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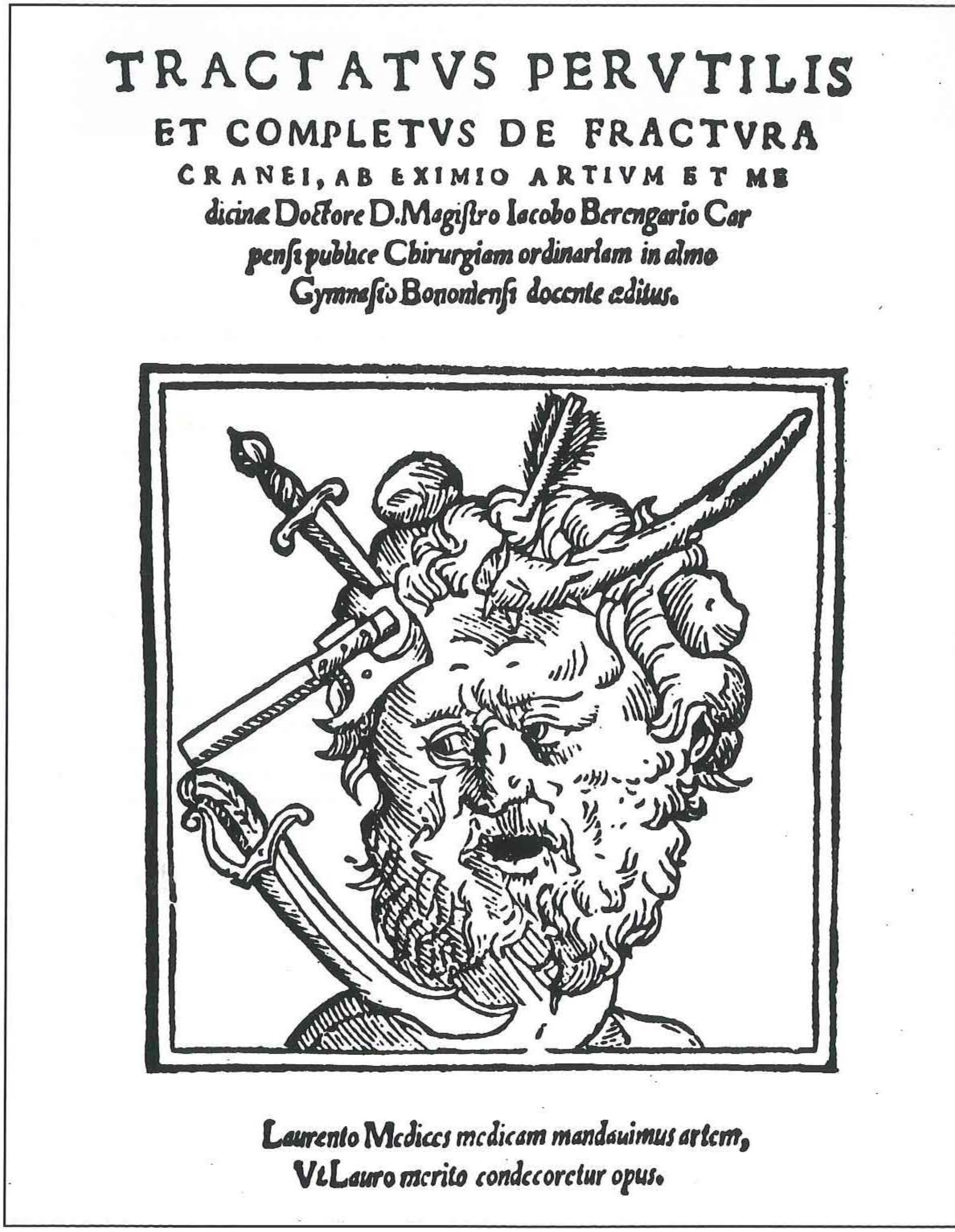
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Listening in on the Cerebellum

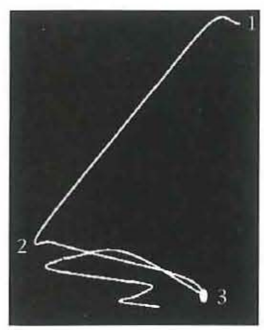
by Douglas L. Smith

The frontispiece of the first known book on the treatment of head injuries, Jacopo Berengario da Carpi's ***Tractatus Perutilis et Completus de Fractura Cranei***, published in 1535. Doctors have been trying to deduce brain functions from brain injuries ever since. (Reprinted from ***Origins of Neuroscience*** by Stanley Finger, Oxford University Press.)

