Cerebellum: Movement Regulation and Cognitive Functions

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The cerebellum is located in the back of the brain, just above the brainstem. Its important function is to regulate neural signals in other parts of the brain. Most is known about its regulatory actions on neurons that control movement and posture.

Introduction

For more than a century it has been known that the cerebellum is an important part of the brain for the control of movement. Although this structure is not necessary for the initiation of motion, movements become erratic in their size and direction when the cerebellum is damaged (a symptom called dysmetria). In addition to its role in regulating and coordinating movement, the cerebellum is considered an important site of motor learning and of adaptation following injury. Changes in the strength of the connections among neurons in the cerebellum underlie these adaptive changes.

The portion of the cerebellum that is closest to the midline of the brain, called the vermis, is phylogenetically the oldest. The vermis regulates the accuracy of trunk, leg, head and eye movements – movements that are critical for the control of posture, locomotion and gaze. The intermediate portion of the cerebellum regulates the accuracy of movements that we call voluntary: the reaching and grasping movements that we use to obtain and manipulate objects with our hands and arms. The most lateral parts of the cerebellum are called the hemispheres, and they regulate higher aspects of behaviour. The hemispheres are small in lower animals but become quite large in humans. The increase in the size of the cerebellum in the course of evolution generally parallels the enlargement of the cerebral cortex in higher mammals, a process that is called encephalization. Neuroscientists are currently discovering how the cerebellar hemispheres are used to regulate higher cerebral processes, processes that plan complex movements and processes that participate in cognition and thinking. These recent discoveries make it clear that the cerebellum does much more than regulate movement.

Organizational and Operational Principles

In this section, the most salient organizational features of the anatomy of the cerebellum are reviewed briefly, and related to operational principles, focusing on a relatively well understood part of this structure, the intermediate cerebellum, which regulates the generation of voluntary movement commands.

There are two main divisions of the cerebellum: the cerebellar cortex and the cerebellar deep nuclei (**Figure 1**). The cortex is specialized for processing extremely large
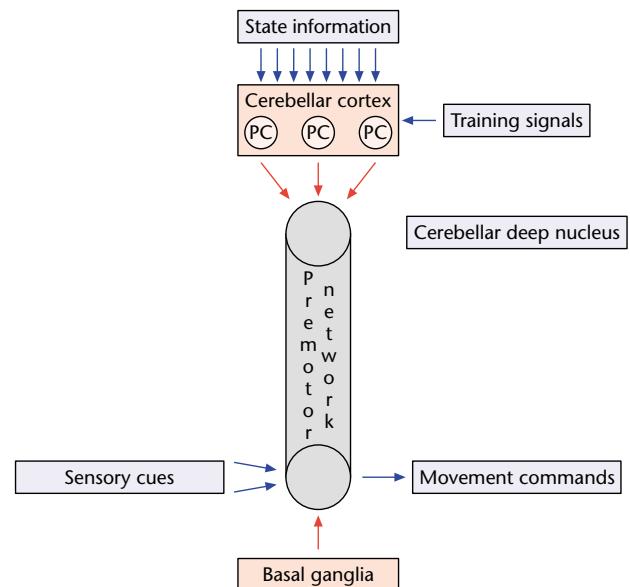

Figure 1 Signal flow through the cerebellum and its relationship to sensory–motor integration in the premotor network. The red arrows indicate an exclusively inhibitory projection onto a small cluster of neurons in the cerebellar deep nucleus. PC, Purkinje cell.

