Although the cerebellum's role in simple movements has long been appreciated, only recently have scientists begun pinning down how it coordinates complex, multijoint movements

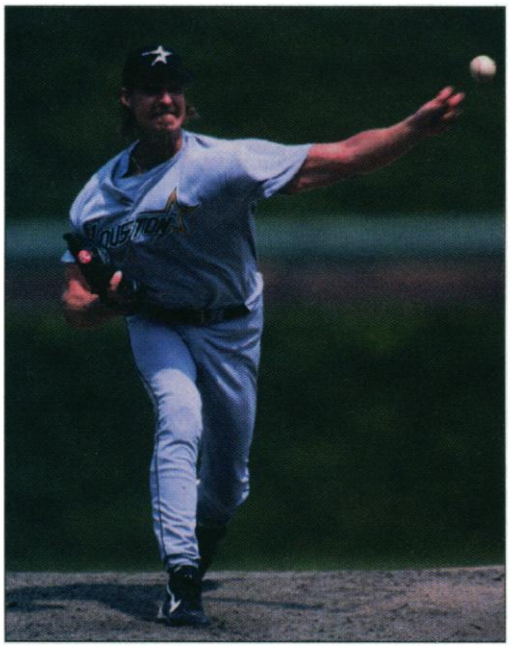
The Cerebellum: The Brain's Engine of Agility

When neurologist Helge Topka sees a patient at University Hospital in Tübingen, Germany, the patient often stumbles toward him with a wide, irregular gait, sometimes taking tiny steps and other times large ones. The patient may tell Topka, in a voice wavering between a shout and a whisper, that cashiers will no longer accept her checks because they can't recognize her signature. Colleagues, she laments, accuse her of drunkenness as she stumbles around the office, slurs her words, and fumbles with cups and pens.

But the patient is not an alcoholic. To the contrary, she never drinks alcohol, because it makes her movements even more uncoordinated. She suffers instead from a degenerative disease of the cerebellum, two apple-sized lobes at the back of the brain that house more than 100 billion neurons. Neurologists have long known that the cerebellum helps coordinate movements, but how it performs that task has been a foggy mystery. Now the fog is lifting: In the past few years, neuroscientists have begun to decipher the cerebellum's precise role in creating smooth, accurate movements. "It's an exciting time for the cerebellum," says James Houk of Northwestern University Medical School in Chicago. "After neglecting it for a long time, people are starting to appreciate it again."

In the past, neurobiologists focused mainly on the cerebellum's role in controlling single-joint actions, such as a simple flex of an elbow or ankle. But those studies provided only vague clues about how the brain coordinates the vast majority of our movements, which involve several joints. Until recently, these complex movements were considered too difficult to study. In the past few years, however, improved technology, such as video-tracking devices combined with computers to help analyze movements, has enabled researchers to get a much better fix on just what the cerebellum does to coordinate such movements.

These studies, involving both humans with cerebellar lesions and lab animals, show, for example, that the cerebellum predicts and adjusts for the multiple forces on a limb during a complex movement, including those propagating from one joint to another. If a person picks up a hammer, say, the cerebellum will activate the extra muscle force needed to operate the arm under the new physical conditions. It also controls the relative timing of various muscle contractions to ensure the speed and accuracy of a maneuver, so that when a person performs an act such as eating, the fork enters the mouth and not the eye. "It's fascinating," says Jonathan Hore, a neurophysiologist at the University of Western Ontario. "Only recently have we gained insight into what's really involved in making a multijoint movement."



Accuracy aid. The cerebellum helps throwers such as Houston Astro pitcher Randy Johnson release the ball at just the right moment to hit a target.

ROB TRINGALI JR. / SPORTSCHROME USA

Less clear at the moment are the neural mechanisms underlying cerebellar control of movement. But even so, researchers expect that the work may yield insights into how to improve coordination in the hundreds of thousands of people with cerebellar damage due to genetic disease, viral infections, strokes, alcoholism, or normal age-related loss of cerebellar neurons.

Soldiers of misfortune

Although studies of the cerebellum's role in complex movements were rare until recently, British neurosurgeon Gordon Holmes provided some early clues about its function in work he did in the 1930s on men who had suffered cerebellar lesions while serving in World War I. Holmes would attach a light bulb to a former soldier's finger and then take long-exposure photographs to outline the path of the finger as the man tried to bring it to his nose. Typically, he would overshoot the target several times, a problem that Holmes attributed to loss of synchronization of the man's shoulder and elbow movements as a result of the cerebellar damage.

Holmes didn't have the tools to determine exactly why the movements were so out of kilter, and in the following decades, most scientists focused on the cerebellum's role in the easier-to-study single-joint actions. Such studies hinted that the cerebellum deals with timing and force issues during movements. They showed that people and monkeys with cerebellar lesions display 25-millisecond delays in reacting to a command to make a single-joint movement. The test subjects also had problems in adjusting for changing forces on a joint.