The cerebellum is the part of your brain that lies above the spinal cord and below the cerebrum, which is the seat of higher thought. The cerebellum got its name (which is Latin for "little brain") because, in humans, it looks like a smaller edition of the cerebrum above it—it has two wrinkled hemispheres, left and right, connected by a structure called the vermis, from the Latin word for "worm." It's part of the hindbrain, evolutionarily the oldest part of the brain, so it probably does something pretty basic; and it's pretty big, occupying about one-fifth of the adult human cranium, so it probably does something pretty important. And, at well over 100 billion neurons, or nerve cells, it contains far more cells than the cerebrum. At the beginning of this century, doctors studying patients with cerebellar injuries concluded that it is the organ of motor coordination—regulating (but not initiating) the muscular commands needed for posture, balance, and voluntary movement. This remains the generally accepted view today, but experiments in Professor of Biology James Bower's lab at Caltech are bolstering his theory that the cerebellum plays a fundamentally different role. We'll get to Bower's theory shortly, but first let's see why the mainstream view prevails.

The first rigorous studies of cerebellar injuries were done by Gordon Holmes, a field neurosurgeon attached to the British army during World War I. The Great War was a great boon to researchers mapping the brain's functions—the widespread use of that marvelous new weapon, the machine gun, provided a bountiful selection of patients with neat, localized brain injuries. By observing what each patient could no longer do, one could deduce the function of the region of brain tissue excised by the bullet. Unfortunately for neuroscience, Holmes was unable to follow many of his cases for extended periods, because they were "of necessity evacuated to England." Still, he noticed several characteristics peculiar to cerebellar injuries.

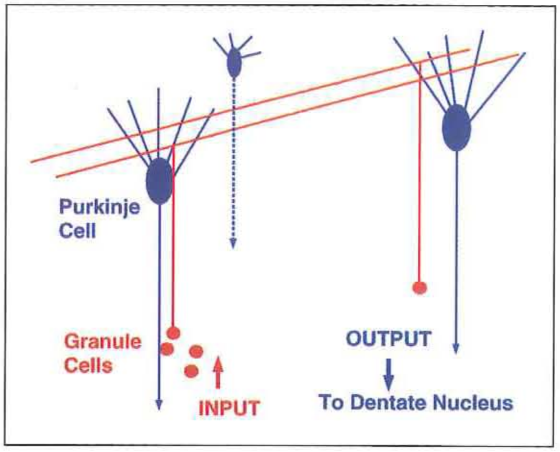
In a classic set of experiments, Holmes attached a small light bulb to the patient's fingertip, and then took long-exposure photographs to map the finger's trajectory when the patient was asked to hold his arm upright over his head and then touch his nose. The patient usually missed the mark, often smacking himself smartly in the face. Then, like a golfer who takes five putts to sink the ball, shooting wide of the cup by inches each time, the hand would flail around the nose in a series of overcorrections. Closer examination of the photos revealed that, whereas an uninjured person would make one smooth, coordinated movement of the shoulder and elbow, Holmes's patients moved each joint separately. They rotated the shoulder to bring the arm down to nose level, then flexed the



The patient started with his arm over his head (1). When asked to touch his nose, he brought his arm down (2), then drew his hand in, smacking himself in the face (3). Adapted from Holmes's *The Cerebellum of Man.*

elbow to bring the fingertip in. His patients also had difficulty with such fine-motor-skill tasks as buttoning their shirts, or striking a designated key on a piano.

The patients had muscle-control problems even when standing still. If Holmes pushed or pulled on the patient's arm after telling him to hold it out rigidly, the arm would move through a greater arc than normal. Or if the patient was resting his arm on a bar that Holmes suddenly removed, the arm would drop considerably before readjusting, whereas a normal person's arm would just bob slightly.



A Purkinje cell looks like a menorah might, if Hanukkah lasted 280 days or so.

The essence of the granule-cell/Purkinje-cell circuit. A nerve impulse arrives at a granule cell (red) and is sent up the ascending fiber, which ends in a T whose arms (the parallel fibers) run perpendicularly through rank after rank of Purkinje cells (blue). The Purkinje cells collect information from the parallel fibers and send it out of the cerebellum via the dentate nuclei, which lie deep in the cerebellum's interior.

Holmes also noticed delays in initiating actions. This was most apparent when only one side of the cerebellum was injured, and the patient was asked, for example, to raise both arms at once. The affected limb would consistently lag behind the unaffected one. The delays got worse, Holmes found, if the patient's attention was distracted during the experiment, or if the patient was taken by surprise—a patient told to expect a command reacted faster than did one to whom Holmes gave a command out of the blue.

