Remapping the Motor Cortex

The primary motor cortex of the brain does not contain an orderly map of the body but is instead a complex mosiac of neurons controlling different body parts

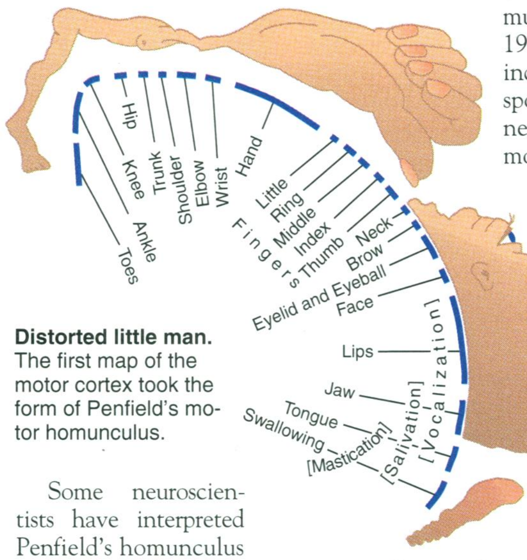
When you're at the gym, sweating your way from one weight station to the next, you may be focused on bulking your biceps or strengthening your pectoral muscles. But in spite of your concentration, even the fanciest weight machine can't work just a single muscle at a time. Multiple muscles must cooperate to choreograph even the simplest movements made by anyone, from an Olympic champion to a couch potato pushing buttons on the remote control.

Such movements do not, of course, begin with the muscles but must be orchestrated by the brain and spinal cord. Recent work from numerous labs, including that described on page 1775 by neurobiologists Jerome Sanes and John Donoghue of Brown University and their co-workers in Steven Warach's group at Harvard Medical School, is now clarifying just how a brain region known as the primary motor cortex helps coordinate muscles to produce a movement.

The findings, which began over a decade ago but have intensified in the past few years, overthrow an earlier view that the primary motor cortex contains an orderly map mirroring the body plan, with a one-to-one correspondence between cortical areas and the body parts they control. Instead, there is now evidence of a complex and disorderly mosaic in which multiple cortical areas control a given body part. "An individual muscle or movement, or part of the body … is represented diffusely, and it is intermingled with the representation of lots of other parts," says University of Rochester neuroscientist Marc Schieber.

Despite its disorderly appearance, this evolving picture of the primary motor cortex provides some intriguing insights into how this brain area may function. The diffuse pattern in which the cortical neurons are wired to muscles may make them ideally suited to select, from a nearly infinite set of possible muscle combinations, the unique combination required to produce any movement. "It could be that inherent in this very complicated, messy-looking patchy mosaic map are solutions to many of these motor control problems," says neuroscientist John Kalaska of the University of Montreal.

The idea of a map in the primary motor cortex dates to the work of Canadian neurosurgeon Wilder Penfield in the 1930s. Penfield electrically stimulated the brains of epilepsy patients during surgery and found that the cortical neurons whose activity caused movement of the various body parts are arrayed in an orderly way that roughly reflects the body plan. The foot and leg lay at one end of the map, followed by the torso, arm, and then disproportionately large areas devoted to the most agile body parts, the hand and face. Penfield depicted his findings in the form of a drawing of a distorted little man, or homunculus, draped across the surface of the cortex.



Distorted little man. The first map of the motor cortex took the form of Penfield's motor homunculus.

Some neuroscientists have interpreted Penfield's homunculus in the most literal way—assuming, for example, that there are side-by-side patches of cortical neurons that govern each of the five fingers of the hand—but most agree that Penfield didn't intend that interpretation and instead only meant to show that there are broad areas of primary motor cortex devoted to governing the leg, torso, arm, and head. At that level of resolution, Penfield has turned out to be correct. But it is the next level of resolution, the issue of how neurons are organized within those areas, that more recent research has begun to unravel.

3D movements a problem

One of the main conundrums the research has had to address is the fact that something as complex as muscle activity or movement is not readily mapped onto a two-dimensional sheet of neurons such as the primary motor cortex. Consider the elbow joint, which is controlled by many muscles working in different combinations to produce different movements. What is more, the elbow doesn't move in isolation; movements of the elbow put force on the shoulder and wrist as well, so other muscles must be activated to stabilize those joints. "You would be expecting too much if you thought you could represent three-dimensional movements and muscles on a two-dimensional cortex and have a neat point-to-point map," says Rochester's Schieber.

Neuroscientists considering this problem decades ago hypothesized a simple solution: They suggested there might be a one-to-one correspondence of cortical cells to individual muscles. But work done in the 1960s and 1970s laid that notion to rest by showing that individual muscles get input from multiple spots on the cortex and individual cortical neurons have branches connecting them to motor neurons that control more than one muscle. "The relationship was not one-to-one, but one-to-multiple," says Yoshikazu Shinoda of the Tokyo Medical and Dental University, one of the researchers involved in this early work.

