

With its million-fiber map, HDFT brings the wiry connections of the brain into better focus than ever before. Here, a healthy brain shows no tracts are disrupted.

A NEW TECHNOLOGY ALLOWS DOCS TO
SEE MISSING CONNECTIONS IN THE BRAIN

BY JENELLE PIFER

MISSING LINKS

Imagine you're talking to a coworker about what you'd like to eat for lunch—a salad. You can see the salad in your mind—the greens, the cherry tomatoes, the dressing on the side. You can visualize the word, anticipate the consonants rolling around in your mouth. You go to say it aloud—*salad*. But the word you know, can see, can feel, can practically taste, escapes you. What's that thing called again? You start to feel like you're losing it.

This was one symptom presented by a recent stroke patient seen by Juan Fernandez-Miranda, an MD and assistant professor of neurological surgery at the University of Pittsburgh and director of Pitt's Surgical Neuroanatomy Lab. "He has expressive aphasia," says Fernandez-Miranda. "He has trouble articulating words."

The patient underwent an MRI, which confirmed the damage was concentrated in the left, language-storing side of the brain. "Some of the areas of the left hemisphere are smaller than normal," says Fernandez-Miranda. But that's really all the MRI could reveal—a thinning of white matter. What the picture didn't show was the nature of the damage: which connections were broken and what exactly was blocking the word's passage from brain to mouth. "Language is a dynamic process, so you need to understand the connectivity between areas to understand the problem."

A new technology developed at Pitt is making that connectivity clear for the first time.

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High-definition fiber tracking (HDFT) runs data from a top-end MRI machine through computational software so that, instead of producing a flat, black-and-white scan of tissue, it generates intricate 3-D images of connective fibers in the brain. Formerly, scientists could only study these connections during post-mortem dissection, or in vague detail through less-precise scans. Now, brain connectivity can be measured, much more thoroughly and accurately, in live patients.

“In warfare and in medicine, it’s hard to defeat an enemy you cannot see,” says Pitt professor of psychology and neurosurgery Walter Schneider, a PhD, whose team developed the technique. “That doesn’t mean you don’t try and do things, but it’s certainly quite difficult.”

Doctors and neuroscientists around the world might use a scanning technique called diffusion tensor imaging (DTI), which measures the movement of water through the brain. The idea is that by watching the way water flows, you can determine the shapes of the fibers it runs through.

The problem lies in the mathematics: DTI software can’t account for instances where the fibers cross. And fibers cross all the time. So when the technology detects water moving in one direction and then another, it simply takes the average. The resulting scans show the major stems of fiber tracts—a valuable and revolutionary breakthrough—but the details are still hazy and can lead to inaccurate diagnoses.

“A fuzzy image doesn’t help you any clinically,” says Schneider, also a senior scientist in Pitt’s Learning Research and Development Center. “[DTI] had the right intent but wasn’t powerful enough to accomplish the goals that were intended.”

Doctors need a technology that can follow a fiber through its crossings, so five years ago Schneider and Sudhir Pathak, a programmer in his lab, set about refining the math. They’d alter the computational method, scan a brain, and show the image to Fernandez-Miranda, one of the world’s preeminent neuroanatomists. “He’d say, ‘Well, that’s good, but it’s wrong,’” recalls Schneider.

Fernandez-Miranda knew enough about fiber tracts from studying dissections to know when the maps were off. Year after year the method got better. “Juan would say, ‘Hey, you got this one right. How about this one?’” says

Schneider. By September 2010, the technique was so precise it could out-predict Fernandez-Miranda. “We could noninvasively get fiber tracts that were better than what he could do with cadaver tissue.

“At that point we hit a critical point of utility and quality, and a lot of the clinical work began,” Schneider says.

Everyone has the same 40 major fiber tracts, connecting certain parts of the brain to others, but—like the way arms and eyes differ in size and shape—the way each tract’s fibers connect can vary enormously. So studying cadavers could only go so far in helping doctors understand what might be happening in their own live patients.

