The brain may be one of the last great frontiers, but scientists thought they at least knew this much—such-and-such region controls thought, another controls emotion, another movement. . . . But there's much more interaction among regions than people thought. Pitt's Peter Strick, an expert on voluntary motor control, knocked the neuro community off its feet with his findings.

BRAIN STUDIES DELIVER DECISIVE BLOWS TO CONVENTIONAL THOUGHT | BY EDWIN KIESTER JR.

THE SWEET SCIENCE OF MOVEMENT

The first punch, high on the cheekbone, snaps the boxer's head back. Instinctively, he raises his gloves to protect himself. Welterweight champion Sugar Ray Leonard immediately seizes the opening to punish his opponent. Left-right-left-right-right, the flurry of punches coming so quickly the other man, flustered and knocked off balance by the fusillade, lowers his hands to shield his body. At that moment, Leonard throws a rocket-like right to the head. The opponent goes down.

To aficionados of what the writer A. J. Liebling called "the sweet science," that exhibition by Leonard, one of the fastest and most skilled boxers of his time, was a classic example of what used to be termed "the manly art of self-defense." To the University of Pittsburgh's Peter Strick, who's also a boxing fan, Leonard's rapid-fire five-punch combination represented something more—a shining example of a subject to which he has devoted a 30-year research career.

Lightning-fast Sugar Ray Leonard rejoices after defeating Tommy Hearns to win the 1981 welter-weight crown.

PHOTOGRAPHY | JEN URICH
EXCEPT WHERE NOTED

FROM LEFT: Nathalie Picard, Donna Hoffman, and Richard Dum with Strick at his breakfast meeting haunt, Foster's in Oakland.

In fact, Strick likes to show medical students video footage of Leonard throwing flurries of punches almost too fast for the camera to catch.

"When Sugar Ray hit a speed bag, obviously he wasn't thinking, 'Now I'll throw the left, now the right,'" Strick says. "The bag moved too fast for that. The punches were all part of one swift, sequential movement that was entirely preprogrammed somewhere in his brain."

Strick, a personable 55-year-old who discusses boxing and basketball as readily as neurons or glial cells, has built an international reputation as an expert on the brain's role in voluntary, automatic, sequential movement, the kind we perform fluidly, almost without thinking of the individual movements, like writing a signature, playing a glissando on the piano—or throwing a five-punch combo.

Strick's mouthful title is codirector of the University of Pittsburgh/Carnegie Mellon Center for the Neural Basis of Cognition (CNBC), senior research career scientist at the Research Service, VA Medical Center, and Pitt professor of neurobiology, neurosurgery, and psychiatry.

He's also a cartographer of sorts. By inserting a mild virus (such as herpes simplex) into an animal's brain and following its progress via staining techniques, his group has been able to watch the virus travel from nerve cell to nerve cell. The result has been a much more complete and detailed map of the brain's circuitry, disclosing previously little-known links between different brain regions.

"The conventional way of tracing brain connections told us which region of the brain connected to which other region, one connection at a time, the immediate inputs and outputs," Strick says. "But imagine trying to understand the New York City subway system or the London underground by only knowing where the train's coming from one stop before yours, and where it's going one stop afterward.

"The virus moves from neuron to neuron, over as many as five connections, and in that way we can look at the network of connections in ways never before possible. It's changing the way we think about the brain and certain areas of the brain.

"You can get a great deal of insight into the function of different brain regions by looking at how they're connected."

"Peter," says W. Thomas Thach of Washington University in St. Louis, a prominent expert in cerebellar research, "has made a cornerstone contribution to a fundamental area of cognition. The sophisticated viral tracing he developed was the pivotal step in what we now know about the field." Mark Hallett of the National Institute of Neurological Disorders and Stroke adds, "Peter is among the best investigators in the world on how the motor system works. His virus work is only his most recent contribution. He was already at the head of the pack before that."

