



Cerebellum

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Chapter 1: John Martin Introduction

John Martin: Well, the cerebellum is a very curious kind of structure. There are more neurons in the cerebellum than in the rest of the brain, so it must be doing something either very complicated or very important. From a functional connective perspective it's really very interesting. It's a motor control structure. The cerebellum provides one of the major inputs to the corticospinal system, it provides the major input to the rubrospinal system, and other brainstem systems, reticular and vestibular spinal systems get a huge amount of input from the cerebellum. The vestibular spinal system, apart from getting direct input from the vestibular apparatus, gets most of its inputs from parts of the cerebellum, and I'll be discussing [that]. Yet damage to the cerebellum doesn't produce weakness, so the loss of cerebellar inputs onto these motor control structures—major facilitatory drive to these structures—doesn't produce weakness. Cerebellum gets information from all the sensory systems, and very strong direct connections from the spinal cord and from somatic sensory receptors. Yet damage to the cerebellum doesn't produce sensory impairments, doesn't elevate sensory thresholds, mechanosensory thresholds, doesn't increase two-point discrimination thresholds, doesn't produce blind spots. So there's a kind of a discordance between something that's very important in the pattern of connections of the cerebellum and what happens when the cerebellum becomes damaged.



Recently there's been a lot of interesting anatomical work and physiological work showing that the cerebellum has an influence on diverse association areas of the cerebral cortex, the pre-frontal association cortex, parietal and even temporal lobe. And yet damage to the cerebellum is not picked up by neurologists as cognitive or emotional impairments. There's a kind of discordance between the pattern of connections of the cerebellum and what happens when the cerebellum becomes damaged. And as I mentioned a few moments ago, at the end of the lecture, Dr Pietro Mazzoni will go through a short presentation on cerebellar disease, and you'll see the kinds of impairments that happen.

But from a research perspective we can identify a small set of important control functions of the cerebellum. What I mean by research perspective—looking at patients with cerebellar disease, looking at animals that are trained to perform motor tasks, and recording the activities of cerebellar neurons during performance of the task, looking at controls and patients using imaging techniques—we can come up with a short list of important functions. And I have that here.

From the perspective of some of its key connections, the cerebellum is important in comparing what we want to do with what actually happens—comparison of intent and action—and as a consequence of this comparison, generates control signals that reduce error on subsequent performance of the motor task. It's involved in motor learning and adaptation, plays a key role in automating and optimizing behaviors. And there's some recent work showing a potential role for the cerebellum in motor cognition, and possibly even aspects of general cognition and language. This is new and controversial, and I'll end with a brief discussion of this because I think it's kind of exciting, pointing new directions where the cerebellar work is going.

The goal of the lecture is to come out with a sense of the functional anatomy of the cerebellum, functional localization in the cerebellum. And first I'll give a brief overview of where the cerebellum fits in the motor system hierarchy. We'll go a little bit into cerebellar neuroanatomy. I'll be focusing a bit more on the principal output pathways of the cerebellum, how the cerebellum influences the rest of the motor systems. Then in the last half of the lecture I'll discuss four experimental



approaches that reveal some of the key functions of the cerebellum.

Chapter 2: Motor System Hierarchy

I showed this slide last week, the motor system hierarchical organization with cortical areas projecting either directly to the spinal cord or through brainstem motor control pathways. The cerebellum, as well as the basal ganglia—which will be topic of the second two lectures this morning—both of these structures influence the kinds of movements we make, the excitability of muscle, as it were, not directly through their actions on the spinal cord, but rather through actions on motor pathways. And for the cerebellum, those actions are directed in a very strong way, both through projections to brainstem motor control systems, and via the thalamus to the corticospinal system.

Now the cerebellum receives a lot of sensory information, somatic sensory information, from the spinal cord by way of the spinal-cerebellar pathways. I'm not going to go into the anatomy of those pathways. They are very complex and it would be a kind of a lecture in and of itself. But it's getting sensory information that occurs as a consequence of our motor actions. It's also getting information from cortical control centers, both executive and the basic primary motor cortex, that's providing a signal for what the intent of the motor system is, and so it's poised to compare intent and action through its comparison of internal control signals and sensory feedback as a consequence of the movements. The influence of the cerebellum, as you can see from this kind of a diagram, is at multiple levels—through different levels of cortex, brainstem—but not directly with the spinal cord.

Let's consider the functional anatomy of the cerebellum. So here's the cerebellum. Cerebellum is packed into very tight, what are termed folia, they're kind of like the gyri and sulci of the cerebral cortex, but they're much thinner and much more densely packed. If you spread out the folia, if you unfold them and flatten them out, it becomes an enormous area. And just checking the literature, and checking the Web, the range is somewhere between 1 and 10 square meters. Even 1 square meter is a pretty big area; 10 square meters, you can fill up a lit-



the hallway with it. So there's a lot of surface area. There are a lot of neurons in the cerebellum, more than the rest of the brain, and they're packed into these thin sheets, and densely packed within the posterior cranial fossa.