But by the early 1990s, some researchers began to have trouble understanding how such small deficits in single-joint movements could account for the severe disabilities displayed by patients like Topka's in performing tasks such as walking, where more than one joint has to move. Indeed, experiments with both monkeys and human stroke patients showed that cerebellar lesions could disrupt complex movements while leaving single-joint movements relatively unaffected.

In 1993, for example, neurologist Thomas Thach, Howard Goodkin, and their colleagues at Washington University School of Medicine in St. Louis found that a man who had suffered a stroke that destroyed the part of the cerebellum controlling his right hand could flex and extend his right wrist,

ILLUSTRATION: K. SUTLIFF

Where Are Our Motor Memories?

When Mark McGwire sends a home run into the stands, give some credit to his cerebellum, which fine-tunes the swing of his bat as he whips it through the air (see main text). But what role the cerebellum played in learning and improving that fearsome swing—or any other kind of complex motor skill such as writing or driving a car—is not clear.

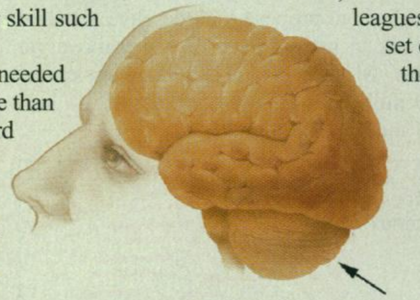
There's little doubt that the cerebellum is needed for the simplest types of motor learning. More than a decade of research by neuroscientist Richard Thompson of Stanford University and others has shown that animals with impaired cerebellar functioning can't learn conditioned reflexes, such as associating a tone with a puff of air so that eventually the tone by itself can cause them to blink their eyes.

And evidence by Mark Hallett's group at the National Institute of Neurological Disorders and Stroke, as well as that of Thomas Thach at Washington University School of Medicine in St. Louis, strongly suggests that the cerebellum is involved in simple adaptive learning, such as adjusting one's body movements to a visual world that has been shifted by distorting spectacles. Healthy people can adapt to this change well enough to hit a target with a ball. Patients with cerebellar damage cannot. Moreover, Thompson's and Thach's teams have shown that damage to the cerebellum impairs memories for conditioned reflexes or adaptive behaviors learned before the damage occurred. This suggests that the cerebellum stores the neural changes that result from learning these actions—the memories.

But when it comes to complex actions like drawing a picture, there's little proof that the cerebellum plays this storage role. In fact, when James Bloedel, Vlastislav Bracha, and their colleagues at the Barrow Neurological Institute in Phoenix set out to test this idea, they found some evidence to the contrary.

In work in press in the *Journal of Neurophysiology*, the Phoenix team showed that cats could remember a complex task they had learned—tracing an L-shaped template—after their cerebellums had been temporarily inactivated. And even untrained cats with inactivated cerebellums could learn this task—albeit very clumsily. But when their cerebellums had recovered, the animals set about relearning the task, presumably to bring their cerebellums into the act and make their movements more accurate. The researchers conclude that the cerebellum does not store memories for complex motor skills, but it is involved in learning the ideal motion for performing them.

These studies imply that the cerebellum fine-tunes complex motor skills rather than storing the memories for them. Still, the cerebellum might direct some other brain structure to form the proper memories. Clearly, more experiments will be needed to pin down the roots of McGwire's swing. **–I.W.**



Anatomy of movement. The cerebellum (arrow) helps coordinate movements and may be involved in learning them as well.

and move single joints of his right thumb and fingers. But he could not combine those individual movements to write, pick up an object, or reach his hand to a target. This indicated, Thach says, that the cerebellum is "specifically wired to bring the parts [of the body] together."

Exactly how the cerebellum does that didn't become clear, however, until 2 years ago when Amy Bastian, Thach, and two colleagues videotaped seven healthy subjects and seven patients with cerebellar damage rapidly reaching toward a small ball suspended in front of them. The hands of the normal subjects went straight to the ball, but the patients' hands first reached beyond the target, and then looped back. The problem resembled what Holmes had seen in his World War I soldiers, but the videotapes enabled the Washington University team to analyze the motions more precisely.

The researchers computed the rotational forces, or torques, on each joint—wrist, elbow, and shoulder—needed to produce those motions. The net torque at each joint is the sum of torques from gravity, the muscle acting at the joint, and interaction torques, which arise when two joints move relative to each other and can either assist or impede a movement. In the cerebellar patients, the interaction torque turned out to dominate the rotational forces on each joint, suggesting that the patients were having trouble balancing forces on their joints during a multiple-joint movement. "One of the things it looks like the cerebellum is doing is controlling interaction torques across multiple joints," Thach concludes.