amounts of information about the states of body parts, of objects around us and of ongoing brain activities. This variety of information is conveyed to the cerebellum by its mossy fibre inputs. The state of body parts is monitored by our kinaesthetic receptors, which signal the forces, lengths and velocities of the many muscles throughout the body and the strain and motion of the skeletal joints. The state of the world is monitored by our tactile receptors, which sense contact forces, shears and locations of nearby objects, and by our visual and auditory systems, which analyse the properties of more distant objects in the world around us. The state of our brain is monitored by collateral projections from brain areas that deal with motivation, perceptions, goals, actions and current thinking. This great variety and large number of mossy fibre inputs project to an even larger number of the small granule cells that are located in the granular layer of the cerebellar cortex. The axons of the granule cells then ascend into the molecular layer to form an enormous sheet of parallel fibres. The latter transmit diverse state information to a large number of Purkinje cells (PCs in **Figure 1**). The PCs have elaborate dendritic fields that are specialized for receiving more inputs (over 100 000 to each PC) than any other cell type in the human brain. Each region of the cerebellar cortex contains a large array of PCs that process their parallel fibres' diverse state information in different ways, allowing the PCs to detect and classify many different patterns of state-related input that may occur. The results of each PC's processing are then transmitted to a small cluster of neurons in the cerebellar deep nucleus, a projection that is exclusively inhibitory (**Figure 1**). Because they are inhibitory, the signals from PCs cannot directly initiate neural activity in the cerebellar nuclei. However, these inhibitory inputs are potent and highly effective in regulating the spatial and temporal patterns of nuclear cell activity, which functions as the output of the cerebellum. The nuclear cells are excited by other causes. Their activity originates both from the intrinsic properties of the neurons and from excitatory synaptic input that comes from collaterals of fibres that project to the cerebellar cortex.

Let us now focus on the intermediate cerebellum and its regulation of voluntary movements. Intermediate regions of the cerebellar nuclei (nucleus interpositus and adjacent regions of dentate) receive excitatory collaterals from mossy fibres that participate in a recurrent network, labelled the premotor network in **Figure 1**. The premotor network for the intermediate cerebellum is comprised of an elaborate set of interconnections between cerebellar nuclei, red nucleus and motor cortex. Intermediate nuclear cells project to the red nucleus directly and to the motor cortex by way of the ventral thalamus. Both the red nucleus and the motor cortex transmit voluntary movement commands to motor neurons in the spinal cord and brainstem via their output fibres (the movement commands in **Figure 1**). Copies of these movement commands are sent back into the cerebellum, via mossy fibres originating in precerebellar nuclei, so as to inform both the cerebellar cortex and nucleus about what actions are currently being commanded. This collateral input to the cerebellar deep nucleus completes the recurrent premotor network mentioned above; it derives from collaterals of the same mossy fibres that provide some of the state input to the cerebellar cortex, although **Figure 1** does not show all of these details.

Since the projections throughout the premotor network are predominantly excitatory, they transmit positive feedback. If positive feedback is sufficiently strong, it will promote regenerative activity, which could provide the driving force that is needed to amplify and sustain activity in nuclear cells in the face of the potent inhibition sent from PCs. Present evidence supports this concept. Regenerative network activity could be initiated by any of the diverse inputs sent to motor cortex or to red nucleus, such as the inputs produced by sensory cues. This raises the question of how the initiation process is regulated. Initiation of network activity appears to be regulated by inhibitory inputs sent from the basal ganglia (**Figure 1**).

Once regenerative network activity has been initiated, positive feedback causes it to grow in intensity and duration, and to spread spatially throughout the premotor network. Inhibitory input from PCs in the cerebellar cortex would be needed to restrain this excitatory drive and to shape it into specific spatiotemporal patterns of neural activity. The intensity and duration of motor cortex and red nucleus activity should be regulated effectively by this process, and the resultant array of signals would specify the composite movement command that is transmitted to the spinal cord to control the limb musculature. This logic suggests that the functional role of the intermediate cerebellum is to ensure that the spatiotemporal pattern of its premotor network activity is appropriate to command accurate movements, particularly of the hands and arms, movements that serve to achieve the brain's intended goals.

How does the cerebellar cortex learn to perform this complex control function? There is a growing body of evidence that PCs learn under the guidance of an array of training signals that are transmitted to the cerebellar cortex by climbing fibres. Our currently limited information about climbing fibres is consistent with the concept that they transmit relatively specific error information to those PCs that are capable of reducing a particular movement error. As each PC is innervated by only a single climbing fibre, its training information can be quite specific. In contrast, recall that the PC receives more than 100 000 inputs conveying state information from its mossy fibre–parallel fibre system. The parallel fibre synapses that were activating the PC just before the climbing fibre discharged are weakened. This learning rule utilizes a mechanism for synaptic plasticity, which is called long-term depression (LTD). Computational models have demonstrated that the learning paradigm outlined here is capable of training PCs to control complex movements accurately, even in the presence of the substantial time delays that are present in

neural pathways. As the capability of a network to overcome time delays requires an ability to predict, it may be surmised that the intermediate cerebellum may be capable of functioning as a predictive controller of the spatiotemporal patterns of neural activity that ultimately command hand and arm movements. Predictive regulation of neuronal populations is also an extremely valuable feature for the postural, gaze and locomotor functions of the medial cerebellum, and for the movement planning and cognitive functions of the cerebellar hemispheres.

