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

Lecture – 54
Cerebellum Part – 3

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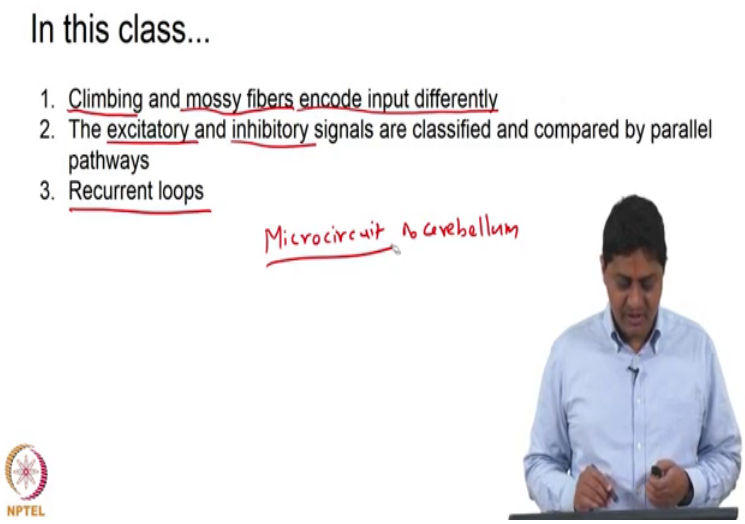

So, welcome to this class on a Neurosciences of Human Movement, this is a part 3 of our discussion on Cerebellum.

In this class will be discussing the details of climbing and mossy fiber inputs and how they encode different types of inputs or different kinds of inputs into the cerebellum and how excitation and inhibition within the cerebellum are compared by multiple parallel pathways and what are the various recurrent loops? In other words, we are interested in this class to discuss the details of the micro circuit of the cerebellum.

It turns out that the cerebellum has thousands of repeating units ofthese micro circuits. So, is a same fundamental unit that gets repeated multiple times within the cerebellum, unlike other regions that, we discussed earlier for example, we discuss the case of primary motor cortex, pre motor cortex, etcetera. Where we said that the situation is that are the representations are more mosaic and there is both convergence and divergence and are regions that control of article part of the body are located over a relatively large area and the motor cortex, etcetera. We discussed earlier, unlike that here what you have

is a relatively regular arrangement, the same micro circuit has been repeated multiple times.

So, that gives rise to questions that what could be the function of this micro circuit? So, how this micro circuit and it is output and it is function, modulate output of the cerebellum as a whole and it is function as a whole. So, those are the questions.

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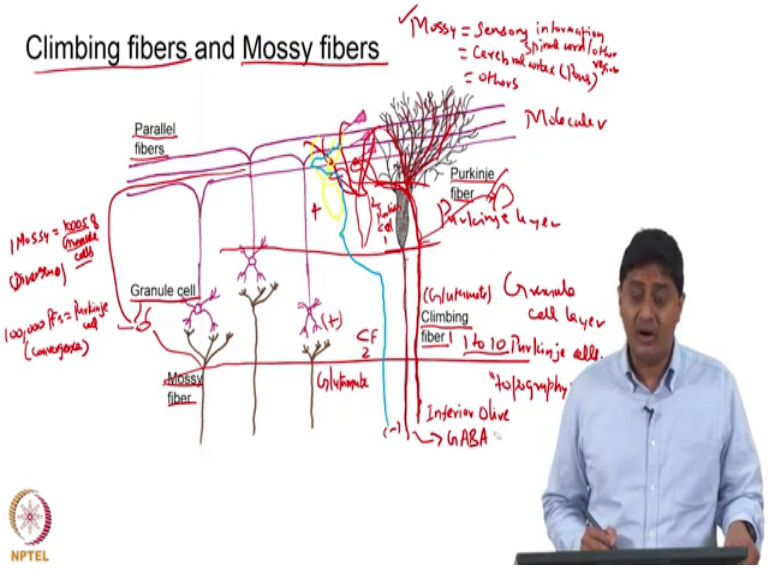

So, in this class we will discuss micro circuit of the cerebellum and the details turns of that the delight in this sort of science is in the details is it not.