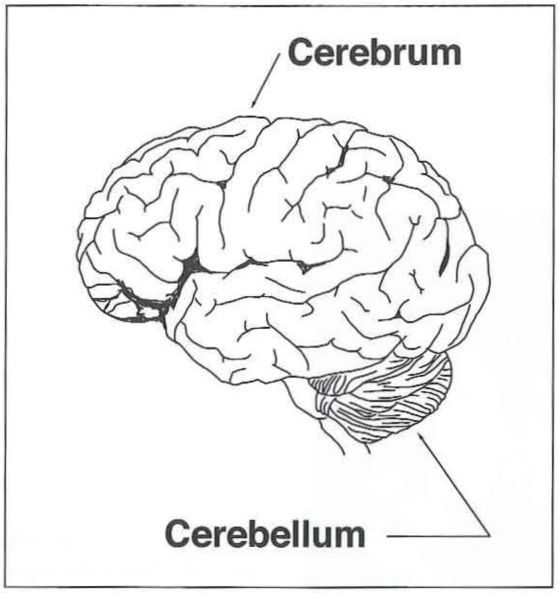
The conclusions seemed clear: the cerebellum is in charge of helping the various muscle groups talk to one another, coordinating movement and body position, and relaying motor commands from the higher brain centers that plan the movements. These functions are normally unconscious, so the patients had to exert conscious control to compensate. As a patient of Holmes with a right-cerebellar-hemisphere injury remarked, "The movements of my left arm are done subconsciously, but I have to think out each movement of the right arm. I come to a dead stop in turning and have to think before I start again."

As seen under a microscope, the wiring diagram of the cerebellar cortex is very simple and regular. Only five basic cell types—the basket, granule, Golgi, Purkinje, and stellate cells—live there, and their arrangement repeats over and over and over again in an endless hall of mirrors. And the simplest reduction of the cerebellar circuitry contains only two types of cells, granule and Purkinje cells, which between them make up a complete input-output system. (The Golgi cells feed back to the granule cells, damping their output; the basket and stellate cells are part of another circuit beyond the scope of this article.) Granule cells collect inputs from outside the cerebellum and send them along parallel fibers that are strung like telephone lines between the Purkinje cells. Each granule cell has one parallel fiber, which feeds perhaps seven-score Purkinje cells. The Purkinje cells pick information off the parallel fibers and send it out of the cerebellum—in fact, they are the cerebellar cortex's only output channel. A Purkinje cell looks like a menorah might, if Hanukkah lasted 280 days or so. Up to 300,000 parallel fibers may be strung through a Purkinje cell, although it only makes contact with one-half to two-thirds of them. If we assume that form follows function, then a uniform circuit implies that the cerebellum applies some uniform process to its inputs. So in light of Holmes's and others' studies, it seemed reasonable to believe that the granule-cell/Purkinje-cell circuit sorts and collates motor controls.

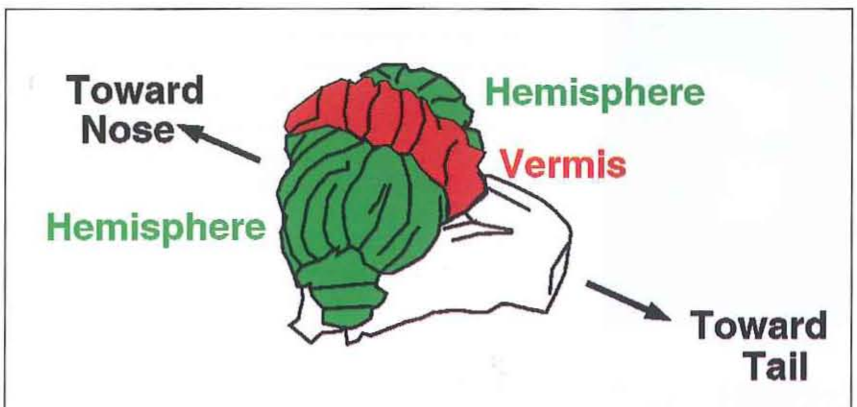
Or does it? If, off in the distance, you see a bicyclist weaving erratically through an empty parking lot, you might assume that the bike's handlebars have come loose. But as you approach, you might discover that the cyclist is practicing a stunt, and is in fact blindfolded. Thus either a mechanical output problem or a sensory input problem can have the same outward effect. Might such an analogy apply to the cerebellum? Could the manifestations of cerebellar damage that appear to be deficiencies in motor control actually result from a sensory failure of some kind?

Bower believes that the cerebellum acts to optimize how the nervous system acquires the sensory data on which it depends. "Sensory surfaces are very, very sensitive," he says. "Small changes in the position of, say, your fingertips can have enormous consequences for the sensory data received by the brain. We believe that the cerebellum is involved in coordinating the fine position of the sensory surfaces—making adjustments of a few microns over millisecond time scales—to ensure that the rest of the brain has the best possible data available to it." Thus, when you reach into your pocket to find a penny, your cerebellum ensures that you have the sensory data necessary to distinguish it from a quarter or a nickel by its size, weight, and texture. The motor-control centers, in turn, use this sensory data to generate accurate instructions to send to your muscles. So if the sensory information is messed up, the control of movement would be less precise. In Bower's view, this accounts for Holmes's observations.

It's actually been known for some time that the cerebellum handles sensory information. In the late 1960s, researchers recording the electrical impulses from granule cells in the cerebellar hemispheres of anesthetized rats found that lightly tapping on the rat's lips or whiskers caused a large response, but when the rat's legs or tail were touched, nothing much happened. This was a surprise, because if the cerebellum is really a motor-coordination center, it should be linked to the parts of the anatomy that walk around; rats don't walk on their whiskers. Instead, the whiskers and lips are the rat's chief organs of touch.