Regulation of Voluntary Movement Commands by the Intermediate Cerebellum

The neural signals that command the production of voluntary limb movements are transmitted from the brain to the spinal cord by the axons of neurons in the motor cortex (M1) and the red nucleus. These movement commands are comprised of activity in very large populations of motor cortex and red nucleus neurons. **Figure 2** illustrates some of the operational principles by using a simplified system including just four M1 command neurons, together with their cerebellar modules. Each of the numbered neurons is assumed to command movement in one of four directions: output unit 1 commands upward movement, 2 rightward, 3 downward and 4 leftward. Each of the output units is reciprocally connected to a cerebellar

nucleus unit that is regulated by inhibitory input from a PC. Adjacent to each module are two waveforms, meant to represent the discharge over time of the associated PC (upper trace) and premotor neuron (lower trace); the lower traces can represent either the nuclear neuron or the M1 neuron as both should burst simultaneously. Divergence of fibres within the premotor pathways (arrows between modules) allows activation to spread between adjacent modules. Consequently, a sensory stimulus (flash of light, or a tone) might activate unit 1. This small activation, although insufficient to drive movement initially, could serve to start positive feedback and regenerative activity within its loop, since that loop's PC inhibition is turned off. The resultant command signal would activate an agonist muscle for upward movement. Activity would tend to spread to the modules controlling units 2 and 4, because their PCs are producing only moderate inhibition. This would activate a co-contraction of right and left muscles that would stabilize the limb. In contrast, activity would not spread to the module controlling unit 3, because its PC is bursting and producing strong inhibition. Therefore, muscles that tend to move the limb downwards would be relaxed. In a more realistic model, there would be many more such modules, each controlling movements in intermediate directions that are distributed throughout the workspace.

This example assumes that the PCs have somehow been programmed to discharge with an appropriate time course. The upward movement command is a strong burst because its PC paused completely for the duration of the movement command. There is no downward movement command because its PC fired a strong burst during the period when positive feedback was present in other loops of the premotor network. The rightward and leftward movement commands are intermediate in intensity because their PCs do not stray much from their spontaneous level of activity. While these assumed patterns of PC activity are compatible with current neurophysiological data, the field is still lacking definitive experiments showing that the correct PCs in the cerebellar cortex generate appropriate patterns. The motor learning mechanisms discussed in the previous section should be capable of ensuring this, but it has not yet actually been demonstrated.

There is also increasing evidence that the motor cortex and red nucleus are organized not in terms of preferred directions of hand movement, but rather in terms of functionally useful groups of muscles. It is easy to see how such a system of 'preferred muscle synergies' might also be controlled by interconnected groups of cortical–cerebellar processing modules. Arrays of modules controlling grasp might be adjacent to, and interconnected with, those controlling limb extension. Postural responses could be coordinated by similar interconnections with modules controlling muscles of the neck, trunk and legs.
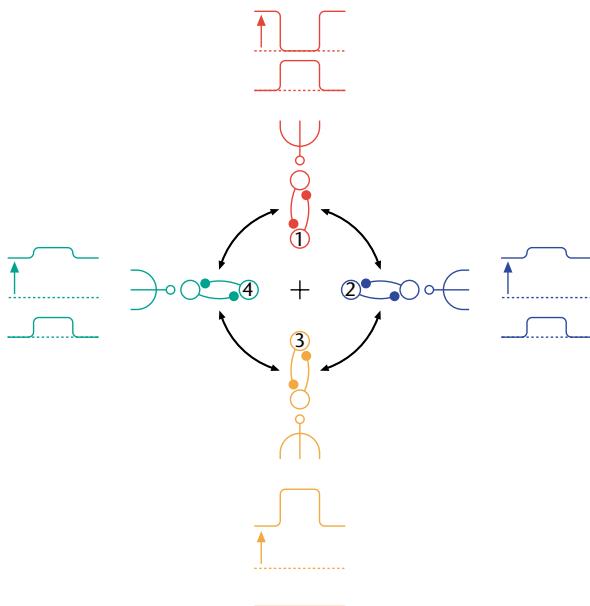

Figure 2 Regulation of movement direction by coordinating a small array of four cortical–cerebellar modules.