So, in started with the climbing fibers and mossy fiber system. So, we said what are mossy fibers? Mossy fibers are I will write this here. So, mossy fibers arise from these are sensory mossy fibers are sensory information are mossy fibers are neurones, that bring sensory information from spinal cord and the other regions of the c n s and they also bring information from cerebral cortex via pons right.

So, they basically bring information from pons and sensory information from spinal cord and other regions and some others some others not discusses detail, but classified as others right, these are the major inputs to the cerebellum or at least one major inputs to the cerebellum. There are 2 major inputs to the cerebellum these are coming from 2 different types of fibers, one is mossy fiber the other is climbing fiber ok.

So, mossy fibers from 1 major input to the cerebellum and they innervate with granule cells right, we showed in a previous class that, they innervate with granule cells and with golje cells in a glomerulus we saw that in the previous class is it not. So, it turns out that each granule cell receives input from a few mossy fibers, but one mossy fiber innervates several 1000 granule cells, 1 mossy fiber 1000 of granule cells.

So, 1 mossy fiber can serves input to thousands of granule cells and is a that make sense right, because granule cells a very large in number mossy fibers are much smaller in numbers. So, there must be a great amount of divergence from the mossy granule system right or the mossy parallel fiber system encodes. Basically a great amount of divergence involves a great amount of divergence from 1 mossy fiber to thousands of granule cells right

So, there is divergence, this is the molecular layer, that is the Purkinje layer whereas, these is the granular cell layer. In the molecular layer the actions of the granule cells, become what are called as parallel fibers and they innervate anywhere between 250000 to one million connections with the Purkinje cells.

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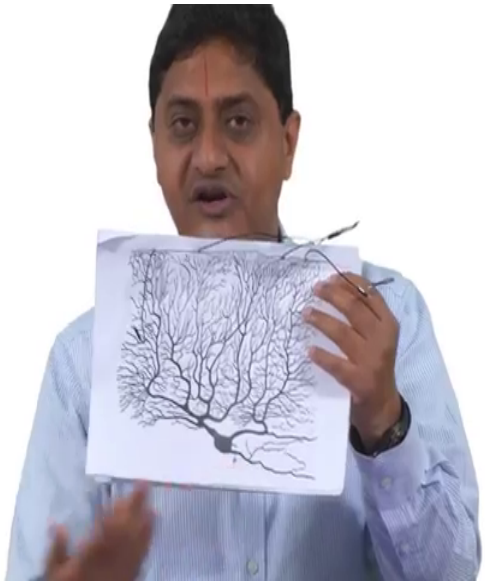

We have seen that earlier. So, in the previous class we showed that, the Purkinje cell as this then unique very distinct Dendritic tree as shown here right, we said that you know there is thickness in the anterior posterior direction actually might look like mediolateral in this picture, but I am showing for the sake of illustration that these two directions in

this paper in this page or anterior posterior direction, but this is very thin in the mediolateral direction, this is something that we discussed in the previous class, but what also happens is that the parallel fibers are perpendicular run perpendicular to the Dendritic trees of the Purkinje cells.

Now, consider that each of these pages is a Purkinje cell for example, so, here is a Purkinje cell and I have several such papers several such pages each of them is a Purkinje cell is it not. So, that is a Purkinje cell, so, that is another Purkinje cell etcetera.

Now, it turns out that they have great amount of territory, they cover great amount of territory in the anterior posterior direction, but each Purkinje cell is very thin in the medio lateral direction and it turns out that the parallel fiber. So, this cables that I am showing here are the equivalents of the parallel fibers right. So, the parallel fibers run primarily in the medio lateral direction in that direction for example, right. So, in this direction so; that means, they are perpendicular, they are perpendicular to the plane of the Purkinje cells in other words, they have the potential to make connections with all these Purkinje cells and several of this.