A recent study by Topka and his colleagues at Tübingen supports that idea. They traced the excessive motion seen in nine patients with cerebellar disease to their inability to generate muscle torque patterns that compensate for either interaction torques or gravity while the limb is moving. And that result ties in with 1996 findings by Steve Massaquoi and Mark Hallett at the National Institute of Neurological Disorders and Stroke.

When these researchers asked nine patients with cerebellar atrophy to rapidly draw a straight line on a tablet, they found that the abnormally curved lines the patients drew could be explained by too little torque at the shoulder relative to the elbow. Hallett suggests that the patients had "difficulty in the rapid creation of force," making it impossible to balance the forces produced by different muscles during a fast movement.

Timing it right

Balancing forces is not the only problem the cerebellum solves in preserving agility and grace. It also coordinates the timing of joint movements. The first quantitative evidence for this came last year in experiments performed on cats by neurobiologists James Bloedel, Vlastislav Bracha, and their colleagues at the Barrow Neurological Institute in Phoenix. First the researchers trained the animals to reach for a vertical bar and use it to trace an L-shaped template.

Using software that correlates the speeds of the various joint movements, the researchers found that under normal conditions, all the joints of the cats' "arms" moved in synchrony. But when the Phoenix team temporarily inactivated sections of the cats' cerebellums with a drug, this coordination was lost; the joints tended instead to move in sequence—first one joint, say, a shoulder, then another, and so on.

New results from Hore's team at Western Ontario also emphasize the importance of the cerebellum in timing movements. Two years ago, the researchers determined what it takes for 10 healthy male recreational softball players to hit a target 3 meters away by throwing tennis balls at it. Coils taped to the men's fingers, hands, and arms relayed joint positions to a computer, and a microswitch on their middle finger was triggered as soon as they released the ball. To hit the target, the researchers found, a thrower had to open his fingers to release the ball within a particular 2-millisecond time frame in the course of his throwing movement. The subjects often missed because their release times varied by about 10 milliseconds.

Now, in as-yet-unpublished work, Hore's team has shown that in nine patients with cerebellar damage from strokes, the timing of ball release varied by as much as 50 milliseconds, resulting in "major disorders in throwing accuracy." These patients also showed major timing irregularities at other joints, indicating that "the cerebellum is of great importance for accurate timing in complex multijoint movements," Hore says.

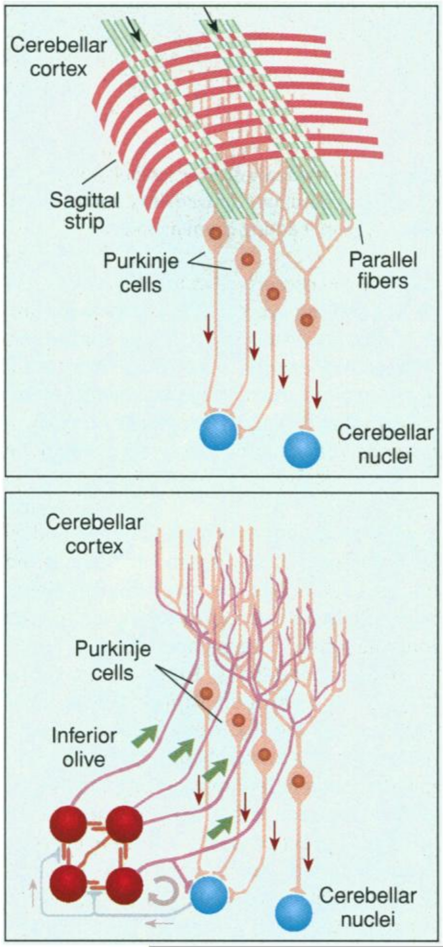
Wires, clocks, and loops

The neurological underpinnings of the cerebellum's actions are not yet clear, but recent results point to at least three possibilities. Based mainly on what's known about the neuronal anatomy of the cerebellum, Washington University's Thach suggests that a neural network in the cerebellum's outer layer, the cerebellar cortex, governs movement coordination. He notes that in the cortex, millions of nerve axons called parallel fibers link the Purkinje cells, which carry signals from the cerebellar cortex to other parts of the brain and body. Thach believes each Purkinje cell governs a specific muscle and that the parallel fibers function as wires that bind different muscles together for coordinated movements. The strength of the connections, or synapses, between the parallel fibers and Purkinje cells, the theory goes, would determine the force and timing of muscle contraction.