Compartmentalization: Microscopic and Macroscopic Modules

The microscopic anatomy across the whole cerebellum is remarkably uniform. The cells and their processes form well-defined circuits in parasagittally aligned compartments, and these microcircuits function, together with their premotor targets, as signal-processing elements called microscopic modules. It is likely that the basic signal-processing functions of one of these modules within either the vermis or the hemisphere is analogous to that of a module within the intermediate cerebellum. The modules in the three regions differ in the kinds of state information their PCs receive. Correspondingly, the PC responses reflect classifications of state that have different significance, and they project to different targets in the cerebellar nuclei.

A microscopic module includes a parasagittally aligned row of about 100 PCs, which send a focused inhibitory projection to a small cluster of nuclear cells. If the module giving rise to these projections is in the intermediate cerebellum, the axons of the nuclear cells project to the motor cortex and red nucleus, and participate in regulating the movement command that is sent to hand and arm muscles. If the module is in the vermis, however, the targeted cluster of nuclear cells may project to a focus in the brainstem, in order to regulate the movement command sent to eye muscles. Finally, if the module is in the hemisphere of the cerebellum, the targeted cluster of nuclear cells may ultimately project to the prefrontal cortex, in order to regulate the neural representation of a cognitive function. Thus, different microscopic modules regulate neuronal targets in different regions of the brainstem and cerebrum, utilizing the different kinds of state information that they receive.

The term macroscopic module refers to a substantial array of microscopic modules that share the same global function. For example, a reaching and grasping command sent by the motor cortex and red nucleus to the spinal cord might consist of neural activity in several hundred thousand corticospinal axons and a thousand rubrospinal axons. The regulation of this command involves a similarly large array of microscopic modules originating in the intermediate cerebellum. Other examples would be the array of microscopic modules projecting to ocular neurons in the brainstem to regulate rapid eye movements, or to an area of prefrontal cortex to regulate a cognitive function. In support of these modular concepts, neuroanatomical studies have demonstrated quite specific channels of cerebellar outflow that target different areas of the brainstem and the cerebral cortex.

Regulatory Functions of the Midline Cerebellum

The midline portion of the cerebellum, the vermis together with the medial nuclear zones that receive its projections, is involved in several regulatory functions, for example the stabilization of head and body posture, the coordination of locomotion and the control of gaze, using combined eye and head movements. The midline cerebellum has separate macroscopic modules for each of these regulatory functions. Among the special inputs that are critical for this part of the cerebellum are vestibular signals (which monitor head orientation and motion), visual signals and signals from various cerebral cortical areas. The downstream projections of these modules target many discrete regions within the brainstem, including a group of nuclei comprising the ventromedial descending system that control muscles of the trunk, the axis and the limbs, and underlie normal balance and locomotion. The various muscles must be well coordinated to control these automatic movements, a process that is accomplished by the combined actions of the many microscopic modules subserving each macroscopic function.

The control of gaze includes several types of slow and fast eye and head movements. The superior colliculus, one of the structures involved in the generation of fast gaze shifts, receives input from a macroscopic module within the cerebellum which is distinct from the one controlling locomotion and posture. Furthermore, slow 'smooth pursuit' movements are dependent on PCs in the flocculus and paraflocculus. If this area of the cerebellum is damaged, smooth pursuit movements are abolished. Unlike other PCs that project to nuclear targets within the cerebellum, these project to neurons within the vestibular nuclei and regulate vestibular neurons (VNs), which function like cerebellar nuclear cells. VNs from both sides of the brain are interconnected to form a premotor network analogous to the limb premotor network discussed above (**Figure 1**). The function of PC input to VNs is to shape their ongoing activity to form a movement command that accurately controls gaze. From the perspective of individual microscopic modules, the parasagittal rows of PCs need to control the time course of individual VN activity. Each VN potentially commands a smooth pursuit movement in a particular direction, and the vectorial sum of the commands generated by the entire macroscopic array of VNs produces a movement that is appropriate for pursuing the moving target.