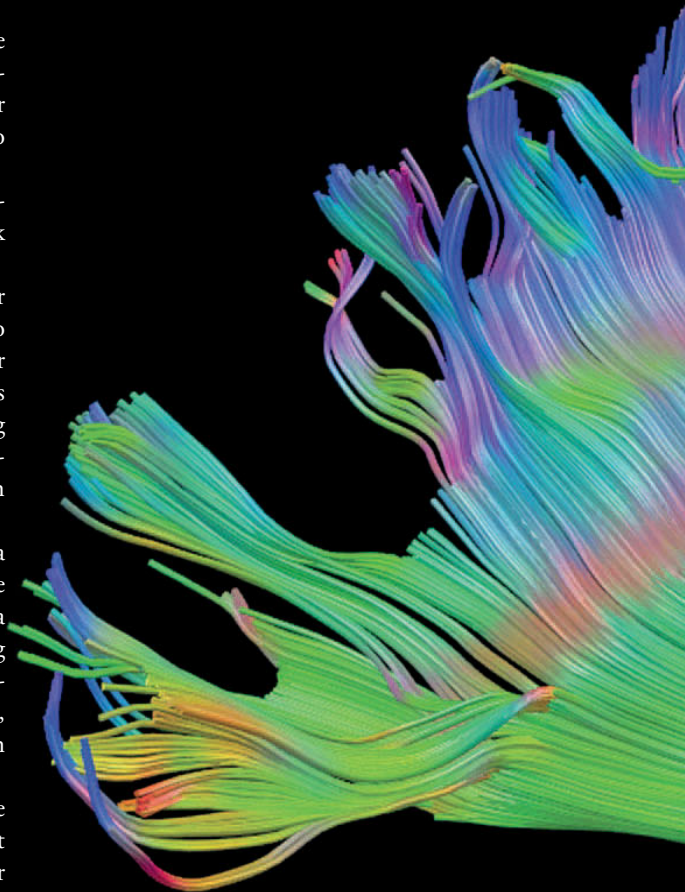
Now the Schneider lab partners with a team of basic scientists (researching things like vision, language, and attention), as well as a team of 10 neurosurgeons who are applying HDFT in the clinic to help people with conditions as diverse as traumatic brain injuries, tumors, autism, and Alzheimer’s. More than 120 patients have been scanned so far.

“For surgery, the application is much more immediate,” says Fernandez-Miranda. A recent patient, for example, presented with a tumor in the left corticospinal tract, which controls movement. A traditional MRI clearly revealed the location of the tumor, but not what surrounded it.

“I have a tumor here,” says Fernandez-Miranda, pointing to a mass on an MRI. “But do I have motor fibers here, or not? How about inside the tumor?” HDFT revealed that only a few fibers passed through the tumor and that most of the important ones had been pushed toward the outside of the skull. Knowing this, they determined that the best approach was from the midline.

In presurgical planning, HDFT can also present patients with the profound opportunity to choose which side effects they’d prefer to deal with. A surgeon can say, for example: If we approach this way, we risk losing mobility; if we go in that way, we might compromise mood control. “Now we have a basis from which to have a meaningful discussion with the patient,” says Schneider.

One of Schneider’s primary partnerships at Pitt is with David Okonkwo, an MD/PhD, associate professor of neurological surgery, and clinical director of the Brain Trauma Research