This is a video, and I'll show it again because it kind of happens quickly, and it's revealing the surface of the cerebellum and the deep nuclei. What popped out a moment ago, were the three bilaterally paired deep cerebellar nuclei. Let me go back and we'll look at it again. So deep to the cortex are the deep nuclei, and there are three of them. There's one that's large and two that are tiny. But this view here is basically a transparent view of what we saw just a moment ago as a still picture. Here we have the cerebellar cortex, and shaded here are the deep cerebellar nuclei. The cortex is here on the surface packed into these dense folia, and the three pairs of nuclei. We've got the dentate nucleus, which is the largest and the most lateral nucleus. In humans it's an enormous nucleus. If you look at the increase in the size of the dentate nucleus throughout phylogeny it really becomes disproportionately bigger in monkeys and humans. The fastigial nucleus is the most medial nucleus, and it's quite small. In people it's very small, in birds and fish it's actually the largest of the nuclei, and we'll see why that's the case in a short while. And then the interposed nuclei are sandwiched between the dentate and the fastigial, and these, too, are not very large in people. They're linked very closely with body surface receptors, and they're enormous, as you would expect, in whales.

Let's look a little bit at the input-output organization of the cerebellum. Here's a dorsal view of the cerebellum and brainstem and thalamus. And this drawing is a horizontal section in this plane—it's actually flipped. This is the dorsal surface in the picture, and this is the dorsal picture in this drawing of the section. What we don't see in this picture is the pons; and this is the ventral surface of the pons, and the pons and the cerebellum are closely attached because of the cerebellar peduncles; and these squiggly lines here correspond to the cerebellar cortex; and the dark tracings deep within the white matter under the cortex are the deep cerebellar nuclei, fastigial, interposed, and dentate. The vestibular nuclei are also shown here, and it's shaded in light blue. It's kind of not really sure whether it's a deep cerebellar nucleus or something entirely different. As it turns out there are



aspects of the anatomy of the vestibular nuclei that are very similar to that of the deep cerebellar nuclei. And so what's probably going on there is that there are multiple populations of neurons, and for some reason in early development they haven't sort of separated out into discrete regions. There's a component of the vestibular nuclei that's very much like the deep cerebellar nuclei. We'll come back to this in a bit.

Now, it's sort of attractive to think that cerebellum means "little brain." There's a cortex, there are deep nuclei underneath the cortex—kind of like maybe the thalamus, so maybe it works a lot like the cerebral cortex where input is fed through the thalamus and then up to the cerebral cortex. Well that's not the case for the cerebellum. Information coming into the cerebellum is directed both to the deep nuclei as well as to the cerebellar cortex, as shown schematically here. And we'll come back to it in a few minutes, but there are two extrinsic inputs to the cerebellum, two major inputs, and they're termed "mossy" and "climbing fibers." But both of these inputs are directed to neurons in the deep nuclei, as well as in the cortex.

Now we know a lot about the microcircuitry of the cortex and less about what it all means. To a first approximation, we kind of think that an important path through the cerebellum is this circuit from outside the cerebellum synapsing on neurons in the deep cerebellar nuclei, and then those neurons, in turn, project out of the cerebellum to contact other areas of the motor systems, notably the descending motor pathways. So there's this kind of loop. Then the function of the side loop through the cerebellar cortex is that of modulating the actions of this pathway. The inputs directed to the deep nuclei are excitatory, and the deep nuclei neurons themselves release an excitatory neurotransmitter at its output. It's a basic kind of circuit, like you think about in other neural systems. The path through the cortex is a little different. The input to the cortical neurons is excitatory, but there's one neuron in the cortex that projects out of the cerebellar cortex to the deep nuclei: that's the Purkinje neuron, and that uses an inhibitory neurotransmitter. It actually inhibits the nuclear cells. It's kind of like in a radio—you turn on a radio and the transmission is from radio waves into the radio, and it's transduced into a sound that you hear, so that's the main information path. And



then by turning the volume knob you modulate that transmission, make it louder or softer. That's what we think the cortex is doing in relation to features of motor learning and adaptation and other complex aspects of motor control.

Let's go into this a little bit further. But to go into it further we have to sort of step back a little bit and consider the global sort of functional compartments within the cerebellum. So I gave you a sense of the basic loop. Now I want to give you a sense of how general categories of motor control are mediated by different parts of the cerebellum, and then we'll re-evaluate circuitry.

Chapter 3: Functional Anatomy of Cerebellum

Here again we're looking at the dorsal surface of the cerebellum and the brainstem and the thalamus and parts of the basal ganglia. And gross anatomically there's a midline region of the cerebellum called the vermis, and then there's the cerebellar hemisphere. The cerebellar hemisphere has an intermediary hemisphere and a lateral hemisphere. If we cut the cerebellum from the pons and flip it around, this is what we see. And so the vermis swings over the top, sort of down in here, the intermediate and lateral hemispheres. But what's important about showing this underneath view is the flocculonodular lobe, which is a distinct part of the cerebellum. It's involved in balance and eye movement control, which I'll mention further in a moment. It's kind of tiny, and it's tucked deep underneath the cerebellum in people. In birds and fish that rely more on this function then this is actually one of the largest parts of the cerebellum.

The vermis and the intermediate hemisphere together are termed the spinocerebellum. And they're termed the spinocerebellum both in terms of its inputs and its outputs. In terms of its inputs, it's getting information—this part of the cerebellum is getting most of its information from spinal cord pathways. A lot of that information, not surprisingly, is to convey mechanosensory information from our muscles and joints and skin up to the cerebellum through the spinocerebellar pathway. The output of the spinocerebellum is by way of the motor pathways back down to the spinal cord. Going down to the spinal cord it's not surprising that it's involved in the control of limb and trunk motor functions.