So, what I have shown is only like 3 or 4 parallel fibers, but the we said the number of parallel fibers are 100 billion is it not that is a very large number. So, these parallel fibers run perpendicular to the plane of the paper like in that and make connections make a synopsis with this Purkinje cells ok.

So, we discussed how Purkinje cells get inputs from thousands and thousands of parallel fibers are granule cell actions right. So, another major form of input to the Purkinje cells is the climbing fibers, where do they originate? We said where where the mossy fibers originate the climbing fibers originate from the inferior olive right. So, these are special in the sense, that these neurones are these fibers, do not make connections with granule cells at the granule cell layer, they climb through that is the reason they are called as climbing fibers, they climb through the Cerebellar cortex, through the granule cell layer, through the Purkinje cell layer and directly into the the molecular layer. Where the Purkinje fiber dendrites are there and then they make connections with several dendrites of the Purkinje cell fundamentally different from the way the granules cells function the parallel fiber system functions, let us remember that 1 mossy fiber can innervate about

thousands of granule cells and the number of inputs received by each Purkinje cell from parallel fibers can be of the order of 2, 50000 to one million.

So, 1 Purkinje cell this is input from about one million parallel fibers or 250000 to one million very large number of inputs are received by 1 Purkinje cell whereas, 1 climbing fiber innervates about 1 to 10 Purkinje cells. So, 1 climbing fiber can activate about 1 to 10 Purkinje cells, but a given Purkinje cell receives input from only one climbing fiber, what do I mean by that? So, let us me repeat that for clarity. So, one climbing fiber innervate suppose there is this climbing fiber, this innervates, this Purkinje cell and let us say there is one more Purkinje cell here, whose Dendritic tree is here.

So, this Purkinje cells then branches out and also innervates these Purkinje cell dendrites and also one more Purkinje cell. So, that is the climbing fiber to Purkinje cell connections right, but this Purkinje cell, I am going to call that as cell 1. It receives input only from climbing fiber 1 whereas, there might be a different climbing fiber that, I am going to now draw in blue for the sake of clarity, this climbing fiber innervates at different Purkinje cell that I am going to draw in a different colour for sake of clarity right.

So, that climbing fibers continuous and innervates these. So, cell 1 is going to receive input from say for example, climbing fiber 1 and say this is cell 2, that is receiving input from climbing fiber 1 whereas, the climbing fiber shown in blue is climbing fiber 2, that is innervating cell 3 or 4. So, I am going to call this as cell 4 that is innervating cell 4. So, a given cell a given Purkinje cell say p c 1 or Purkinje cell 1 is receiving input from only 1 climbing fiber, either from climbing fiber 1 or from climbing fiber 2, but climbing fiber 1 itself can innervate multiple Purkinje cells ok. So, that can be of the order of 1 is to 10. So, 1 climbing fiber can innervate multiple Purkinje cells, but that given Purkinje cell can receive input from only 1 climbing fibre.

So, it since like there is a fundamental difference in the way this, systems function what you have at the mossy parallel fiber Purkinje cell system? What you having? First is a great amount of divergence, 1 mossy cell can innervate thousands of granule cells and hundreds of thousands of granule cells are parallel fibers innervate Purkinje cell. So, 1000000 for example, parallel fibers innervate Purkinje cell. So, what is this? This is convergence, is it not.

So, you have this great divergence convergence of inputs from the per from the mossy system whereas, in the climbing fiber system, you do not have this, you have direct relatively direct inputs and by the way the inputs that are given by the climbing fibers are fundamentally a different, when compared with the inputs of the mossy system right or the mossy granule cell system.

Also important to node is that the climbing fibers, that arise from similar regions of the inferior olive project to a relatively small area. So, there is topography. So, climbing fibers arising from similar areas in the inferior olive project to a relatively a small area in the Cerebellar cortex and the Purkinje cells, that receive inputs from this region also project to a relatively small area in the deep cerebullar nuclei, we are not done with the discussion of the micro circuits, there is more actually what is the nature of these connections? What is the nature are these inhibitory or excitatory?