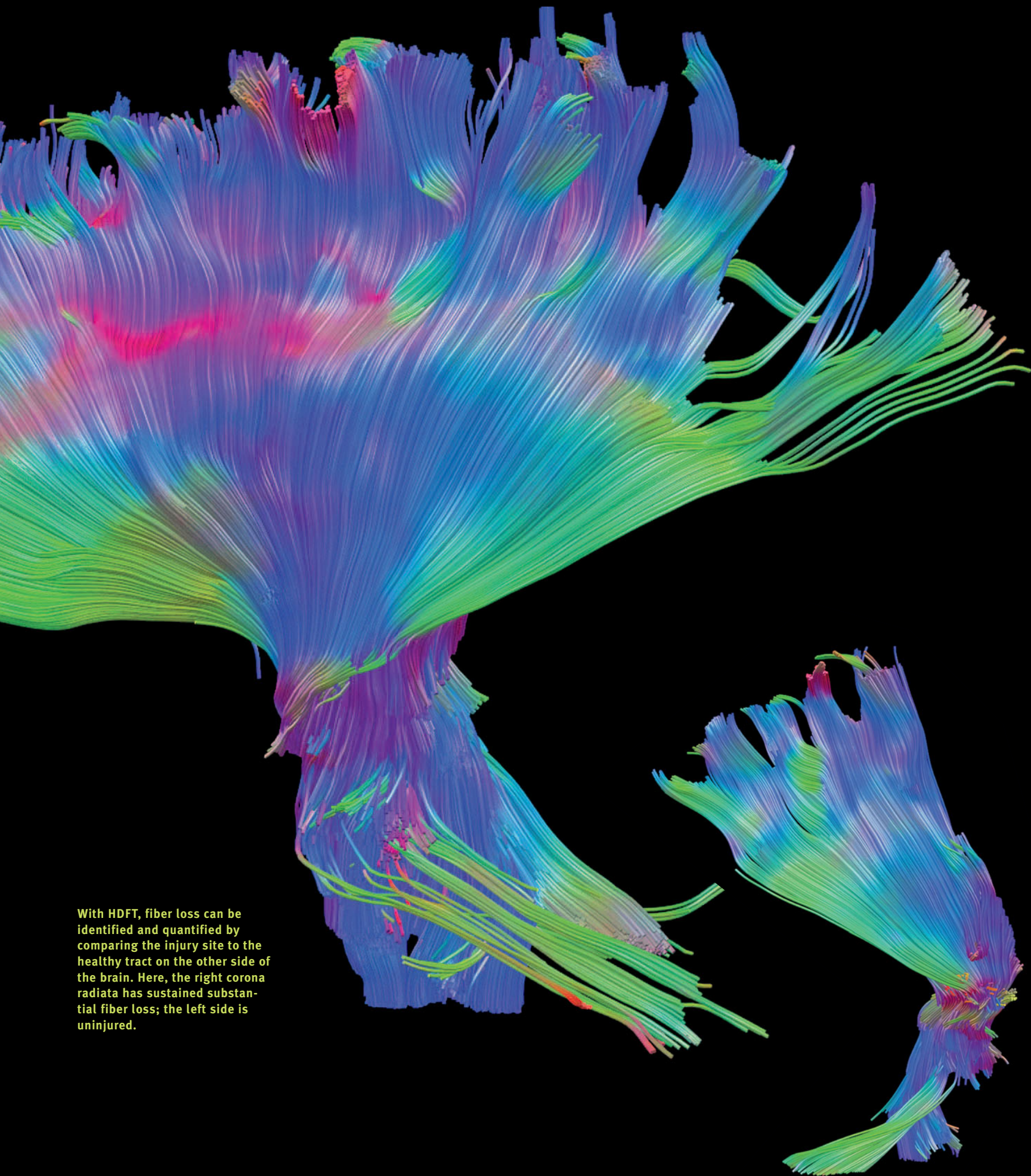


Center. They are using HDFT to guide treatment of traumatic brain injury. In the United States, TBI occurs in 1.7 million people annually and is the most common cause of death between ages 2 and 35. In most TBI cases, an MRI doesn’t show doctors much—maybe some swelling or bleeding, but not the actual damage. This leads to a diagnosis that doesn’t tell patients, with much certainty, what’s wrong or how they can expect to heal.

“Having an ambiguous diagnosis is really problematic,” says Schneider.

“It’s okay to say, ‘You have swelling in your head. It’s a head cold, and it’ll clear up in three days.’ But not to say, ‘We don’t know, you may never work again in your life.’”

Because doctors can’t see what’s broken in the brain, they rely on outward manifestations—the symptoms—to determine therapy. Recently a patient with TBI (who’d flipped his ATV, end-over-end) presented with limited



With HDFT, fiber loss can be identified and quantified by comparing the injury site to the healthy tract on the other side of the brain. Here, the right corona radiata has sustained substantial fiber loss; the left side is uninjured.



mobility in his arm, hand, and leg. Traditionally he would have started intensive physical therapy in each area, in the blind hope of regaining function. But with HDFT, his doctors can be more realistic, and strategic.