Bastian, Thach, and their colleagues provide some indirect evidence for this hypothesis in a study that will appear in the October *Annals of Neurology*. When the researchers studied motor skills in five children whose cerebellar cortexes were cut in the center to remove brain tumors, they found that the children could reach, pinch, speak, and kick normally, and could even hop on either leg. However, none of them could coordinate their two feet to walk a straight-line tandem gait, the classic drunk drivers' test. "This is the kind of deficit you'd expect if parallel fibers crossing the midline—which have been cut—coordinate the two sides of the body," says Thach.

Neurophysiologist and cerebellum expert Rodolfo Llinás of New York University Medical Center isn't convinced. For one thing, he asserts, the connections between parallel fibers and Purkinje cells are too weak to produce the muscle-combining effects Thach is postulating. Llinás, along with NYU colleagues Eric Lang and John Welsh, has been amassing support for a different hypothesis: that the cerebellum's coordination of complex movements is orchestrated by a structure called the "inferior olive" located just below the cerebellum.

This idea is also based partly on neuronal anatomy. The olive sends so-called climbing fibers up to the cerebellum where they wrap around Purkinje cells like vines around a tree, exerting a powerful influence on them, Llinás says. In addition, since the early 1980s, Llinás's group has gathered clues that the inferior olive cells in rats fire at regular, clocklike intervals every 100 milliseconds. This ticking occurs in concert with natural actions including tongue-flicking and whisker-twitching. Such findings have led Llinás to propose that the olive acts like a clock to set the pace of every move we make. "Movements are generated in steps of 100 milliseconds," he contends. "You hiccup your way through life."



Two views. In one view of cerebellar action, the strength of connections between the parallel fibers and Purkinje cells in the cerebellar cortex determines the force and timing of muscle contraction *(top)*. But another *(bottom)* ascribes the coordination to the rhythmic firing of neurons from the inferior olive that connect with the Purkinje cells, and there are other views as well.

In this view, subgroups of olive cells that become simultaneously active determine which muscles contract or relax on a given tick. These subgroups are selected by linked groups of Purkinje cells in the cerebellar cortex that send inhibitory messages through the cerebellar nuclei to the olive. These messages prevent the entire olive from "ticking" by temporarily walling off particular groups of olive neurons, or so the theory goes.

But this hypothesis is also controversial. In studies published in 1995 and 1997, Thach and Jeff Keating, now at the University of Pennsylvania, saw no evidence of clocklike activity when they recorded from inferior olive nerve endings in the monkey. "Our problem with the clock is, we couldn't hear it tick," Thach says.

Of course, neither Thach's nor Llinás's theory may be entirely right. For one thing, both ignore a possible role for the motor cortex, a part of the brain's surface that initiates voluntary movements. Indeed, researchers such as Houk at Northwestern believe that communication between the motor cortex and the cerebellum powers coordination.

In support of this idea, the Northwestern team cites experiments in which they've shown that inactivating parts of either structure in animals can produce coordination deficits. In addition, their recent data suggest that the neurons of the cerebellar nuclei, which control various body parts, are organized in a way that would make it impossible for the parallel fibers to recruit them in groups for various actions, as the other theories hold.

Houk proposes instead that muscle groups are recruited as neurons in the motor cortex and cerebellum alternately talk to each other, causing excitation to spread from neuron to neuron in each brain structure. As a neuron controlling a hand, say, excites one for the wrist and then the shoulder, a person might reach forward to grab something. "You need pathways to the cerebellum to amplify what the motor cortex is doing and coordinate the muscles," Houk says.

All these theories still require a few leaps of faith—and more work to determine which is correct. But researchers are finally getting close to understanding just what the cerebellum does to keep our joints in sync.

–INGRID WICKELGREN

Additional Reading

A. J. Bastian, T. A. Martin, J. G. Keating, W. T. Thach, "Cerebellar ataxia: Abnormal control of interaction torques across multiple joints," *Journal of Neurophysiology* **76**, 492 (1996).

S. Massaquoi and M. Hallett, "Kinematics of initiating a two-joint arm movement in patients with cerebellar ataxia," *Canadian Journal of Neurological Sciences* **23**, 3 (1996).

M. S. Milak, Y. Shimansky, V. Bracha, J. R. Bloedel, "Effects of inactivating individual cerebellar nuclei on the performance and retention of an operantly conditioned forelimb movement," *Journal of Neurophysiology* **78**, 939 (1997).

H. Topka and J. Dichgans, "The cerebellum and the physics of movement," *Behavioral and Brain Sciences* **20**, 2 (1997).

J. P. Welsh and R. Llinás, "Some organizing principles for the control of movement based on olivocerebellar physiology," *Progress in Brain Research* **114**, 958 (1997).

TOP: ADAPTED FROM J. R. BLOEDEL *BEHAVIORAL AND BRAIN SCIENCES* 15, 4 (1992) ADAPTED FROM R. LLINÁS, E. J. LANG, J. P. WELSH, *LEARNING AND MEMORY* 3, 445 (1997)