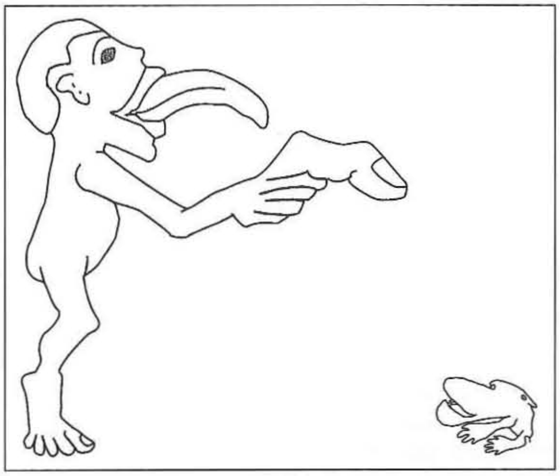
While the human cerebellum nestles under the centers of higher thought (right), the rat's cerebellum rides atop the rest of its brain like the shell on a snail (below).



We now know that, in general, large regions of the cerebellum collect visual, tactile, and auditory information. While some regions of the cerebellum are devoted to sensory information that reflects the positions of the animal's limbs in space and the tension of its muscles (called proprioception—an internal sense of one's self, if you will), the largest part of the cerebellum is devoted to the external senses. Furthermore, the proportion of the cerebellum devoted to each class of sensory input varies from species to species in a way that mirrors how each creature explores its world. Thus, the cat cerebellum draws tactile information from the mouth and forepaws, and has stout conduits from the eyes and ears. Echolocating bats are wired for sound. Electric fish have cerebellar structures that sense disturbances created by prey swimming through the electric field the fish generates. Similarly, the platypus devotes much of its cerebellar wiring to its electrosensitive beak. These electrosensors are astonishingly acute, registering the infinitesimal electric fields generated as the prey's muscles contract—not even the swishing of the gills goes unnoticed. (Picture a berserk platypus starring in *Friday the 13th, Part LXVI*—its victims cowering in the darkness, desperately trying to hold their breath to avoid detection.) In humans and other primates, the tactile inputs to the cerebellum come from the hands and fingers. In addition, the spider monkey has a strong cerebellar connection to a patch of hairless skin, like that on the palm of your hand, on the underside of the tip of its tail. "Spider monkeys frequently use this part of their tail to explore the ground, and objects around them," explains Mitra Hartmann, a grad student in Bower's lab. "And sometimes they carry their tails over the top of their heads to sense the environment in front of them."

So what is the cerebellum doing with all this sensory information? This question is very hard to answer when your subject is anesthetized, or, worse, thinly sliced on a microscope slide. Bower's hypothesis that the cerebellum acts to fine-tune how sensory data is gathered implies that it should

Adapted from *Essentials of Neural Science and Behavior*, Kandel, Schwartz, and Jessell eds, published by Appleton & Lange.



Sit, boy. Speak. Good rat. In the somatosensory cortex, which is where the cerebrum (as opposed to the cerebellum) processes tactile information, the acreage of cortical real estate devoted to input from each part of the body is proportional to the extent to which we use that body part to feel out our surroundings. The human and rat above are drawn in those same proportions, although not to the same scale. Thus, humans tend to explore with the thumb and tongue (as any parent of a one-year-old knows); rats rely on the lips and snout. Furthermore, the cortical regions that handle adjacent parts of the body adjoin one another. But in the rat's cerebellum, the regions that respond to different parts of the body are all jumbled together, as shown in the map of cerebellar region crus IIa at right. The colors correspond to the colors on the rat's face below.

be very busy when the animal is exploring its environment—a time when accurate sensory data are likely to be particularly important. But anesthetized animals don't take much interest in their surroundings, so, in order to explore that hypothesis, you need to record from a wide-awake animal that's poking its nose into things. Literally—the parts of the cerebellum that Bower's lab studies are devoted to the sense of touch.

Until recently, it was quite difficult to tap into the brain of a freely moving animal. The electrical signal from a single cell is minuscule—about two-tenths of a millivolt when recorded right next to the cell. Since the signals are so small, you need a preamplifier near the source, i.e., mounted on the animal's head, to push the signal up the wire to the data-acquisition system. Thanks to silicon technology, we now have multichannel preamps small enough for rodent haberdashery. These preamps inspired Hartmann and Upinder Bhalla (PhD '93) to design and build electrode arrays that could be permanently implanted into a rat's brain. Says Hartmann, "In the last five or ten years, the notion of doing chronic recordings from freely moving animals has really taken off." Researchers can now examine the animal's neural activity as the rat goes about its rat business for weeks or months.