Are things that we should start discussing in turns out that the mossy granule cell system is an excitatory connection, it is input is excitatory it is a neurotransmitter is a glutamate right and the climbing fiber Purkinje cell system is also excitatory, it is, it is neurotransmitter is also glutamate.

However, there is a difference in the way this function that detail, we will discuss and the granule cells also excite the Purkinje cells whereas, the Purkinje cells actually there outputs or inhibitory, the output of the Purkinje cells are basically governed by Gaba inhibitory.

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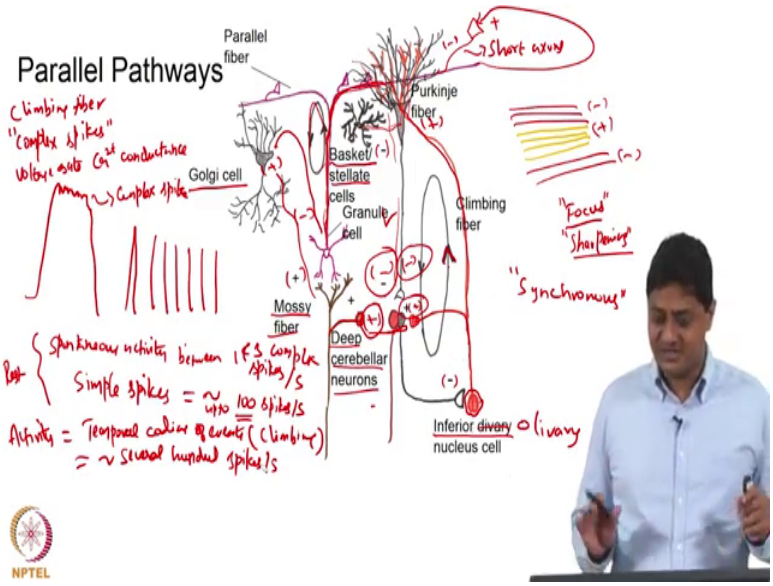

What is not shown or other details that are showing for example, in this picture right. So, it turns out that there is more to this then the, what were shown previously. So, for example, the climbing fiber that originates in the inferior olive proceeds and actually actually innervates the Purkinje cell actually makes thousands and thousands of connect, thousands of thousands of synopsis with the Purkinje cell dendrites right, but they also branch out and excite the deep Cerebellar nuclei neurones, neurones in the deep Cerebellar nuclei are also excited are also excited by the climbing fiber system, but the Purkinje cell is actually inhibitory. So, what is happening? Is a comparison of excitation and inhibition that is probably what has been performed is it not.

So, the Purkinje cell inhibits the deep Cerebellar nuclei right. So, that forms are recurrent loop that is shown here right. So, there is, so there is a excitation the travels in this direction another, there is inhibition the travels down into the deep Cerebellar nuclei from the Purkinje cells, but it is not just then in turns out that what is also true is that the deep Cerebellar nuclei can also modulate can also modulate the functions of the inferior olive, this is inferior olivary nucleus ok

So, the deep Cerebellar nuclei can also modulate the functions of the inferior olive by inhibiting them. By the what is also what is not mentioned previously is that the inferior olive right, it has it is special in the sense that within the brain within the among the excitable sense. There are a few cells that conduct electronically, we discussed

previously communication between cells happens into manners basically synopsis are of 2 types, one is electrical synopsis and the other is chemical synopsis, is it now mostly we have discussed chemical synopsis, which are the most prevalent, but there are some cases where the synopsis are electrical are the connections are other electronic that kind of activity that kind of phenomenon happens in the inferior olive, where cells in the inferior olive communicate with the other cells in the inferior olive through what are called as gap junctions. Very, very special these are also found in cardiac cell for example, but that outside our discussion.