Now the cerebrocerebellum anatomically corresponds to the lateral hemisphere. The cerebrocerebellum gets most of its input from the cerebral cortex, with diverse areas involved in sensation, cognition, emotions. This area of the cerebellum is involved in the planning of movements, as well as more. And we'll see the more aspect shortly. In humans the cerebrocerebellum is physically the largest. Then we've got the vestibulocerebellum, which anatomically corresponds to the flocculonodular lobe; it gets most of its input from the vestibular apparatus. Through its outputs, it's involved in the control of eye and head movements, and through its projections to spinal pathways in the maintenance of balance. These are the three functional divisions: spinocerebellum, cerebro-, and vestibulocerebellum. What's fascinating is that the underlying circuitry for each of these regions of the cerebellum is identical. So the microcircuitry is identical. What distinguishes the functions of these different functional divisions of the cerebellum is not the microcircuitry, but the kinds of inputs and where the cerebellum neurons are projecting the outputs. But the intrinsic circuitry is the same.

Let's look further into that. This is a section, it's a sagittal section—that's not so important for our purposes, Nissl-stained section through the cerebellar cortex. And so there's a region out here that doesn't contain many neuronal cell bodies, then there's a region in here that's very thin, and then one that's densely packed with cell bodies. This outer region is called the molecular layer, then we've got the Purkinje layer; and that's where the Purkinje neurons are located, the cell bodies are located; and then the granular layer, which has a collection of interneurons. This has the highest neuronal packing density of any area in the brain. Then finally there's the underlying white matter of the cerebellum.

In the next slide I'm going to blow up this area and we'll look at some of the microcircuitry. This would be one of the folia, a folium of the cerebellum, cut in cross section. Here we're looking at a folium, it's running along here. And so there are a fair amount of identified neurons within the cerebellar cortex. Beginning with inputs, there's the climbing fiber input which originates from one place in the nervous system, the inferior olivary nucleus; and then the other input is the mossy fiber, and that mossy fiber input comes from just about anywhere,



spinal cord, various kinds of brainstem nuclei.

The output neuron of the cerebellum is the Purkinje neuron—that's this guy here—and then we've got a variety of interneurons that I'll talk about in a moment. The output neuron, the Purkinje neuron, is truly an extraordinary cell. Here's the cell body, and that cell body is living within the Purkinje layer, and it sends off apical dendrites into the molecular layer that reaches probably a millimeter or more in length. On this enormous dendritic array are many hundreds of thousands of synaptic contacts, integrating information from a lot of sources.

Now interneurons. We've got the granule neuron which is slightly shaded here. That's an excitatory interneuron. And then we have three classes of inhibitory interneurons—the stellate, the basket, and the Golgi—which are also here.

Let's look at a particular circuit, let's look at the mossy fiber circuit. Input from the mossy fiber coming from a variety of sources in the brainstem synapses on granule neurons in the granular layer. The granule cell sends an axon up into the superficial part of the cortex, and when it gets up there the axon bifurcates and runs along the long axis of the folium in order to contact many thousands of Purkinje neurons. But each contact is kind of very minimal, just one or two synapses on a given Purkinje neuron. And then the output here. An excitatory input activates the granule neuron, and this is also excitatory—activates the Purkinje neuron—but the Purkinje cell is inhibitory to its output. So excitation is transformed into inhibition. This will come back in the context of the basal ganglia in an hour or so.

The other major input is the climbing fiber input, and that comes directly to the Purkinje dendritic array. The reason why it's called a climbing fiber is that the axons wrap around the apical dendrites, like a vine around a tree, and make many thousands or tens of thousands of synaptic contacts. It's probably the strongest synapse in the nervous system. Then the output is again directed towards the deep cerebellar nuclei, excitation is flipped into inhibition. The inferior olivary nucleus is the only source of climbing fibers. Mossy fibers come from elsewhere.



What about these inhibitory interneurons? Well, basket cells, stellate cells, Golgi cells, the net effect of these inhibitory interneurons is to restrict the extent of cortex that's activated. One idea that we have is that in making very fine movements, like individuated finger movements, that the cerebellar control of that kind of behavior is very fine tuned, so there's just a small population of Purkinje neurons may be activating its output, as opposed to more diffusely activating the cerebellum; and there in turn diffusely activating its target systems in order to control multiple muscles, more and more diffuse kinds of behaviors. But the specifics we really don't yet understand.

Chapter 4: Organization of Cerebellar Circuitry

Now let's come back to the general organization in relation to the circuitry. This is a kind of a flattened out roadkill view of the cerebellum. This portion up here would be tucked underneath, and this portion down here would be tucked underneath down there, and this is flocculonodular lobe. So we've got the spinocerebellum. That, remember, corresponded to the vermis and intermediate hemisphere. The vermis is the portion that's on the midline. Purkinje neurons within the vermis send their output to synapse directly onto neurons of the fastigial nucleus—that's the deep cerebellar nucleus. The fastigial neurons send their output to contact neurons in the medial descending pathways, the pathways that are involved in axial muscle control. Purkinje neurons in the intermediate hemisphere synapse on neurons in the interposed nuclei, which in turn project to the lateral system, the rubrospinal system, the lateral corticospinal system. Together the lateral and the medial systems are important in motor execution—lateral for limbs and medial for axial and proximal control.

Purkinje neurons within the cerebrocerebellum in the lateral hemisphere project to the dentate nucleus, and the dentate, in turn, projects to a diverse set of motor areas in the frontal lobe, by way of the thalamus—not only the primary motor cortex but pre-motor areas; and we'll see it projects to association areas as well. It's involved in planning of movements and probably a lot more in people.