Preparing a rat for a preamp hat is a three- to six-hour surgical procedure in which Hartmann inserts arrays of up to eight electrodes into one or both hemispheres of an anesthetized rat's cerebellum. Each electrode is a wire less than 50 microns in diameter—thinner than a rat's whisker. One end of each electrode is painlessly inserted into the rat's brain, while the other end is attached to a connector about the size of a Pez candy. The electrodes and the connector are glued to the rat's skull with the same acrylic that dentists use to make retainers; what you have after the operation is a punk rat with a plastic Mohawk. The rats don't seem to mind their new hairdos and fancy

The electrodes and the connector are glued to the rat's skull with the same acrylic that dentists use to make retainers; what you have after the operation is a punk rat with a plastic Mohawk. The rats don't seem to mind their new hairdos and fancy hats, and upon recovery from the operation, they behave just like their more conventionally attired cousins.

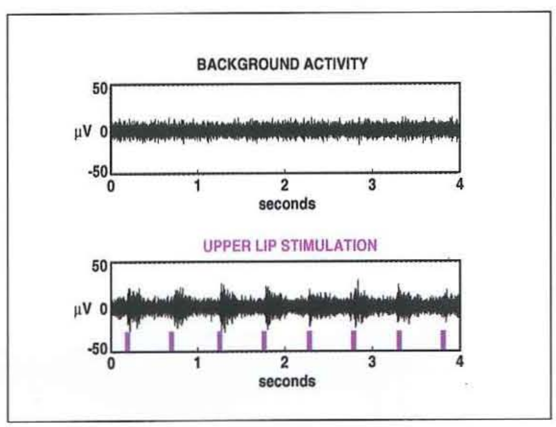
hats, and upon recovery from the operation, they behave just like their more conventionally attired cousins. The matchbook-sized preamp, which plugs into the connector, is moved from rat to rat.

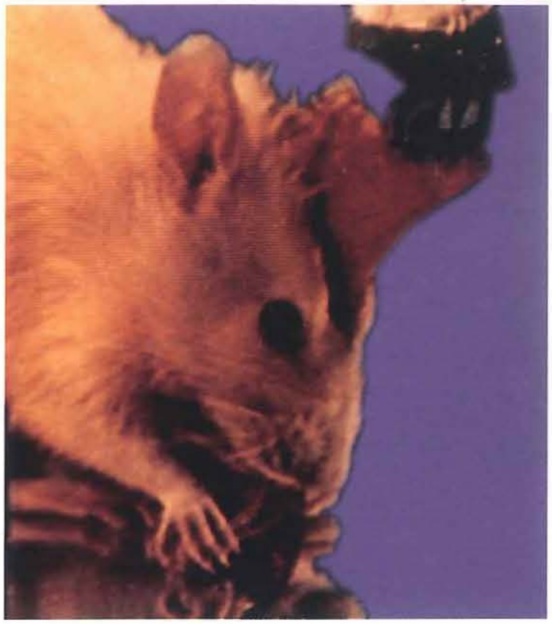
The electrodes feed both an oscilloscope and a loudspeaker—like Jodie Foster's character in *Contact*, Hartmann actually listens to her life forms. "The speaker is very important, because it's much easier to hear a short, sharp burst than it is to watch for it on an oscilloscope. If you blink, you'll miss it. It's very convenient that a lot of the power in neural signals falls within our audible range, which is a feature of our own neural apparatus. I like that idea, because it's kind of recursive." Neural activity sounds like AM radio static.

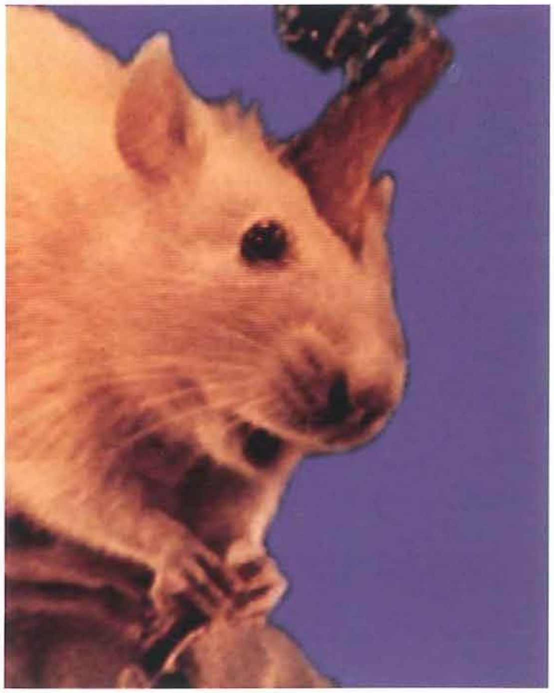
So Hartmann has been eavesdropping on rats resting, eating, grooming, and just generally being rats, while at the same time videotaping them to correlate their behavior with the recorded neural signals. The particular cells she's wire-tapped live in a region called crus IIa, and respond when the lip and whiskers are touched—in the case of the rat in the accompanying pictures, the upper right lip and its attached whiskers. Because the granule cells are so small—five to six microns in diameter—her best guess is that she's hearing a couple of hundred cells at once. (Purkinje cells are much larger, and could in theory be isolated by an electrode this size, but for several technical reasons we can't yet record from them in rat cerebellums.)