Strick came to Pittsburgh in 2000 from SUNY Upstate Medical University in Syracuse, New York, bringing with him three longtime colleagues as principal investigators: the husband-wife team of Donna Hoffman (an expert on brain control of arm movement) and Richard Dum (renowned for his work on the spinal cord) as well as Nathalie Picard (whose discoveries have lent insight into how motor learning affects and changes regions of the brain). He also brought with him a primate colony, many of whose inhabitants, he notes, "have lived with us 15 years."

When Strick emerged from graduate school, what intrigued him most was the brain's role in voluntary movement, particularly movement of the hand. As his colleague Dum eloquently

"When Sugar Ray hit a speed bag, obviously he wasn't thinking, 'Now I'll throw the left, now the right.'"

points out, how we humans use our hands is what distinguishes us from other creatures, and what we use to make our world unique. Skillful hands allow us to create tools, build houses, paint pictures. The hand can perform hundreds of simple and complicated movements, from grasping and gesturing to playing a Beethoven sonata. Yet humans mostly use their hands automatically, without consciously thinking about the individual movements and without connecting movements to what signals are sent down from upstairs. A concert pianist does not deliberate about which finger strikes which key, but concentrates on phrasing, tempo, fortissimo, and diminuendo. The keystrokes are almost automatic, the result of trained fingering.

Strick's interest in voluntary movement, he acknowledges, may stem from his days as a schoolboy athlete. He attended high school in Philadelphia, where he was a basketball teammate of Reggie Jackson's (the same Jackson who turned to baseball and became known as "Mr. October" for delivering clutch home runs for the A's and Yankees in the World Series).

"Reggie wasn't too tall then, he grew after high school, but he was a strong forward with an incredible vertical leap, and he had an old-fashioned two-hand set shot from the top of the key. He was fascinating to watch. He was one of the few in those days who had learned how to dunk."

By the time Strick earned a PhD in neuroanatomy at the University of Pennsylvania, his own hoop time was relegated to the playground, half-court variety. After four years at the National Institutes of Health, in 1976, he went to Syracuse, where he held joint appointments in neurosurgery and physiology. There, he assisted neurosurgeons with the treatment of intractable movement disorders, like Parkinson's disease.

Then and now, most scientists pursued one or two techniques for investigating brain function. For example, some observe brains damaged by stroke or experimentally lesioned animal brains. Some electronically stimulate the brain and monitor what happens. . .

Strick prefers to pursue many approaches: "No one approach can give you the necessary breadth and perspective.

"Suppose one were to rely solely on the lesion approach to unravel the function of a brain region." He compares the lesion method to taking away a car's spare tire. "Remove the spare. What do you learn? One could come to the conclusion that the spare tire has no function because immediately after its removal, the car suffers no negative consequences. Obviously, the spare is needed for a certain specific set of circumstances. Unless we test those conditions, we learn very little about the function of the spare. The same is true for some brain lesions."

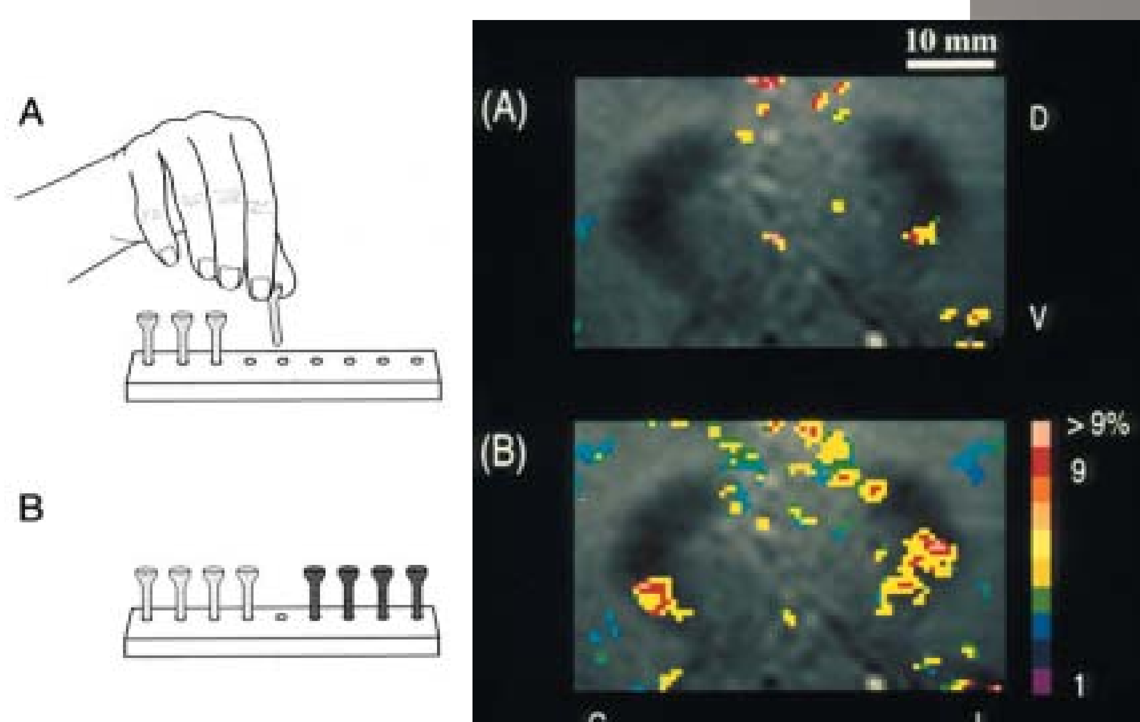
Among his many investigations in the '70s and '80s, Strick explored how the normal brain made fluid movement, like Jackson's dunk shot, possible.