So, within the within the inferior olive so, there are these gap junctions and electronic coupling between this. So the, it turns out that there is, it is because of electronic coupling. If 1 climbing fibers fires all the climbing fibers that are electronically couple to it fire, leading to relatively synchronous activity of the climbing fibers ok. So, and because deep Cerebellar nuclei can control the extent to which the activation comes from the inferior olive in a way modulation of Cerebellar activity is performed by the cerebellum cerebellum, it within this or deep Cerebellar nuclei within the cerebellum controls to, what extent it is going to be excited or inhibited?

So, to some extent that is controlled by the deep Cerebellar nuclei here, but there is one more loop right, the mossy system excites the granule cells and they also excite the mossy system also excites the Golgi cells right, what happens is that the Gol, what happens is that the granule cells excite the Purkinje cells, which further inhibit the deep Cerebellar nuclei, but it turns out that the mossy system also causes an extension of the deep Cerebellar nucleus. So, once again, what is happening is an excitation is first given to the deep Cerebellar nuclei and that excitation is carried to the Purkinje cell layer, which then causes and inhibition the output of the Purkinje cells is always inhibitory.

So, that causes an inhibition. So, at this stage what is happening? Is a comparison of that excitation and that inhibition at that level and also a comparison of that excitation and that inhibition right. So, there is this loop, but what is not discuss is the case of Golgi cells, mossy fibers also excite Golgi cells and this Golgi cells inhibit. Golgi cells are inhibitory interneurons, they inhibit the granule cells. So, there is loop here ok. We discuss the case of the climbing fibers and mossy fibers, what are and the output from the Purkinje cell, this is always inhibitory, what we have not discuss is the case of inhibitory

inter neurons other inhibitory inter neurons, there are 2 major inhibitory interneurons, in the molecular layer these are Basket cells and stellate cells right.

Stellate cells are star shaped cells, that is a reason they are called as a stellate cells. These have relatively short axons and they cause inhibition of nearby dendrites of the Purkinje cell, they are there excited by the parallel fibers. So, they receive excitatory inputs from parallel fibers and they inhibit nearby dendrites of the Purkinje cells. Whereas, Basket cells are unique, they also receive inputs from a parallel fibers, but they project on to the Purkinje cells, sometimes he to the cell bodies of the Purkinje cells and nearby dendrites of the Purkinje cells causing relatively strong inhibition, when compared with the stellate cells they inhibition caused by the Basket cells us relatively strong and there function.

So, there function in such a way that when there are. So, let us remember that, there are going to be thousands and thousands of parallel fibers right. So, the Basket cells function in cause inhibition in such a way that, only some of these inputs are going to actually cause only some of the inputs are going to actually cause excitation, while ensuring that the remaining ones continue to be inhibitory. So, these are inhibitory these are. So, are there effects, are there effects are controlled or modulated in such a way, that among thousands of parallel fibers a central flank alone will cause and excitation whereas, the others will not cause that that and that that acts is not on the parallel fibers, but rather on the Purkinje cells.

So, in a way it is functioning to cause focus or sharpening of the parallel fiber input, Basket cells function to focus or sharpen the outputs of the Purkinje system. So, different functions by both are inhibitory interneurons both stellate and Basket cells are inhibitory interneurons, but their functions are different right.

So, what are the other things? There are other cells who functions are not discuss in this in this class excitation inhibition balance that happens at multiple levels right. First there is excitation of the deep Cerebellar nucleus by the inputs namely the mossy system and the climbing fibers system and these are in whereas, the deep Cerebellar nuclear inhibited by the outputs of the Purkinje cells and the Purkinje cells themselves are excited by the climbing fiber and the mossy parallel fiber system right and the output of the Purkinje cell is modulated by inhibitory information that is received from the stellate and Basket cells ok, this is what we have discussed.

So, for and what else are there what is the special nature of the climbings fibers and it is output is something that, we must discuss at the climbing fiber produces what are called as complex spikes. What are these? It turns out that the climbing fiber causes relatively large aptitude action potential in the Purkinje cell and then several bus of high are several high frequency bus of relatively smaller aptitude action potentials, this is because of protracted time, this is because of protracted voltage gated calcium conductance.