Her studies have confirmed that these granule cells deal only with sensory information, even in an awake, moving animal. Says Hartmann, "That result in and of itself was surprising to many people, because they expected at least some modulation of the response by motor activity. Or maybe even that the response to touch was subsidiary to a motor response." The clearest-cut example of the distinction between motor and sensory activity was furnished by the rats as they dined.

This rat responds to stimulation of the upper right lip and whiskers, as shown in the graph below. The vertical axis is the change in the granule cells' electrical output (plotted in millionths of a volt) rela-tive to a baseline voltage. The purple lines mark when the whiskers were touched with the wooden handle of a Q-tip.

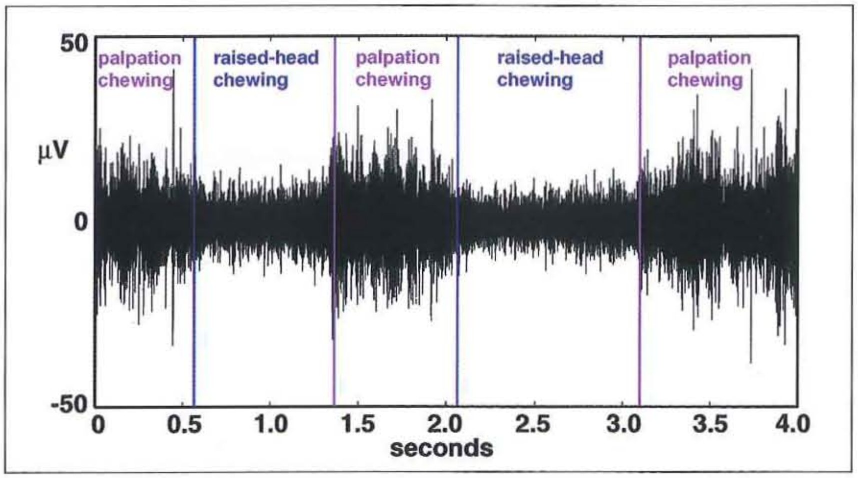






As you may have noticed on a walk through the park, squirrels, rats, and other rodents eat in a multi-step process. First, they hold the food steady with their forepaws and move their lips back and forth across its surface, exploring the food before biting into it. "It's a little bit like holding a whole loaf of bread in your hands and having to figure out how to get a bite out of it," Hartmann explains. Then the animal takes a bite and begins to chew, while at the same time continuing to nuzzle and explore the food with its lips. Hartmann has christened this behavior "palpation chewing." And finally, the rat removes its lips from the food, raises its head, and continues to chew before swallowing. This is called "raised-head chewing," for obvious reasons, and presumably lets the animal look around to avoid becoming a meal itself. In both palpation and raised-head chewing, the motor activity (the chewing) is identical, but the granule cells fired only during palpation chewing—a SH-SH-SH-SH-SH-SH-SH-SH-SH in time with the food touching the rat's lips.

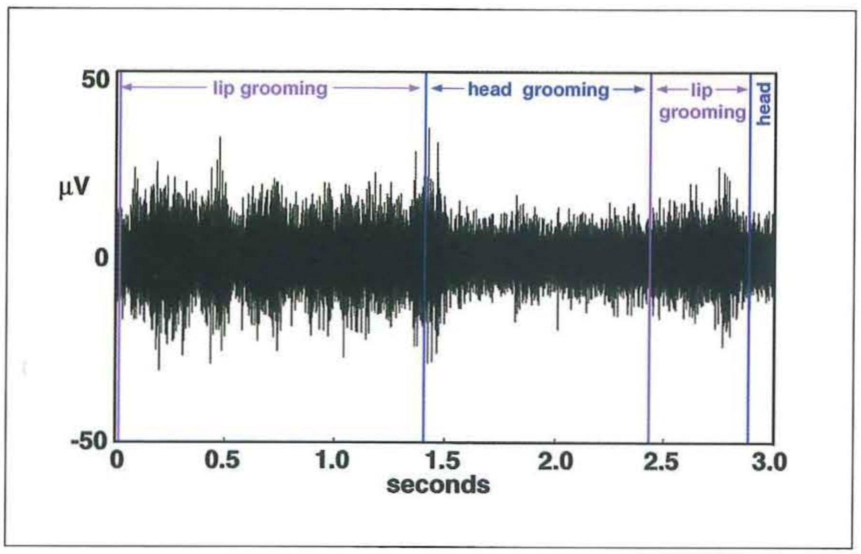
Watching the rats groom themselves confirmed



Top: Palpation chewing.
Bottom: Raised-head chewing.
Left: The granule cells pulsed with activity during palpation chewing.

Rats groom the way cats and bachelors do—they moisten a forepaw and slick back their hair.