Important components of the state information to the pursuit module are the signals from visual centres that monitor the motion of visual targets. Errors in the pursuit of a target are detected by climbing fibres that are sensitive to the motion of the target across the retina, called retinal slip. This provides the source of training information which, through the process of LTD, adjusts the synaptic

weights of the state information signals that the PCs receive. Each microscopic module receives climbing fibre inputs which are most sensitive to a particular direction of retinal slip. The module has output connections that command movements capable of correcting that direction of retinal slip. This process goes on in parallel in all of the microscopic modules until the array of output commands produces an eye movement that correctly eliminates retinal slip during the pursuit of the visual target. It is worth noting that this learning occurs despite the fact that the visually derived training information is delayed by about 100 ms. Hence synapses must be adjusted according to what they were doing before the detection of retinal slip. This is probably accomplished by the operation of a short-term memory function at the level of individual synapses, called a 'synaptic eligibility trace'. In this manner, PCs are able to generate a command that predicts where the eye should be in order to prevent retinal slip errors.

Cognitive Functions of the Cerebellar Hemispheres

The cerebellar hemispheres project mainly to the lateral cerebellar nuclei (also called dentate), and the dentate nuclei send prominent projections to a surprisingly large number of areas in the frontal lobes of the cerebral cortex. The frontal lobes have long been viewed as the brain regions where higher cognitive functions reside. Therefore, the prominent projection from the cerebellum to these areas implicates the cerebellum in higher cognitive function. The availability of brain imaging for research on human subjects has generated an impressive amount of data showing that the lateral cerebellum becomes active when a person participates in cognitive tasks or engages in the solution of difficult problems. Even some language operations, such as the generation of appropriate verbs from a list of nouns, give rise to activity in the lateral cerebellum.

Understanding the neurophysiology of cognitive signal processing is a particularly challenging problem. In order to use the time-honoured technique of microelectrode recording from single neurons profitably, animal subjects need to be trained in meaningful tasks, ones that invoke the higher levels of signal processing that are critical for cognition and problem solving. Remarkably, it has been possible to train monkeys to perform a 'working memory' task; this requires remembering a particular sensory event for a period of time, and then using this information to guide an informed behaviour. Neurons in localized areas of the prefrontal cortex show sustained discharges during the memory period that represent a neural correlate of the animal's working memory. When the sustained activity is disrupted, the monkeys cannot remember the sensory event to which they need to respond.

How might the cerebellum become involved in this cognitive function? We know from anatomical studies that a specific group of neurons in the dentate nucleus projects via the thalamus to this particular area of cerebral cortex. In analogy with the sustained activity in M1 during movement command generation (**Figure 2**), we anticipate that memory activity may be sustained and regulated by microscopic modules between the prefrontal neurons and the interconnected neurons in the cerebellum. Amplification and regulation of this sustained activity is important, as it would ensure the accuracy of what is being remembered. More experimental work needs to be done to confirm and elaborate this theory.

Summary

The cerebellum has a number of compartmentalized modules that share a similar circuitry and appear to be involved in the amplification and regulation of activity in the other parts of the nervous system with which they interconnect. Studies of the compartment that regulates voluntary movement commands have helped neuroscientists to understand some of the fundamental signal-processing mechanisms that occur in the various microscopic and macroscopic modules. Loops between neurons in the cerebellar nuclei and the nerve cells in the brainstem and cerebral cortical areas with which they connect provide a mechanism for amplifying signals in specific modules. This amplification is then regulated by the Purkinje cells in the cerebellar cortex, which are specialized for analysing information about the state of the body, the state of the world around us and the internal state of the brain. Their classification of state information is guided by learning mechanisms that adjust the synaptic inputs in a manner that allows Purkinje cells to predict and classify future states. As a consequence, the behaviour of the organism can be adaptively regulated to achieve success in its interactions with the environment. These are the concepts about the operation of the cerebellum that neuroscientists are currently testing and elaborating in order to form a general perspective of cerebellar function and how it relates to the wide range of human activities.

Further Reading

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