Finally there's the vestibulocerebellum, part of the flocculonodular lobe. Purkinje neurons in the vestibulocerebellum project directly to the vestibular nuclei, so that's why they're a lot like the deep cerebellar nuclei, because they're getting a monosynaptic input from the Purkinje neurons. This system is involved in eye movement control and balance.

I showed this slide last week, which is the somatotopic organization of the ventral horn. The interposed nuclei feeding into the lateral systems, and those lateral systems descending laterally in the cord to influence the lateral part of the ventral gray matter and the vestibulocerebellum—in the context of balance influencing the medial spinal cord systems here.

This will emerge as a dense circuit for the output of the cerebellum. I'm just showing it to sort of walk you through it. If you're interested in looking at this further you should consult a textbook because it's really too complicated to just step through here. But briefly, the lateral hemisphere and the intermediate hemisphere involved in limb control and balance and planning—the output of those parts of the cerebellum cross the midline and project to brainstem nuclei as well as the thalamic nuclei. The brainstem nuclei, notably the red nucleus, one of its projections is a cross-projection to the spinal cord, and the projections to the thalamus to the cortex. And of course we have the lateral corticospinal tract, a cross-projection to the spinal cord. So notice that there are two points of decussation: one here at the output of the cerebellum, and one at the level of the crossing of the motor pathways. And so this circuit underlies ipsilateral cerebellar control. Damage to the cerebellum or the cortex or deep nuclei is going to impact control ipsilaterally. This contrasts to the vermal and vestibular cerebellar control of body axis muscle. Here the deep nuclei project in a bilateral way directly to a variety of brainstem nuclei, reticular formation, vestibular nuclei—and that has a bilateral effect on movement control.

By the way, there's also a small ascending projection from the fastigial nucleus, in particular up to cortex, and then back down through the ventral corticospinal tract; and that's the small component of the corticospinal system that's important in some aspects of axial muscle control and balance. So we have these two con-



trasting systems. And this is the one that we think about a little bit more, the double-crossing of the output pathways resulting in ipsilateral cerebellar signs.

Chapter 5: Functions of the Cerebellum

Now I'd like to turn our attention to the functions of the cerebellum. I'm going to hit on three points: feed-forward control, motor learning, and some non-motor functions. Now feed-forward control was introduced by Dr Krakauer last week in the context of movement control plasticity. Feed-forward control—another term for it is anticipatory control—and it's very proactive as opposed to feedback kind of control. And much of our movements are directed—visually and goal-directed movements have an important initial anticipatory control function. For example, we're driving in a car, we see a stoplight and we put our foot on the brake pedal. It's a learned association, it's not like a reflex, it involves a lot of learning and a lot of context. As a passenger you see the red light, and unless you're like my wife you're probably not going to be putting your foot on the floor of the car. You see a light here, this is a green light, so that means acceleration. You don't just blindly apply these kinds of behaviors, they're very much context dependent. Predicting the location of a baseball, and a batter is trying to hit it. Maybe they can't even see the ball coming at them, so it's even more complex than just a simple visual motor transformation; they're actually anticipating where that ball is going to be at some point; and hitting ducks in a penny arcade. Those are all aspects of anticipatory control.

What's the cerebellum's role in this? Well, it's a very low level kind of control, a very subconscious kind of control. We don't really understand intuitively what happens when we learn these associations, they just sort of happen. And they're a very particular kind of associations. There's little generalization that may occur. So a pink light may not invoke the same kind of response at a red light—certainly amber doesn't.

The learning of these relationships are implemented through the projections of the cerebellum to the medial pathways. And some of the expression of lost anticipatory control in cerebellar disease are the delayed responses to stimuli. This



may not be something that one sees clinically, but tested experimentally one sees prolonged reaction time. There have been some studies in monkeys that suggest that delayed responses of the motor system to sensory information from muscle spindle receptors might contribute to tremor. And impaired anticipatory control can contribute to some of the errors in movement extent in cerebellar disease, like the hypo- and hypermetria.

Let's turn to motor learning. Now there's been a lot of work on the cerebellum's role in motor learning. This is a little bit esoteric, but it's a neat and pretty clear expression of the role of cerebellum in adapting our sensory awareness to movement control. This is kind of a single case presentation of a patient who is a world-class dart thrower. This is work of a neurologist at Washington University. And so she had a unilateral stroke involving occlusion of the posterior inferior cerebellar artery (PICA). What the investigators did was to examine her ability to throw darts; and she could do this with either hand, before and after putting on horizontal displacing prisms. These are prisms you put on over your glasses and it can displace the world right or left by varying degrees. If I had these prisms on, my head is straight but I'd be looking off to the side, and you'd go to shake your hand like this. Well what happens? Before she puts on the prism she's asked to throw darts, and we're just looking at the horizontal error. The bull's eye is kind of at zero, and if she's off to the right or to the left, we're measuring that as displacement from that midline region. She puts on the prisms, and not surprisingly the first time she throws a dart its way off, because she thinks that that's where the dartboard is, because that's where she sees it. But she's getting feedback that she's missing it by a long shot, and so over a remarkably short period of time—remember each dot corresponds to a new throw—she's pretty much back on target. Maybe after 10 or 20 dart throws she's as accurate as she was before. Take the prisms off and now that adaptation is maladaptive, and so it flips to the other direction. But she learns actually a bit more quickly to come back to accuracy. Actually you can train people and animals to perform under these two conditions, and they can be pretty quick in adapting.