So, the calcium conductance fundamentally different from the previous discussions that, we have had in this case, what happens is the climbing fibers cause calcium conductance for a relatively long time to persist in the Purkinje cells causing this at the action potentials are going to be like this right. This is called as a complex spike ok, this is different from the action potential that is going to be caused by a parallel fiber. The parallel fiber is going to cause a regular action potential. So, that are seen as these right.

So, at rest what happens? At rest when a person is at rest, spontaneous activity of climbing fibers cause as anywhere between 1 and 3 complex price per second. So, even when you are at rest, when you are sitting quietly not doing any activity the climbing fiber causes between anywhere between 1 and 3 complex spikes per second. Whereas, the activity of the mossy parallel fiber system causes simple spikes at rest sometimes even up to up to 100 spikes per second.

The acts the results of this action on the Purkinje cells are fundamentally different, because one is causing complex spike are relatively large amplitude output followed by several smaller amplitude action potentials. It is not clear, whether the smaller amplitude action potentials of the complex spike or actually communicative or actually used in the communication down the Purkinje cells, but note even at rest the simple spice can be as high as 100 spikes per second, what happens during activity? During activity climbing fibers.

So, this is at rest during activity climbing fibers, produce activity that temporally codes actions or temporally codes evens. So, temporal coding of events by the climbing fibers whereas, the activity that happens, due to simple spikes, due to the mossy parallel fibers system can cause up to several 100 spikes per second so that, activity is relatively of high frequency of high frequency. So, also not so, this means it seems to us that the difference that, the climbing fiber and mossy fibers fundamentally code different things, it seems

like that the climbing fibers system is more of a presence or absence switch or it acts more like and signal for the start or end of a event right.

Whereas the activity of the mossy system in some sense, encodes the amplitude are the the extent to which the activities happening. So, one is a start stop switch, it can be considered and that the climbing fiber acts more like and even signal are presence or absence of an event whereas, the mossy system encodes, the actual amplitude of the even there is more to this is a very simple description of what is a actually happening and the actual situation is way more complicated. I would made, an attempt to explain this in some terms at least, we should make an attempt to understand this at some level.

So, I have not done justice to the complexity of the cerebellum, here that is not the aim, this is a course on our on this topic. The aim if you are those were interested can; obviously, check various research articles in this, we have we cannot do justice to this in this particular class ok.

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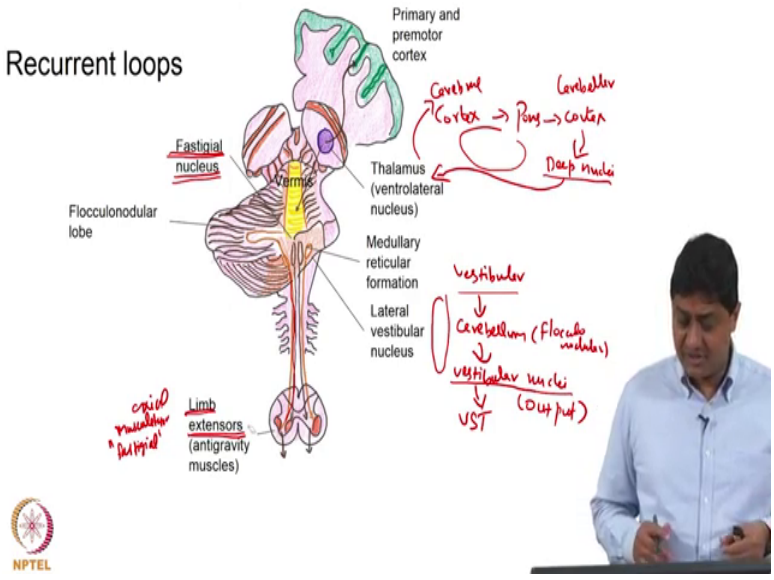

So, and there are multiple recurrent loops within the cerebellum, what are these? What are the various recurrent loops within the are between the cerebellum and other parts of the. So, first this is. So, it receives input from the cortex. So, the cerebellum receives input from the cerebullar cortex via the Pons via and then.