Eventually, he became interested in tracking brain connections. He tried several methods of injecting dyed substances into individual neurons and then monitoring the substances' movement. Then, in 1986, he came upon the viral tool.

Viral tools for tracing brain circuitry had actually been devised years earlier, set aside, and then revived by the late Hans Kuypers at Cambridge University in England. Kuypers injected a virus to chart brain connections in laboratory mice. Strick felt the method could be adapted for primates, and thus could have greater application for humans. He spent a couple of sabbaticals studying with Kuypers in Cambridge, then returned to Syracuse to put his lessons into practice.

Perfecting the technique took years; but he and a graduate student, Frank Middleton, reported success in primates in 1994. Their paper in *Science* was a heads up to cognitive investigators throughout the world, Thach recalls. Using viruses and antibody tracers attached to them, they were able to trace a multineuronal pathway to the prefrontal cortex, an area involved in higher executive functions and working memory, from the cerebellum—supposedly out of the thinking/emotion loop. In experiments with other students, Strick later showed that the prefrontal cortex and cerebellum were part of a closed loop circuit that continuously communicates information back and forth between the two remote structures.

Then in another eye-opening experiment,



With colleagues in Minnesota, Strick was among the first to report that the computational power of the cerebellum is applied not only to controlling movement but also to cognitive functioning. In A (above), study participants were asked to perform a straightforward task—i.e., moving the pegs, one by one, from one end of the board to the other—which slightly activated the dentate nucleus of the cerebellum, not surprisingly. When the participants were presented with a puzzle (B) that was much more difficult to execute, activation in the dentate nucleus was three to four times larger.

If you try to write your signature with your opposite hand, that hand will still follow the same pattern of movements to form the letters, however illegible the result.

Strick collaborated with Seong-Gi Kim and Kamil Ugurbil at the University of Minnesota. The group was the first to use functional magnetic resonance imaging at high magnetic field strength to examine the activity of the dentate nucleus of the cerebellum in humans. During scans, all subjects displayed substantial activation of the dentate during attempts to solve a pegboard puzzle. The area activated was three to four times greater than when activated during simple movements of the pegs. These results provided unmistakable evidence that the cerebellum was plugged into the thinking process.

Remember, the cerebellum—the fist-sized brain structure at the back of the head that sits atop the spinal cord—traditionally had been considered a lower brain center. Most thought it was concerned with such basics as coordination and balance, primitively signaling via the spinal cord when and how the muscles should act and move. It was thought to be removed from more sophisticated matters such as thinking and feeling.