This is with the good arm. What happens on the side where there's been PICA occlusion? Well, before she puts on the prisms, her performance is not much dif-



ferent from before. That's not surprising with a lot of these well practiced behaviors. But now we're asking her to do something different with the prism. And look what happens: immediately there's an increase in error, but there's no adaptation. In fact, it may even drift a little bit worse. In contrast to the good side, where she adapts quickly, there's no adaptation on the impaired side. Not surprisingly when the prism comes off, she goes back to normal behavior instantly because there's no maladaptive response that has to be now re-adapted. This points to the importance of the cerebellum in this aspect of motor learning involving adapting our sensory awareness and matching it with what's needed in controlling particular movements.

In this experiment it identifies non-motor functions of the cerebellum. This is something that has been coming up more recently in human brain imaging studies and a lot of animal studies. In this experiment it's a normal human subject, and it's functional magnetic resonance imaging. And so what we see here is kind of like an earlier picture that I showed, but flipped. Here's the cerebellum, cerebellar cortex. This is the region of the deep cerebellar nuclei, and this is the base of the pons. This white stuff here is the region of the fourth ventricle and CSF in the fourth ventricle. The color scale here is from green—which means that there's very little increase in blood flow in these areas and minimal neuronal activation—to bright red, which is maximum neuronal activation; and that's with a run of blood flow, and that transforms into more activity in neurons.

And so there are four tasks that we're going to look at, two are sensory and two are motor. In the two sensory tasks the first task is here, and what the subject is doing is basically just sitting in the scanner with his or her palm face-up, and sandpaper of different degrees of roughness are drawn across the fingertips, just like is shown here. They're monitoring the change in blood flow within the cerebellum. It's partly sensitivity and partly just the anatomy that you tend to pick up a little bit more of a signal within the deep nuclei, because everything is sort of collected together. Now in this very passive kind of stimulation paradigm, there's little activation of the deep nuclei, and it's mostly on the ipsilateral side. In this condition the subject has to discriminate roughness, so not just sit there passively but actually has to think about whether something is a bit rougher or less



rough. When you add that discrimination element it increases the amount of activation within the deep cerebellar nuclei, and you can see areas of cortex coming up. In fact, some areas become maximally activated. So there's no movement going on here, it's just things that are going on up in the subject's head. This clearly points to the ability to dissociate cerebellar activation from production of a movement.

This is further shown in this pair of experiments down here. Now the subject has to perform a motor task. The subject's hand is in a little bag. There are ball bearings in the bag, and the diameter of the ball bearings are different. In this condition the subject basically has to pick up with simple oppositional movements of two fingers, pick up a ball bearing and drop it—pick up, drop, pick up, drop—during the scanning period. Even though this is a very precise kind of movement there's hardly any activation of the cerebellum. Here the subject has the same sort of motor task, but instead of doing it mindlessly, now the subject is picking up ball bearings that have a particular diameter, so they're making discrimination, so they have to feel it. When you add the sensory component to the task it causes maximal activation of the cerebellum—in fact bilaterally here. So again, it's more than just simple movement control. Here it's probably the combination of sensory input that's important in triggering and guiding the movement. This shows that it can be involved in non-motor functions; this shows that the cerebellum may not be involved in a fairly skillful kind of movement, and it's not until we tack on sensory discriminations that we maximally activate the system. It's more complex than we would've thought.

How is this kind of control implemented? Well, it's implemented in a very direct way through the cerebellar projections onto the medial and lateral pathways, especially the corticospinal tract. The intermediate cerebellum, the output projecting into the VA / VL nuclear complex of the thalamus, and from here through the internal capsule to the primary motor cortex for executing movements—this would be the key pathway.

How would more complex functions of the cerebellum be implemented? Well, many of these functions can be incorporated into motor programs via projections



to diverse frontal motor areas, the so-called pre-motor areas, supplementary and pre-motor cortex. And here, again through the VA / VL complex but through different sub-nuclei, through the internal capsule to pre-motor cortex involved in the planning—as opposed to the direct execution of movements.

And then finally, how does all of this learning and non-motor of the cerebellum become incorporated into control? We think that an important aspect is to become incorporated into our motor strategies, and this is through projections to pre-frontal cortex. Now we're really thinking about the dentate nucleus and lateral cerebellar hemisphere and its projections to the medial dorsal nucleus of the thalamus; and from the medial dorsal nucleus to the dorsal lateral pre-frontal cortex, which is involved in diverse higher functions, including movement strategies and working memory. But of course all of these things are happening concurrently during any kind of movement, as we're optimizing the movement. This is a good example of parallel output control from the cerebellum.

Chapter 6: Cerebellar Cognitive Affective Disorder

Now this is a nice segue into the last point that I want to make, which is kind of pushing the envelope in terms of non-motor functions of the cerebellum. This is something that is largely the work of a group of neurologists up at Harvard where they've been examining patients who primarily have damage to the posterior part of the cerebellar cortex and parts of the vermis, and they've termed this condition a cerebellar cognitive affective disorder. What they see is less in the way of movement control impairments and more in the way of impairments in executive functions, spatial cognition impairments, frank personality changes, and language disorder aspects. Now this could be a lecture in and of itself, but it's really very intriguing because we've got in the human cerebellum a huge dentate nucleus, huge lateral hemisphere—and lord only knows how much of that is projecting to some of these integrative areas of the thalamus and then up to cortex. I've just shown what we know from the monkey, the projections through the medial dorsal nucleus to dorsal lateral pre-frontal cortex and anterior cingulate cortex; and so that's one path by which the cerebellum can influence cognition and emotion.