With individual cortical neurons linked to multiple muscles and each muscle in turn linked to multiple spots on the cortex, researchers began to wonder if there was a different kind of rhyme or reason to the wiring. Perhaps the muscles driven by an individual neuron might work in concert to produce a given movement.

Studies that began in the late 1970s and are still going on today have shown that such a correspondence does exist. This work got under way when Paul Cheney and Eberhard Fetz, at the University of Washington, Seattle, developed a means of correlating the activity of single cortical neurons with the activities of muscles used by monkeys in performing trained movements. When they used the method to study simple wrist movements, they found that certain individual neurons controlled muscles that worked together in a synergistic way, producing wrist extension, for example. Those same neurons also inhibited muscles producing the opposite movement. "This is a good example of functional synergy that is well-suited for producing movement in a particular direction at one joint," says Cheney, who still studies muscle synergies at the University of Kansas Medical Center in Kansas City.

The synergy discovered by Fetz and Cheney was not limited to just one joint, as

SOURCE: Y. SHINODA, J. YOKOTA, T. FUTAMI, *NEUROSCIENCE LETTERS* 23, 7 (1981).

other researchers showed. Roger Lemon, at Cambridge University, U.K., applied Fetz and Cheney's technique to the fingers, whose amazing dexterity led many researchers to argue that they, more than any other body part, must be controlled by a one-to-one neuron-to-muscle correspondence. But Lemon reported in the mid-1980s that he hadn't found such a fit. "Most of [the neurons] address a number of different muscles," says Lemon. "They also span muscles activating at the wrist with muscles that activate the fingers."

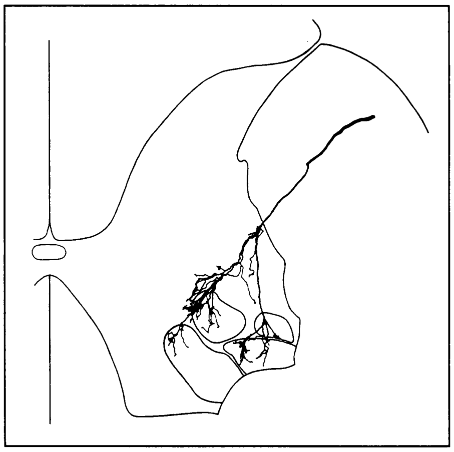
Then, just last year, Brian McKiernan, Jennifer Karrer, and their co-workers in Cheney's lab expanded the notion of synergy even further. McKiernan reported at last November's meeting of the Society for Neuroscience that when they studied monkeys doing a task that involves reaching forward with one arm—a movement that employs wrist, elbow, and shoulder—they found individual neurons that appear to control muscles at all three joints. In their study, multijoint connections weren't a fluke; nearly half the neurons the team sampled were linked to muscles at more than one joint.

The bottom line is that many cortical neurons control synergistic sets of muscles, and most muscles are controlled by multiple sets of neurons. But those findings alone don't rule out the possibility of an orderly, albeit somewhat fuzzy, map. For example, within Penfield's arm zone, Cheney says there seem to be "separable regions for distal muscles [that control the wrist and hand] and proximal muscles, proximal being elbow and shoulder." Such zones were in fact identified in the arm zone of the primary motor cortex by John Murphy and his colleagues at the University of Toronto in the 1970s. They found a cluster of neurons controlling the hand area, with neurons controlling the more proximal areas of the arm arranged in concentric horseshoe shapes around that core.

Mixing it up in the cortex

That horseshoe-shaped map may not resemble the arm of the homunculus, but it nevertheless constitutes a map, with contiguous areas representing the parts of the arm. But the idea of individual contiguous areas was called into question in 1978, when Peter Strick and James Preston, at the Veterans Administration Medical Center and the State University of New York Health Science Center at Syracuse, found that the primary motor cortex contained a second cluster of hand-specific neurons.