Looking back, Strick offers a perspective on the cerebellum in terms that would sound familiar to anyone who has sipped a second martini: "Some cerebellar neurons are quite sensitive to alcohol, and if you drink too much, you can experience wobbliness, dizziness, unsteadiness, what is called 'ataxia.' Your speech becomes slurred, uneven. The alcohol reaches your cerebellum and affects your balance and motor movement. But there are also changes in behavior. You may become less inhibited. You may become aggressive. Your judgment is impaired. Maybe you make bad decisions. Now we're not just talking about simple movement and posture. What we call executive function has been interfered with.

"Clearly that portion of the cerebellum is involved with more than how you stand or move."

Strick's work substantiated what a rather unlikely pair of neurological commentators had been stating, to sometimes disdainful hoots, for several years. "Peter," says Henrietta Leiner, "confirmed in experimental work what we had been saying theoretically." Henrietta and Alan Leiner, who are married, both 88, and living in a retirement home in Palo Alto, California, are not neuroscientists by training but computer scientists. They became intrigued by the resemblance between computer wiring and brain circuitry. After her children had grown, Henrietta Leiner enrolled as a nondegree student at Columbia University to study neuroanatomy, bringing home armloads of texts to pore over diagrams of how the brain was put together. The couple concluded the role of the human cerebellum in human behavior had been vastly underestimated.

"You could clearly see that a huge number of fibers connected the cerebellum to the so-called higher brain centers," Henrietta Leiner, the more talkative of the two, said recently.

"When you see such a cluster of wiring in a computer, you know that a great deal of information is being communicated." Scientists had been using the monkey brain as a model, but it has far fewer such fibers than the human brain. In humans, the fibers are denser, and the dentate nucleus is larger. "The human cerebellum is clearly different," Leiner continues, "and much more involved than anyone believed. We call it 'the treasure at the bottom of the brain.'"

Strick read the Leiners' article, "Does the Cerebellum Contribute to Mental Skills?" when it was published in collaboration with neurologist Robert S. Dow in the journal *Behavioral Neuroscience* in 1986. Strick was, shall we say, skeptical of the paper: "I thought they were nuts." But when his own laboratory outlined the very connections between cerebellum and "higher centers" as the Leiners had predicted, he became a believer. Repeatedly, in experiments like the peg game, the cerebellum "lit up like a Christmas tree" (as Leiner likes to say), not only when the subject was actually moving pegs, but when mulling over the next move, brow furrowed, but hands still.

ERICA LLOYD

Henrietta and Alan Leiner

"The most important thing Peter has contributed," Leiner says, "has been to show for the first time that the cerebellum not only sends fibers and information to some prefrontal areas of the cerebral cortex but also receives fibers from these same areas. No one had ever seen that before. That means the cerebral cortex can talk to the cerebellum and exchange information. That kind of feedback loop is central to the computer.

"That concept led to a whole 'engineering way' of looking at the brain."

"The conventional view of the brain used to be one of localization," Richard Dum says. "This part of the brain controls movement, this part controls thought, this part does feelings. They each have their own discrete roles. But there is a lot more interaction and cooperation going on than was once believed. We have seen that the brain is much more complex than people thought."

Those complexities between voluntary motor movement and other regions of the brain are what intrigue Strick.

He cites an example. When you write your signature, you do it in one swift, practiced, fluid movement, like Sugar Ray Leonard throwing his combination of punches. You don't think about how to form the loops of the Es or when to cross the Ts. And if someone interrupts you midway through your scribbling, you may have to go back and start over. You can't just pick up where you stopped.

So what part, or parts, of the brain guides the pen?

If you try to write your signature with your opposite hand, that hand will still follow the same pattern of movements to form the letters, however illegible the result. Same if you hold the pencil between your toes and try to write that way. It won't exactly match your signature on a check, but, Strick says, "a handwriting expert comparing them would say they're by the same person. It's the same if you hold the pencil between your teeth. So it's not just a matter of hand and arm movement. The blueprint for that skill is stored somewhere within the brain."

But where? And in what form? Is the blueprint located in one place or throughout? Does that blueprint inflict structural changes, chemical changes, changes between the neuronal connections, changes in the way neurons reach out to each other? Those questions remain to be answered.

"That is," says Strick, "why I still have a job." ■