By mapping what percentage of a given fiber tract is damaged, Schneider can determine whether or not function is likely to return. For the patient in question, HDFT revealed projection to the hand was 97 percent lost, to the arm 67 percent, and to the leg 60 percent. Although he could still move his arm, the man's club hand would likely never heal. "People can get over losing a limb: They understand it. They grieve the visible loss. They move on," Schneider says. "You do nobody any good to tell them to work hard at something that's impossible. We need to know how much is left so we know how best to invest hard but limited hours of rehabilitation to bring back function."

The good news: Even though the patient couldn't move his leg at the time, Schneider knew he had enough fibers remaining to walk again. "That's going to take months of hard physical therapy," Schneider says. "We would tell a patient, 'It's not going to be easy, but we have scientific evidence that suggests it's going to come back. It's still okay to work on the hand but concentrate on the leg.'"

The technology can monitor how well a particular therapy works by keeping track of which fibers regrow. It's probably not possible to grow a new fiber if all the fibers of a tract are gone, Schneider says, but it is possible to increase the size of an existing fiber. "If you have a dirt road, we can make it into a highway. If you don't have the dirt road, we can't."

In the case of Fernandez-Miranda's stroke patient mentioned at the start—he'll likely begin language therapy similar to what would have been prescribed without HDFT. But with HDFT, his doctor can see, in detail, whether the therapy is changing anatomy. "You can first understand better the disease," says Fernandez-Miranda. "By doing that, eventually, I think we'll be able to design better therapies."

While HDFT is more accurate than any other technique available, there are still blind spots. "We can detect a 20 percent loss of a tract, but it has to be a reasonable size tract," Schneider says. There are some tracts where if you lose 1 millimeter, you'll never come out of a coma. "We aren't that good yet," Schneider says.

"We've made enormous improvements in the last three years, but we certainly haven't run out of ideas." His goal, Schneider says, is to make what his team developed 18 months ago obsolete. ■



The left arcuate tract connects areas of the brain responsible for understanding language and expressing it. The damaged tract of a stroke patient (right) is visibly thinner than the normal one (left), which explains why the patient can find the right word but can't say it.

THREADS OF LANGUAGE AND A VIEW OF TEMPLE GRANDIN'S BRAIN

As news spread about Walter Schneider's HDFT technology, autism activist Temple Grandin caught word. She wanted to have her brain scanned. Until that point, the new and immensely precise scanning technology had not been used to examine the brain of anyone with autism. "We were able to look at what might be different in terms of her fiber tracts," Schneider, Pitt professor of psychology and neurosurgery, says.

There are three subclasses of people with autism: those who never learn a language system at all; those who repeat what they hear without understanding meaning; and those who are capable of language but at times have a hard time verbalizing, even though they know what they want to say. Grandin is among the latter. (Grandin, who has a PhD in animal science, now lectures widely on autism as well as animal behavior and has written six popular books.)

Upon reading the scan, Schneider saw that fibers in Grandin's motor system—in regions thought to control repeating what you hear and naming what you see—were barely there: The tract was more than 90 percent smaller than a control subject's. "I told Temple, 'Your language may have been hanging on by a thread,'" says Schneider. "It was enough, with intense training, to grow it."

Yet Grandin had four times as many fibers connecting her visual system and frontal cortex, "potentially supporting her high visualization abilities," says Schneider.

The two hope to partner on a project to map the brains of people in all three subclasses. So far only four patients with autism have been scanned using HDFT.

Typically, parents notice symptoms of autism when a child is between 18 months and 2 years of age. "The highest priority should be to establish effective communication as soon as possible," says Schneider, whether that communication is verbal, pointing, or otherwise, to minimize psychological damage and stimulate language and cognitive abilities. HDFT can help decide which method to choose.

"The prize is to get a very early diagnosis so that you can speed the development of functional capability to be much, much earlier," says Schneider. —JP