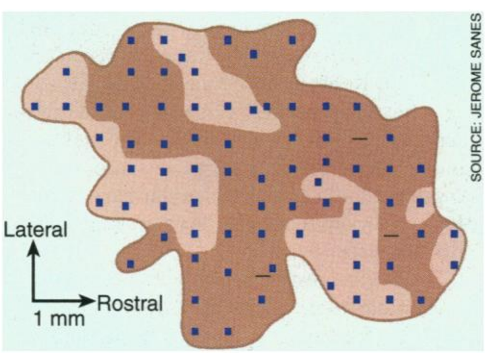
Strick and Preston's finding foreshadowed the further fragmenting of the map that was to come. Several studies published within the past 5 years suggest that the arm area is in fact riddled with zones that specialize in hand control, intermingled and overlapping with other zones that control the



One to multiple. A cortical neuron links up to two different sets of motor neurons controlling the arm.

upper arm. In the early 1990s, for example, Sanes and Donoghue at Brown, with Steven Leibovic at the Massachusetts Institute of Technology, measured the responses of 14 hand and arm muscles in monkeys while electrically stimulating neurons all over the arm area of the motor cortex. They found a mosaic of cortical patches that control hand muscles, separated by other patches that activate muscles of the upper arm. There was also plenty of overlap between areas controlling the arm and those controlling the hand; it was in one of those overlap zones that Cheney's group found the neurons that control muscles of the wrist, elbow, and shoulder.

In 1993, Schieber, then at Washington University in St. Louis, and Lyndon Hibbard, also of Washington, took a different approach to the same problem. Reasoning that the artificial electrical stimulation applied by Sanes and Donoghue might not reflect normal cortical activity, they instead recorded the activity of primary motor cortex cells while monkeys were making trained movements of different fingers. Like Sanes and Donoghue, they found that widely spaced sets of neurons are involved in each finger movement. Although the set for each finger was different, there was extensive overlap among the neurons included in any one set. That, says Schieber, suggests that "the control of whether the thumb moves or the little finger moves is not handled by a spatial map," but instead depends on the activity pattern of a whole population of neurons.



Patchy mosaic. Finger *(light)* and arm *(dark)* areas intermingle in monkey motor cortex.

Researchers study monkey motor cortex because they can't stick electrodes into peoples' heads, and monkey brains are the closest approximation to our own. But noninvasive imaging studies are confirming that the human motor cortex indeed resembles that of monkeys. Studies using positron emission tomography (PET) in several labs have suggested that the areas controlling arm and hand movements are interspersed with one another in the primary motor cortex.

And now two studies, one by Sanes and Warach and their co-workers in this issue, and another by Stephen Rao of the Medical College of Wisconsin in Milwaukee and his collaborators, published in the May issue of *Neurology*, have applied functional magnetic resonance imaging, which has a higher resolution than PET, to the problem. These results show even more convincingly that individual finger movements are apparently controlled by networks of neurons that occupy overlapping areas within the primary motor cortex. "The pattern that you see is unique for each hand movement," says Sanes, but the different patterns "overlap by about half."

The picture emerging from all this work is one in which neurons scattered throughout a given large body zone of the primary motor cortex (such as the one representing the arm) can be called on to activate the multiple muscles necessary for a movement. And that, says Lemon, now at Queens Square Hospital, London, suggests that rather than a spatially organized map, there is an entirely different kind of map, "a map of combinations of muscles, arranged in useful ways, almost like books on a shelf that you can pull out when you need them." In such a scheme certain neurons might control a coordinated set of muscles to produce a common component of many movements, such as reaching forward with the arm, while others would be added to provide the fine-tuning necessary to make that movement unique.

Getting it together

But if those neurons are scattered around the arm area, what provides the look-up system, as it were, to pull the right books off the shelf? Sanes points to a 1991 study by George Huntley and Edward Jones, at the University of California, Irvine, that he thinks may provide a clue. Jones and Huntley showed that an extensive network of connections links neurons throughout the arm area of the primary motor cortex, but doesn't cross over into the neighboring areas that control the face and torso. That, says Sanes, is just the kind of pattern that would be required to connect the scattered neurons involved in arm movement.

Such connections would reduce the need for an orderly map, adds Schieber, because neurons could be called into action in a way analogous to how computers store files on a disk. "The computer can write different bits and pieces of one file at different spatial locations on the disk," he says, "then it goes from place to place on the disk, picking up pieces of information it wants."

Such a dispersed system would be well suited to providing plasticity—the constant reforming of neural liaisons associated with learning, which is known to go on in the motor cortex as a person or monkey learns new motor skills. "The horizontal connections ... would allow new representations to emerge and to come back to their original forms in a very dynamic way," Sanes says.

The new findings also provide clues to a special function that primary motor cortex may play in movement control. The cortex is not absolutely necessary for movement; other brain areas also make connections with the motor neurons of the spinal cord. Cats can walk even when their cerebral cortex has been removed, and monkeys without a primary motor cortex can be trained to make many types of movements. Such findings raise the question of what essential tasks the primary motor cortex performs.