To sum up, cerebellar lesions in the doctor's office don't produce weakness but more along the lines of incoordination and errors. Patients lose the ability to anticipate the consequences of motor actions, lose the ability to make corrections—like this patient with the PICA occlusion—an inability to adapt to the horizontal displacing prisms. Motor learning requires a lot of sensory awareness, and we think that that's sort of the key to beginning to understand some of the non-motor functions of the cerebellum. These functions are going to be mediated through complex projections through frontal motor areas, and then ultimately through the descending motor pathways.

The cognitive and emotional disturbances are very curious. We've got a sense of the anatomy that could underlie this, but we really don't have the foggiest idea of what it really all means. But what's kind of intriguing is that it may be that some of this skill learning and automaticity that we understand a little bit better in movement control may also apply to learning skills in language, learning skills in reasoning as well.

The bottom line is that there is no bottom line, there's no single function. Clearly it's mostly involved in motor and in motor learning and optimizing our motor behaviors, but some of these learning and optimization algorithms are probably going to apply to cognitive emotional behaviors as well.

Thank you.

So let's not take a break. We're set to go for Dr Mazzoni. This is Dr Pietro Mazzoni. Dr Mazzoni is a neurologist in the neurology department, and his research area is that of movement control and movement disorders.

Chapter 7: Pietro Mazzoni—Cerebellar Dysfunction

Pietro Mazzoni: I will give a brief presentation on the clinical signs of cerebellar dysfunction, and give a very quick overview about cerebellar diseases. This is difficult. Last year I tried to do it as an overview, listing all the possible diseases



or most of them, and that doesn't really work. So what I will do is have three slides—there are three types of diseases: one sporadic, one hereditary autosomal dominant, one hereditary autosomal recessive, and I will give just an example of each of these categories and leave it at that. It's a very large area of neurology.

But before that I'll just show the clinical signs with a few video clips. This is cerebellar dysfunctions and clinical signs, the 15-minute version.

I listed the dysfunctions the way we do in neuro examination. We start from the top towards the bottom in the areas of the head or cranial nerves. One dysfunction is in the eyes, and you get nystagmus. Nystagmus means oscillation of the eyes, repetitive movements of the eye—that's a very general term. In particular you know it as the eyes beating to one side, in one direction, very fast and coming back slowly. And you'll see an example of this. For those of you who already know what nystagmus is, a special point is that it may be gaze evoked, meaning it happens when you're looking to one side or the other—that can happen with any kind of nystagmus. It can be horizontal, vertical, or torsional. The eyes can go horizontal, vertical, or rotate in a beating fashion, and if you see that, it's a strong sign of cerebellar dysfunction. Other dysfunction like vestibular nerve injury can give you nystagmus that is always horizontal but if you see a vertical or torsional component, then it's a strong clue the patient may have an infarct and deserves admission to the hospital. The saccades can be slow and the saccadic dysmetria (I'll say what dysmetria is in just a moment), speech can be dysarthric, pasty, and difficult to understand and disorganized and it can also have a rhythm problem. It sounds like scanning speech. You hear an example that's not quite perfect but the rhythm of speech can be affected. Going down, when you examine the limbs, you look for trajectories in movements. You get dysmetrias. Dysmetria is abnormal metrics of movements. Metrics are speed, accuracy of movement, so if you make a movement back and forth, dysmetria just means that you don't go correctly; it may be that you miss the target or it may be that you get there in a non-straight fashion. And so dysmetria means the same thing for saccade, that you miss the target. You'll see an example of that.



Dyssynergia means bad force organization, and it's an example of trying to maintain force and there's an abnormality of organizing forces. Dysdiadokinesia is a special word, because if you can say it fast three times in a row you become a neurologist or you can do residency. So dysdiadokinesia is a compact way of saying impaired rhythm of rapidly alternating movements. You'll see an example of that, but basically if I ask you to do something repetitive back and forth, like this, you see a very special deficit from cerebellar dysfunction. "Intention tremor" is in quotation marks always—never leave the quotation marks out because it's a debatable term. A tremor can be a rest or an action, but if you start saying intention, you have to know what intention is, and we don't know what intention is, especially in the context of a neurological exam. What we mean is that it gets worse towards the end. Not only cerebellar lesions do this, but cerebellar lesions can give you tremor that as you make a movement, becomes bigger and bigger toward the end. The other reason for the quotation marks is that dysmetria can look like that also. If you try to move fast and you're not moving straight it looks like a tremor. So these two things both happen but they can look like each other. Hypotonia means that tone is decreased, and that's unexpected, unusual; we can't explain why, but I'll show you an example of that. Now gait ataxia is a fancy word that keeps us neurologists separate from the rest of the masses—ataxia, Parkinsonian, hemiparetic—and you shouldn't let us cheat you out of understanding what it is. Ataxia means for gait, wide-based and with irregular cadence. So wide-based you can see the feet are far apart. The rule is more than your shoe size is abnormal. Imagine a patient's foot, turn it sideways, if the heels are more than that much apart that's a wide-based gait, one manifestation of positional ataxia. The other is cadence. You can close your eyes and listen to the walk. If it's like this it's normal; if it's like this, but irregular, is also ataxia.