So, basically it goes via the Cerebellar cortex and via the deep nuclei of, what are the deep nuclei? We said that the deep nuclei these are the dented interposed and Fastigial nuclei, this nuclei are the major output structures of the cerebellum via the deep nuclei, the project to the ventrolateral Thalamus and from the Thalamus to the primary and pre motor cortex, that is controlling movement. So, that is that completes 1 loop right from the cerebral cortex back to the motor cortex right.

So, that is one loop what is also there, what is also there is the inputs that are received from other regions for example, we will take one case of vestibular input that is received, so vestibular input source as an information about head orientation and the position of the head right. So, in other words, it is useful in maintenance of balance and posture right, if this is somehow if there is a disturbance somehow that is detected by the vestibular system and cerebellum. So, the vestibular system to the cerebellum as in the Floculonodular loop and back to the vestibular nuclei and further into the vestibulospinal tract right.

So here, once again you have a recurrent loop that start from the vestibular system to the vestibular nuclei. It turns out that the vestibular nuclei are special in the sense that, they act like deep nuclei of the cerebellum. Vestibular nuclei are also among the major output structures of the cerebellum. So, vestibular nuclei although they are located outside the cerebellum, actually at functionally similar to the deep nuclei of the cerebellum acting as the output structure of the cerebellum and also the case of the information, that is received about balance and posture and maybe visual information this is received in the vermal and the paravermal area right.

So, are the intermediate area of the cerebellum, that projects to the again goes through the Cerebellar cortex and then it projects to the Limb extensors and axial musculature via the Fastigial nucleus. The output in this case happens to be the, Fastigial nucleus once again the input that is shown here. So, once again the input is coming from multiple sources, but the output is on the Limb extensors and more axial musculature to for the maintains of balance and posture.

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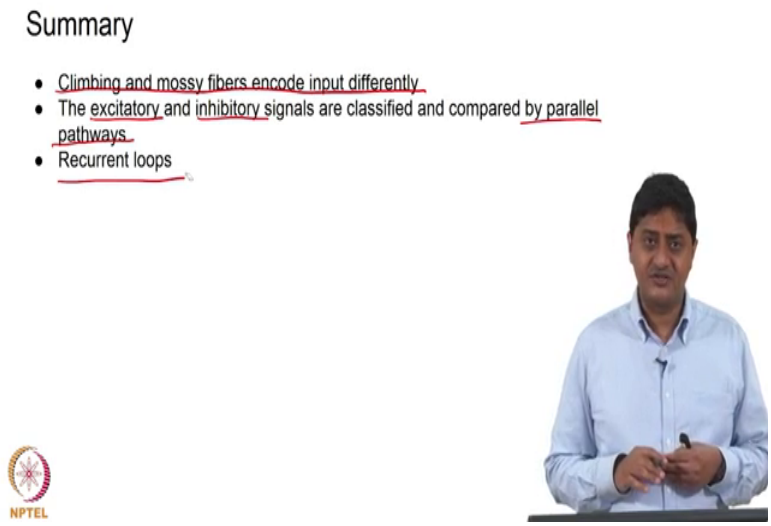

Ok. So, in this class we have seen that, the climbing and mossy fibers encode different types of inputs and the excitatory and inhibitory signals are classified by multiple parallel pathways. We have seen this we have discuss some of this, as in the first excitation from the mossy and climbing fiber system is to the deep Cerebellar nuclei and mossy system further excites granule cells and which excites the Purkinje cells, in a divergent convergent manner.

Whereas, the climbing fiber directly and with greater influence excites the Purkinje cell, where and the Purkinje cells inhibit the deep Cerebellar nuclei. So, there is a comparison of excitation and inhibition that is happening and there are several recurrent loops that happen between the cerebellum and other regions of the brain. So, we will continue the discussion on cerebellum in future classes.

So, thank you very much for your attention.