Again, the granule cells pulsed as the lip was touched.

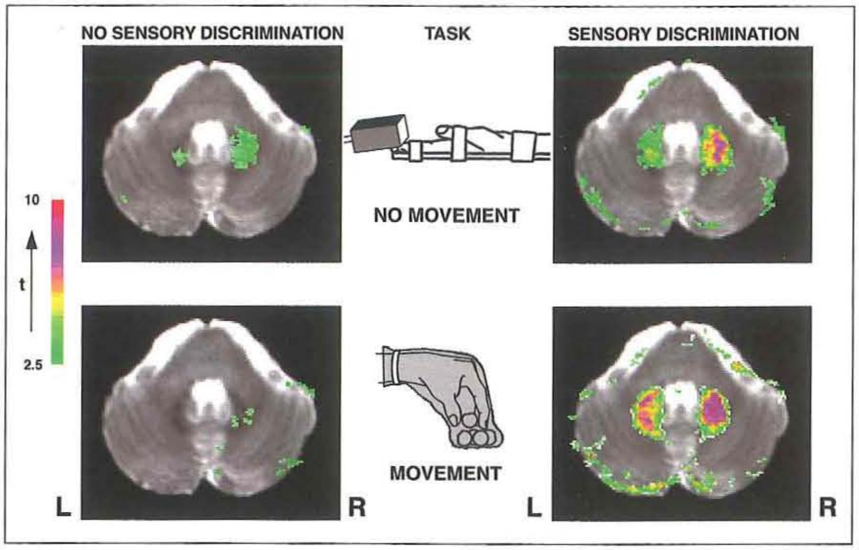


that the bugged cells were dealing only in sensory information from one locale. Rats groom the way cats and bachelors do—they moisten a forepaw and slick back their hair. When the rat groomed its upper right lip, the granule cells responded, but when it was grooming elsewhere, they didn't.

But by far the session that recorded the most sustained bursts was when the rat was trying to get at a chunk of pretzel wrapped in tissue paper. ("Rats prefer pretzels to chocolate," says a bemused Hartmann.) As the rat nuzzled the paper, trying to figure out how to get to the goodie within, the granule cells went nuts every time the lip touched the tissue.

Doggone it, I *know* there's a pretzel in here!

The central, testable nub of Bower's theory is that the cerebellum is going to be busiest when it's choreographing the sensory apparatus to get detailed information about an object the rest of the brain is interested in. Looked at another way, the theory predicts that the cerebellum should be quieter when sensory receptors are being stimulated but the brain is not using the information it's getting from those receptors. This idea is difficult to test, however, with a rat. It's hard to know, for example, when a rat is interested, and when it's ignoring the stimulation. Perhaps rats pay constant attention to all stimuli—as we might, too, if we spent all our time surrounded by organisms a thousand times bigger than ourselves. So in order to test the theory further, it was necessary to study an animal whose mind's workings are



Left: Functional Magnetic Resonance Imaging measures the level of dissolved oxygen in the blood as a proxy for brain activity—busy regions get extra oxygen to fuel their work. The gray background image is an anatomical MRI scan of the cerebellum, on which the functional data have been overlaid in color. The scale labeled *t* shows cerebellar activity compared to baseline levels measured when the subject was lying quietly. In the upper two panels, the fingertips were rubbed with sandpaper; in the right-hand panel, the subject was asked to judge the sandpaper's texture. In the lower two panels, the subject was handling unseen balls; in the right-hand panel, the subject had to judge their shape. The activity is actually greatest in the dentate nuclei (the two dark, crescent-shaped bodies near the midline), which collect the Purkinje cells' output.

more accessible—*Homo sapiens*. But even the most eager grad students don't generally volunteer to have electrodes inserted into their heads, so the Bower lab is collaborating with a group headed by Dr. Peter Fox at the University of Texas Health Science Center in San Antonio. The Fox group uses functional Magnetic Resonance Imaging (fMRI) techniques to watch the activity of human cerebellums as various tasks are performed. People have their pluses as experimental animals—we're much easier to train than rats, which require weeks of coaching. On the minus side, fMRI provides a very indirect measure of brain activity.

The human experiments involved stimulating the subjects' fingertips, which we use for tactile exploration much the same way rats use their lips and whiskers. (Also, unless you know the subject very well, it's best to avoid playing with a Texan's whiskers.) Fox's group started by determining how much cerebellar activity resulted from passive stimulation of the fingertips—the equivalent of stroking an anesthetized rat. Since people can't be anesthetized just to explore their cerebellums, the volunteers were told to do the next best thing—to lie motionless in the fMRI machine and pretend they were watching C-SPAN coverage of the Department of Labor's budget committee hearings. Their limp fingers were then lightly rubbed with sandpaper, resulting in a low but discernible cerebellar response. Next, the subjects were told to focus their thoughts on the sandpaper and decide how coarse it was. The cerebellum flared to life—a result consistent with Bower's theory.