Chapter 8: Clinical Examples

And now some examples. You're going to see nystagmus. The patient is looking voluntarily, following my finger left and right, but you see that the eyes beat up and down—actually it's diagonal. The beats are fast in one direction, slow in the other. That's nystagmus of most kinds. The fact that they're vertical is strong proof that this disease is cerebellar, not just a temporary quick infection or



inflammation of your ear. Here is making saccades up and down, and they're slow. Keep those in mind. You shouldn't be able to see an eye moving during saccade; you see the beginning and the end. And these are hypermetric saccades. The eye comes back to the midline, overshoots, and then goes back. Those are hard to see. Should I play that again? I won't repeat every one of them, but the eyes are difficult. You're going to see the eyes moving with nystagmus, diagonal beating. The saccades are hard to see. You're going to see the vertical saccades; you'll see the eye actually moving as if it were a slow tracking movement in a moment, and that makes it slow. If you see the eye moving during a saccade, that's a very slow saccade. That one is slow, right there. That one is slow, that one is even slower. And here sometimes you'll see that the eye bounces a little bit before stopping. That's because it overshoots a little bit and then corrects. I'm going to move on because they're never going to be very clear in 15 minutes.

If you have audio then you should hear the patient speaking. Can we have audio? Can we try again with audio? The computer volume is up, the input is in. It's just one slide with audio. You're going to hear the speech is slow. Dysarthria is obvious. Dysarthria means you sound like you're drunk or slowed—it's pasty and the enunciation is not good, different from an accent, which is what you heard in me asking him what to say. Many neurological problems can cause dysarthria. You may also have noticed that the tone of the sentences were not quite right. The pitch will go up and down, and the speed between syllables was not quite right. It's not the best example of it, but that's an aspect of scanning speech, the timing of speech and the pitch reflecting prosody, and when the pitch goes up and down in a sentence gets affected. And that reflects a coordination problem that is quite specific to cerebellar impairment—specific meaning pretty much only a cerebellar lesion can cause it, but it's not common. You can have cerebellar lesions without this.

You're going to see the first half a second, which is nothing, and then you're going to see dysmetria—that's abnormal trajectory, so the line of the movement is not straight. And then dyssynergia, he won't be able to hold his hands in one position steadily. I'll show you a little bit more. The trajectory of a finger-to-nose



test, normally straight. He actually missed the target, and on the way there the movement is not quite straight. So how that can look like a tremor—here oscillations, but those are mostly corrections to the normal trajectory. That's a finger-to-nose test and it's dysmetric, it's not straight. This is the heel-to-shin test. It's a check for trajectory of movement in the limbs. See how he makes a wave, S-shaped wavy movement? That's abnormal heel-to-shin. It reflects dysmetric control of the legs.

This is also dysmetria, it's a finger tracking task. I ask him to hold his finger right in front of mine, and stay with it, wherever I go. He overshoots and then comes back. See that? And there are [inaudible] oscillations after the movement to make corrections for the error.

Here it's more about force. It's a checking task, we call it a checking task. We ask him to check his movements or posture. I'm asking him to hold his arm steady. Every time I do it, I push down and let go—he hits my hand. Most people after a couple of trials don't hit my hand anymore. The hand is there to prevent a severe impairment from hitting his face, a problem for hitting his face. That's impaired checking, impaired control of steady force. And as Dr Martin said, that's not weak; he doesn't have any problem of strength, but there's a problem controlling how to apply strength over time.

This is dysdiadochokinesia. The task is to tap your hand on your thigh, first palm down and then palm up, and then do it as fast as possible. If you're weak you do this slowly, but you never repeat. He repeats, he gets the rhythm wrong, it can't alternate all the time. That's specifically cerebellar, we call it a coordination problem. Something about the timing of movement is impaired. He can do it slowly, and ask him to do it as fast as possible and instead of not being able to go fast—he does speed up—but he ends up making mistakes on repetition. Only a few happen, but if they happen that's cerebellar. This is impaired alternating movements of the feet. See how it's irregular? He can make every movement in the range that's required. Every movement that he makes is normal, but he can't make a sequence of them all the same. That's dysdiadokinesia.



Finally I have gait ataxia. You're going to see gait ataxia. It's wide-based and the cadence is irregular. He also looks a bit unsteady. Never let a patient do this without first walking with him. You're going to see him walk alone, and he looks a bit unsteady, but I'd already walked with him before and determined that he could do it by himself.

And then arm hypotonia is very hard to show in a video the way we normally test it because it's a feeling. It turns out that if you can see tone reflecting in the arm swing. If you have rigidity, as in Parkinsonism, the arm swing is reduced. If you have excessive low tone, the arms flail a little bit, so you'll notice that also.

The gait is borderline wide-based. It's not as wide-based as you can see sometimes. This is a chronic cerebellar degeneration, so he's adapted and it's not very severe in terms of wide-based, but many steps are wide. That's not quite the distance between the heels that most of us have. His arms every once in a while flail a little bit, they go a little bit more than most of our arms will go, right there. That's hypotonia. And then the sequence of steps and timing is irregular.

Two slides on localization. You can localize sideways, that's actually, the [inaudible] are here, and then there's a lateralization slide. As far as localizations, you heard a lot about the anatomy. You can map some of these deficits, as Dr Martin already said, as far as medial cerebellar, hemisphere and vermis, lateral cerebellar hemisphere and vestibular cerebellum. Axial signs, like gait ataxia, happen from medial cerebellar hemisphere and vermis lesions. The example is alcoholic cerebellar degeneration, which can give you pure midline cerebellar degeneration. If you hit on a hemisphere, for example, with a mass lesion like an astrocytoma, you will get appendicular signs—that's a fancy word for limb—and you get limb dysmetria on one side if it's focal, a mass lesion.

