THIS WAY IN

New Imaging Captures the Brain's Complexity

Imagine that you're walking past a building. From the outside, it appears to be in perfect shape. The windows, doors, roof, and framing all look sound. But then a structural engineer comes out the front door wearing a hard hat and tells you to step away—the building could fall down at any time. From the moment he went inside, the engineer could see visible signs of damage—large cracks in the load-bearing walls, columns buckling—that indicate a deteriorating and decaying structure.

It's too late now for the building: There's too much damage to its internal structure. Any attempt to shore it up would just be delaying the inevitable. But what if that structural engineer could see *inside* the load-bearing walls and columns? Then he might be able to detect the earliest signs of deterioration *before* it was too late to fix them.

That's exactly what some of the world's leading physicists and radiologists are trying to do with the human brain and nervous system, using an advanced form of magnetic resonance imaging (MRI) called diffusion kurtosis imaging. It's still fairly new and experimental, but standard MRI systems can be retrofitted to use the technology without adding more than a few minutes to a traditional MRI scan.

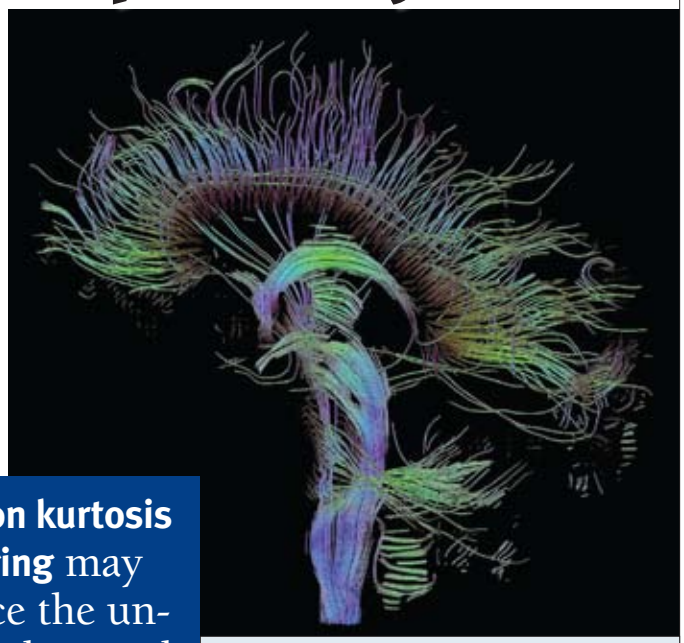
Radiologists use standard MRI to measure the volume of structures in the brain. When a person has Alzheimer's disease, standard MRI may show a decline in the overall volume of the hippocampus, an area of the brain that plays a critical role in memory. But standard MRI cannot show the changes in the brain that develop *before* the hippocampus starts to shrink—a time when drug therapies on the horizon might be able to change the course of the disease. That's where diffusion imaging—and beyond that, diffusion kurtosis imaging—comes in.

"MRI looks at water," explains Joseph Helpern, Ph.D., professor of radiology, psychiatry and physiology & neuroscience at New York University's Langone Medical Center. Dr. Helpern is one of the original developers of diffusion kurtosis imaging. "The beautiful clinical images provided by MRI tell us a lot about the gross anatomy of the human brain; they can even give us some information about the biophysics [such as volume and speed of movement] of the water in the tissue."

But to really understand what's going on in the brain, it may not be enough to look only at how much water there is or how fast it's moving. Another key parameter is called *diffusion*. "If I had special goggles to let me watch water molecules 'walk around' in a swimming pool, I'd see that the water moves randomly, not in any one direction," Dr. Helpern explains. "But eventually, I'd see that random motion develop into a spherical pattern where the water has been. That's diffusion."

If your pool has structures in it—like your brain does—the water will move in more defined patterns. A wall might cause the water molecules to diffuse on one side but not the other. If the pool has long plastic tubes in it, the water inside the tubes can move along the length of the tubes, but not between the tubes.

CONTINUED ON P. 10



THOMAS SCHULTZ

Diffusion kurtosis imaging may advance the understanding and early diagnosis of diseases such as Alzheimer's and multiple sclerosis.

DIFFUSION KURTOSIS IMAGING is at the cutting edge of brain science. You can help support similar advancements: Buy a "virtual brain" through the AAN Foundation (for as little as $5) and help make a difference in the lives of people affected by neurologic disorders. Go to patients.aan.com/donations/index.cfm? or call (866) 770-7570 to find out more.

CONTINUED FROM P. 9

The microstructures of the brain, such as the neurons and axons, are like those walls and tubes—they keep the water moving in a certain direction and prevent it from moving in other directions. Using diffusion imaging, scientists can see these very fine microstructures—not visible on standard MRI—and learn if they're working properly. For example, water moving along an axon in the brain should not move very far in a perpendicular direction because it's constrained by the boundaries of the axon. But if diffusion imaging shows that water is starting to flow not just along the axon but more upward and downward, this may indicate that the axon is losing its protective myelin—a marker of multiple sclerosis (MS). And, a number of studies have shown that diffusion imaging is more sensitive than standard MRI to the early changes in the brain that predict future memory decline in dementias such as Alzheimer's.

But even regular diffusion imaging has its limitations. To map some of the more unusual movements of water molecules in the brain, Dr. Helpern and a colleague, NYU Associate Professor of Radiology and Physiology & Neuroscience Jens Jensen, Ph.D., devised diffusional kurtosis imaging. Think of going from ordinary diffusion imaging to diffusion kurtosis imaging as going to see the movie *Avatar* in a regular theater—and then seeing it again in 3-D.

