic. Important to note is the relationship between the nigrostriatal neurons and the corticostriatal neurons.

So, the cortical neurons project say for example, a particular spine the nigrostriatal neurons project to the same spine in many cases proximally in such a way that it can influence or profoundly influence the cortical input. So, the cortical input is a main input coming in from the cortex, it is influenced by the dopaminergic system. So, the dopaminergic system is sort of a gain tuner is sort of a modulator that we can use to change the response of the medium spiny neurons right. And importantly how thalamus and thalamostriatal or neurons from the thalamus projecting onto the striatum influence, it turns out that thalamus and interneurons project closer to the cell body of the medium spiny neurons thus having a greater influence on the medium spiny neurons.

So, let us remember what happens; the inputs from the cortex and the substantia nigra pars compacta arrive at a distance, arrive at dendritic trees at a distance from the cell body or soma of the medium spiny neurons. Whereas, the thalamus inputs and inputs from interneurons arrive at the cell body or closer to the cell body of the medium spiny neurons. So; that means, the chance that the neurons in the thalamus and the interneurons will influence the output of the medium spiny neurons is greater when compared with the chance that, cortical neurons or nigral neurons basically the dopaminergic neurons from the substantia nigra pars compacta and the glutamatergic neurons from the cortex influencing the medium spiny neurons is lesser when compared with interneurons and the neurons of the thalamus.

Also so that means, another thing to note is the level at which this happens right. So, the amount of neurotransmitter released may cause an excitatory postsynaptic potential in the medium spiny neuron, it may not be sufficient to cause an action potential. To have an action potential you must have a relatively strong cortical and nigral input; in such a way that it leads to spatial or temporal summation leading to an action potential in the medium spiny neurons. Whenever there is an action potential in the medium spiny neuron what is going to happen? GABA is going to be released and onto what structures? Basically GABA is going to be released on to the pallidal neurons which are essentially if it is a GPi neuron, GABA is going to be inhibiting the GPi neurons which is inhibiting the output neurons or the thalamocortical neurons.

So inhibition of the GPi neurons essentially open the gate for say a movement to happen. Note this function is different in whether the medium spiny neuron is part of the direct pathway or the indirect pathway. so, that something that we will have to discuss. So, intrinsically the medium spiny neuron also receives inputs from the large interneurons acetylcholine and other neurons inter neurons prodicing GABA importantly it the parvalbumin expressing fast spiking interneurons projecting closer to the soma here say for example, projecting closer to the soma very powerful influence on the activity of the medium spiny neurons right.

So, depending on whether a medium spiny neuron is forming part of the direct pathway or the indirect pathway the output and the behaviour will be different. For example, if the medium spiny neuron is forming part of the direct path way, then it will have D 1 receptors for dopamine and will get excited whenever dopamine is released right. Whereas, if medium spiny neuron is forming part of the indirect pathway it will have D 2 receptor for Dopamine thus getting inhibited right so, this varies depending on whether this is forming part of the direct pathway or the indirect pathway alright.

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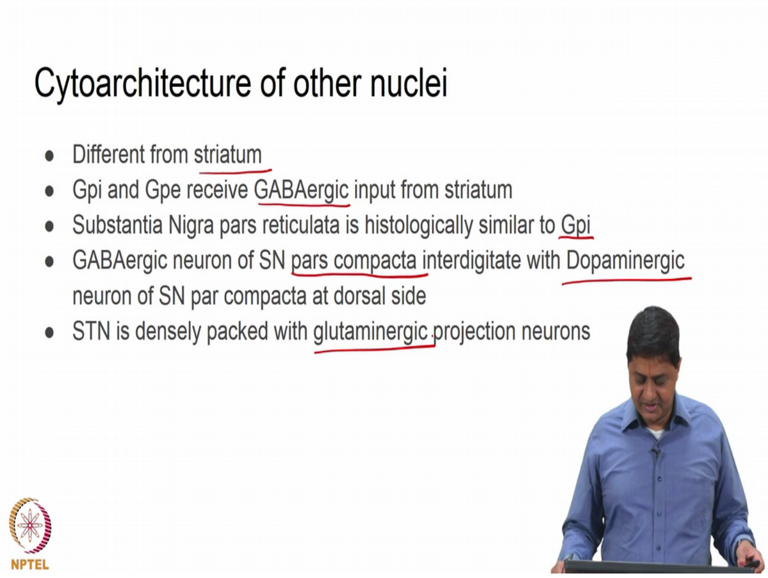

Importantly is the cytoarchitecture of other nuclei are different from that of the striatum GPi and GPe receive GABAergic input from the striatum we discuss this is earlier.

And pars reticulate is histologically similar to GPi basically pars reticulate can be considered to be downward displaced, GPi or the same structure separated by the internal capsule right and GABAergic neurons of the pars compacta. So, pars compacta also has other neurons that are GABAergic that interdigitate with dopaminergic neurons of the pars compacta right whereas, subthalamic nucleus is composed of glutaminergic projection neurons.

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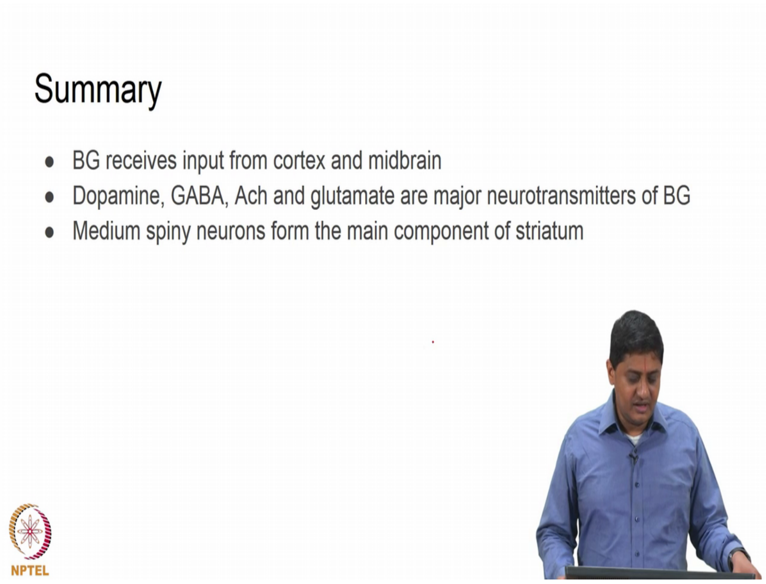

So, in summary basal ganglia receives inputs from several regions in the cortex, and also receives inputs from the midbrain and from thalamus. And important neurotransmitters are Dopamine GABA acetylcholine and glutamate and medium spiny neurons form the main component of the striatum and a major function of basal ganglia is dictated by the function of the medium spiny neurons. So, with this we come to the end of this lecture.

Thank you very much for your attention.