Then from the vestibular cerebellum you see some eye abnormalities that I showed you, and the balance abnormalities that I didn't show you. Nystagmus, gait ataxia, and a brainstem infarct is a common example because it'll catch the pathways to the vestibular cerebellum or related structures. As far as organization, you've seen this in a slide with the drawing, and here I'm testing your ability



to recall from working memory that picture and then translate words into a visual image. But just to spell it out very obviously, a lesion of the right cerebellum produces right side cerebellar signs. That's because the right arm is controlled by the left cerebral hemisphere—fibers that go down to the left midbrain and pons. Those fibers go across and go to the right cerebellum; and then they cross back and go into the left medulla; and they cross again at the position and go into the right spinal cord. So right cerebellar lesions gives you ipsilateral signs.

Chapter 9: Categories of Cerebellar Diseases

The categories of cerebellar diseases are sporadic, meaning one person has it but with no relationship to a family—or familial, hereditary, either dominant or recessive pattern. Three slides. Examples of sporadic cerebellar conditions, I made them visual. Chiari malformation is a structural problem. The cerebellum slides down into the spinal canal and pressure here can give you ataxia. The vermis and the tonsils, midline structures can go into here and be compressed and so you get gait ataxia. A tumor—cerebellar astrocytoma—young people, that's bad. Even though it's very slow and you can adapt very well to it, but you still want to take it out. A cerebellar infarct, right here. Alcoholic cerebellar degeneration, not obvious, but this is the vermis and you see space between the folia. This is the hemisphere and you don't see space between the folia, so the midline vermis is very much affected. It's why alcohol eventually makes you unsteady all the time, and supposedly damage to this brain structure makes you unsteady acutely when you walk out of the bar. Multiple system atrophy, it's a Parkinsonian syndrome. This cerebellar would be normal in many people of old age, but then you should see black also in the cerebral, whereas this cerebellar atrophy is quite out of proportion to the rest of the brain; so this is a cerebellar atrophy condition, OPCA [olivopontocerebellar atrophy], or multisystem atrophy in this case.

Then autoimmune conditions are worth mentioning because paraneoplastic condition, meaning antibodies to a tumor, cross-react—and here's a Purkinje cell—can give you cerebellar signs up to ten years before the tumor actually becomes clinically manifest. Knowing about this weird rare condition that has names like anti-Hu antibodies, anti-ANA 1—and many of them are the first two initials of the



person's last name, or the scientist's last name, so go figure. You find yourself saying anti-Hu, learning how to pronounce it, but you save someone's life because this can go with lung cancer, testicular cancer, and breast cancer, so you want to know that they exist. Celiac disease is also very common, and symptoms sometimes affect the cerebellum. This is a Purkinje cell with antibodies against it.

Dominant diseases are the SCAs, the spinocerebellar ataxias, 1 through 25, and counting. Used to be 1 through 8, and over the past ten years it's grown to 25 and who knows how many? And then episodic ataxia. They're all overlapping in the clinical manifestations. But SCA 3 was one of the first to be recognized, and the most common, spinocerebellar ataxia. It got its own name because it was named before we knew about so many of them, Machado-Joseph disease. And it's one example that they chose because it's most common. Just to tell you a couple of general principles. General principles are that the variable onset, this one is adolescence to late adulthood. Second, you have cerebellar things, cerebellar signs—dysarthria and dysmetria. In many of them you get plus signs, non-cerebellar things, gaze palsy, pyramidal signs. The eyes don't move—that's not nystagmus—that's a weakness of the eye muscles, inability to move the eyes. Pyramidal signs means corticospinal tract signs, you actually get weakness and spasticity. That's a general principle—these cerebellar diseases you get a cerebellar syndrome plus something else for most of them. The course can be very long, and many of them, at least twelve, are due to a CAG repeat expansion. You will have heard of this by the end of the morning, about Huntington's disease, but many very rare diseases seem to work by abnormal expansion of three base pairs in the DNA. So it's actually a special category of diseases. If we fix one of them by genetic techniques, we may be able to fix many rare diseases.

Friedreich's ataxia is what it shows as an example of recessive. It's also the most common recessive inherited ataxia. But here, to have to remember a dot dot dot, because in a dominant right now that's a closed category. I told you everything except I haven't listed each one of them. These are the ones we know. Whereas here you have Friedreich's ataxia, ataxiatelangiectasia, vitamin E



deficiency, and anemia, and a French person's name another ataxia, it goes kind of flat in different directions; we're still discovering them, and some of them are treatable, very few; but you want to know that some of them are treatable so when you go in the list you make sure that you send the tests for the ones that might be treatable.

Friedreich's ataxia follows some of the principles of the dominant ones. You have gait ataxia and then limb ataxia, so you get cerebellar signs; and then you have special features, non-cerebellar. In Friedreich's ataxia case you get polyneuropathy—again granule tract degeneration, which leads you to get weakness with hyperreflexia you get from neuropathy, but up going towards extensor plantar response, or Babinski sign, because of the corticospinal tract degeneration. Sometimes you can recognize them from a clinical presentation. The course can be very long, and this one is also repeat expansion; it's a different repeat, it's GAA, and the different mechanism, different category.

And then one very important function of the cerebellum is so that you feed your little sister a popsicle.

That's it. Thank you.