SUNY's Strick proposes that the multimuscle connections of cortical neurons make the primary motor cortex particularly suited to guide complex actions that require the coordination of several muscles. In support of this hypothesis, Strick and co-worker Donna Hoffman have shown that monkeys with lesions in their primary motor cortex, while severely handicapped at first, can be rehabilitated to do many simple movements that depend largely on single muscles, such as flexing and extending their wrists. As Strick and Hoffman found earlier this year, however, the animals never regain their ability to make smooth diagonal movements that use two muscles simultaneously, such as wrist flexion with deviation to the side. To make that diagonal movement, Strick says, the monkey is reduced to using first one muscle, then the other, producing "zig-zag movements, as if tacking like a sailboat." That, he adds, suggests that "moving on the diagonal is something that would require the unique branching patterns of the cortical neurons."

So out of the remapping of the primary motor cortex comes not only a new understanding of how this brain area is arranged, but also new insights into its crucial role in complex movements. And that means that whether you are pumping iron or doing something as routine as tying your shoes, you can thank your primary motor cortex that you can glide smoothly through the movements without any zigs or zags.

–**Marcia Barinaga**

Additional Reading

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CHEMISTRY

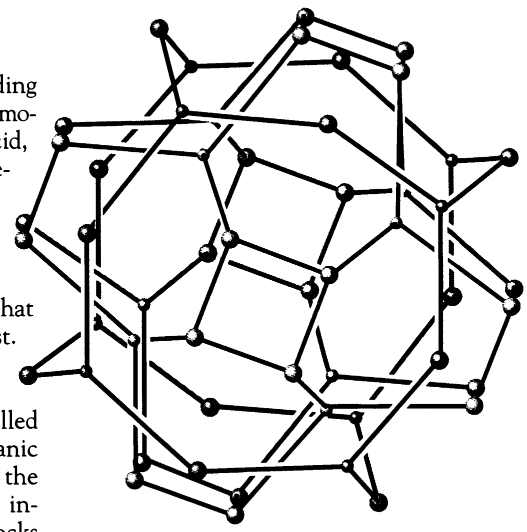
Sentencing Molecules to Prison

Chemists undoubtedly rank as the world's most proficient jailers. They are now adept, for example, at placing single atoms in solitary confinement, using as jail cells hollow molecular cages such as the 60-carbon molecules known as buckyballs. Researchers have long wanted to build a different kind of prison, however—one with cells large enough to house large groups of molecular prisoners. In those close quarters, chemists hope, the molecules might react in new ways. But such large cages have proved to be hard to build.

Now serendipity has intervened, and a group of Australian researchers has succeeded not only in creating larger cages but in trapping molecules inside them. The researchers, led by Richard Robson of the University of Melbourne, reported in the 17 May *Journal of the American Chemical Society* that an experiment meant to produce one kind of structure yielded something quite different: a crystalline lattice with a regular array of spherical cells 23 angstroms across. X-ray crystallography showed that these chambers were big enough to trap as many as 20 large organic molecules from the solvent in which the structure takes shape.

"It is pretty exciting," says Jeffrey Moore, an organic chemist at the University of Illinois, Urbana-Champaign, because the small confines of the cages may allow researchers "to steer chemical reactions down a different chemical path" from the one the molecules would take on their own, perhaps yielding new and useful products. And because the molecular cages can easily be dissolved by acid, researchers should easily be able to recover any reaction products they create.

Initially, Robson says, he and his colleagues Stuart Batten and Bernard Hoskins set out to make a new type of zeolite—a porous crystalline structure that can act as a molecular filter or a catalyst. To do so, they blended four building blocks—ions of zinc, cyanide, and nitrate, and large organic molecules called tri(pyridyl)1,3,5,-triazine—in an organic solvent. Intermolecular forces caused the building blocks to self-assemble—but instead of forming porous crystals, the blocks arrayed themselves in planes made up of cagelike compartments interspersed with rings.



SOURCE: ROBSON *ET AL.*

Cagey chemistry. Two structures interlock to create a secure molecular jail cell.

The planes then stacked, interpenetrating so that the rings in one plane encircled the cages in the other. "It was purely accidental," says Robson. "We had no idea this sort of thing was possible." The result was a high-security molecular prison for the solvent molecules: Because the rings reinforce the cages with additional molecular bars, "there isn't any room for anything to get in or out," Robson says.

Next, the researchers hope to trap reactive molecules, such as alkenes, to see whether the confined geometry encourages them to form novel structures. Ordinarily, alkene molecules prefer to link up with hundreds and thousands of their kind to make long polymer chains. But the jail cell limits the number of molecular building blocks, preventing such chains from forming. Under those circumstances, Robson believes, the molecular building blocks may instead produce ring-shaped structures with novel chemical properties.

Whether such products will ultimately prove useful, Robson says, "we won't know until we try." Either way, the researchers hope to learn whether their tiny prisons are as good at transforming molecules as they are at trapping them.

–**Robert F. Service**