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But the critical test was still to come—Bower had predicted that simply moving the fingers without making a sensory judgment would produce less activity than if the moving fingers were also being used for sensory discrimination. In this set of experiments, the subjects were first asked to pick up and drop small, unseen balls, then asked to handle them again and identify their shape. The result was quite remarkable—there was no cerebellar response when the balls were grasped and released, but shape discrimination set the cerebellum ablaze.

While the human studies were remarkably consistent with the predicted results, only with implanted electrodes can researchers actually see what small groups of neurons are up to. So Hartmann and Bower returned to their rats for, well, ratification. They decided that having rats use their lips and whiskers to distinguish between different textures would be a good analog to the human fMRI experiments. But as we've seen, getting inside a rat's head isn't so easy. The experiment would have to be designed to exploit behavior one could reasonably expect from a rat in such a way that the experimenters could be sure that the rat was actually interested in the stimulus and was making a discrimination based on it. Designing the task properly, and training the rats to perform it, was going to be a big job—especially since Murphy's Law of Behavioral Biology states, "Under standard experimental conditions, the animal will do as it damn well pleases."

Enter Carolyn Chan and Angela Poole, two Caltech undergrads who not only helped design and build the apparatus, but also trained the rats. The general plan was to have the rats learn that a rough texture pointed the way to a sugar-water reward. This led to the design of the experimental cage: one wall had a central door, big enough to admit the rat's head, and a syringe filled with sugar water in each corner. Both syringes were

The rats are trained for their role in the experiment before the surgery is done. Here Hartmann sets up the video camera while her colleague gets used to the box. The metal door is visible under the rat's chin; black construction paper keeps the rat from seeing the wheel. One of the two syringes can be seen in the foreground.

Harmonica lessons might be more fun, but nuzzling a bolt is a steady job.

kept full, so that the rat couldn't tell by the smell which one would dispense the reward on any given trial. Behind the door was a lazy Susan (an old bicycle wheel, actually) around whose rim were a series of threaded, horizontal rods—decapitated bolts from Caltech's physical-plant department. The left and right halves of the bolts each had one of three different textures: coarse threading, fine threading, or no threading. During each trial, the door opened, the rat stuck its head out, felt the bolt, and then walked over to the syringe of its choice. If it picked the one closest to the coarser texture, it got a sweet sip. As the rat was drinking (or futilely sucking on the wrong syringe), the door closed and a stepper motor spun the wheel, bringing a new bolt to the door. This way, the rat couldn't see the wheel spin, and there was no scent of a human croupier that might have influenced the rat's decision. Because there were three possible textures, the rat couldn't simply choose the texture that pointed to the reward the previous time. Instead, the rat actually had to evaluate differing degrees of coarseness and pick the coarsest one.

Hartmann, Chan, and Poole were able to train the rats to choose the correct syringe nearly 80 percent of the time—much better than the 50 percent success rate that random chance would bring. So the rats clearly learned to perform the discrimination. But Hartmann, who is now writing up her PhD thesis, is still analyzing the neural data from the experiments.

Bower stresses that he's not proposing that the cerebellum actually interprets the world around us, but that it merely works to ensure that the data arriving at the higher brain centers that *do* do the interpreting is as clean and useful as possible. And although his lab's work to date has revolved around touch, Bower says that similar logic could apply to sight and hearing as well. (Remember, other species, including our own, devote much of their cerebellums to either or both of these senses.) The eyes and ears rely on muscle-tension information to know where they're pointed. Even a couch potato, eyes glued to the TV and inert but for one channel-surfing thumb, makes continuous tiny eye movements from object to object on the screen. Bower compares the cerebellum's role of supporting the rest of the brain's activities to that of your car's cooling system. "The radiator responds to your rate of speed by increasing the coolant flow, and thereby helps your engine run better, but it doesn't itself propel the car. If the radiator springs a leak, a lot of things will happen—the air conditioning will fail, and eventually the car won't run at all. Yet these effects aren't directly related to the radiator's structure or chief function."

Viewed through the prism of Bower's theory, the behavioral effects that cerebellar injuries cause make perfect sense. The muscle-control problems Holmes described would be due to an injured cerebellum being unable to ride herd on the quality of data from the limb-position and muscle-tension sensors, meaning the motor centers would have a fuzzier sense of how the body was poised, and thus movement plans would be less accurate. Similarly, the delay in initiating a movement would be explained by the motor centers taking longer to organize and coordinate movements from the lousy data, throwing the movement's timing off.

Bower's theory might even help to explain some aspects of the most baffling form of mental illness. He explains, "It has often been suggested that at least some forms of autism may be related to the inability of the child to deal with sensory data. Autistic individuals sometimes report that, at different times, the world provides too much or too little sensory data. Cerebellar dysfunction could very well be a contributing factor, especially if the result is inconsistent control over sensory data acquisition. And, indeed, recent MRI studies, performed in Eric Courcesne's lab at UC San Diego, have indicated that cerebellar activity patterns in some autistic children are abnormal." □