Diffusion kurtosis imaging may be particularly important for understanding injuries to the gray matter of the brain, which has become a key part of MS research in recent years. Most MS therapies only treat the inflammation caused by the disease. But in the pipeline are several treatments that could be neuroprotective—that is, keep the neurons and axons in the brain's gray matter from breaking down.

"We need a valid, sensitive marker to monitor a patient's response to these neuroprotective treatments, and I believe kurtosis has the potential to be this marker," says Mathilde Inglese, M.D., Ph.D., associate professor of radiology and neurology at NYU. "Kurtosis may also help us diagnose MS as early as possible, and studies have shown that early diagnosis leads to a better clinical outcome."

Diffusion kurtosis imaging is also likely to advance the understanding and early diagnosis of dementias like Alzheimer's disease, something Dr. Helpern and Dr. Jensen are now investigating in an NIH-funded study involving 80 patients with mild cognitive impairment—a precursor to dementia—and 80 age-matched controls. "We're getting better information with diffusion kurtosis imaging, which is likely to give us a better way of characterizing the changes associated with Alzheimer's disease at the earliest possible stage," says Dr. Jensen. "At some point, we hope to have therapies that can stop or slow down the progression of the disease. And if we catch it early, we can hopefully prevent most of the worst damage done by Alzheimer's disease." —*Gina Shaw*

MEMORY | LANGUAGE | VISUAL | SPATIAL | LOGIC | NUMBER

NEUROBICS

Color Confusion

Here is a colorful brain twister called the Stroop effect, invented by John Ridley Stroop in 1935. The color names below are written in a variety of colors. Try reading the list out loud, as fast as you can. It's harder than it looks, because your brain gets confused between reading the word and naming the color, a phenomenon that psychologists call *interference*.

Now try naming the colors of the words out loud, as fast as you can. Ignore what the words say; only pay attention to the actual colors. Most people find this task harder, because it is difficult to suppress our well-trained impulse to read what the words say—what psychologists call *response inhibition*. But with practice the task gets easier and easier, demonstrating our brain's incredible ability to rewire itself.

DIRECTIONS:

To test your Stroop effect prowess, see if you can answer these two questions.

1. **Find the six words that correctly name the actual color the word is written in.**
2. **Find the 12 words that correctly name the color of the following word or preceding word. Note: Consider that the word at the end of one line is followed by the word at the beginning of the next line.**

Enjoy the Stroop effect? Play Color Match, a game based on the Stroop effect, on the brain game site lumosity.com. —Scott Kim

RED BLUE YELLOW GRAY
GREEN BLACK RED GREEN
YELLOW BLACK BLUE GRAY
YELLOW BLACK RED BLUE
GRAY RED BLACK GREEN
BLUE GREEN YELLOW GRAY
YELLOW BLACK RED BLUE
BLACK GREEN RED GREEN
BLUE GRAY YELLOW GRAY

ANSWERS ON P. 38

NEUROLOGY NEWS

When Should People With Dementia Stop Driving?

A new guideline by the American Academy of Neurology (AAN) helps neurologists determine when people with Alzheimer's disease and other dementias should stop driving. (The AAN develops "clinical practice guidelines" to help neurologists make decisions about the prevention, diagnosis, treatment, and prognosis of neurologic disorders. Each guideline makes specific recommendations based upon a rigorous and comprehensive evaluation of all available scientific evidence.) It's an update of the AAN's 2000 guideline, which concluded that "patients with mild dementia categorically should not drive," says Donald J. Iverson, M.D., lead guideline author and a neurologist with the Humboldt Neurological Medical Group, Inc., in Eureka, CA. "The update softens the message to 'should strongly consider discontinuing driving,'" Dr. Iverson explains. The guideline is published in the April 20, 2010 issue of *Neurology* (and a summary of it for patients and caregivers is available at **aan.com/guidelines**; search for "driving and dementia").

> Updated guidelines recommend that people with mild dementia should **strongly consider** discontinuing driving.

Clinical trial evidence illustrates that patients' driving skills deteriorate with increasing dementia severity, according to the guideline. Yet studies also show that as many as 76 percent of dementia patients pass an on-road driving test, making a recommendation that patients with dementia absolutely should not drive under any conditions too restrictive, says Dr. Iverson: "[The guideline authors] wanted to preserve the patient's autonomy to some extent. Giving up driving is associated with depression and increased awareness of mortality. We wanted to limit that as much as possible."

Guideline authors reviewed 422 out of 6,000 studies published between 1970 and 2006. Among their recommendations, the authors recommend physicians use the five-point Clinical Dementia Rating (CDR) scale to identify those dementia patients who are at an increased risk for unsafe driving. The CDR scale—which detects cognitive and functional impairments—is based on a physician's examination of the patient as well as information from caregivers.

Indeed, caregiver concerns about the driving ability of a person with dementia are a useful part of the evaluation process, the guideline authors note. For example, they found that a caregiver's rating of the patient's driving as "marginal" or "unsafe" is probably useful, whereas a patient's self-rating of "safe" is not.

What behaviors may indicate an increased risk for unsafe driving? Guideline authors identified these, among others: a decrease in the number of miles driven; the avoidance of driving in certain situations, such as at night or in the rain; a recent history of collisions or moving violations; and aggressive or impulsive personality traits.

Dr. Iverson compares stopping driving to "the same end-of-life issue as financial conservatorship, transition to assisted living, or advanced health directives." The decision to stop driving, he says, should be made after the clinician, patient, and caregivers or family discuss it openly. In addition, state laws may be considered, because some states require doctors to report any medical conditions that may impact driving ability.

The guideline also suggests follow-up evaluations every six months may be useful to determine whether driving risk has increased. —*Kierstin Wesolowski*

Warning Signs of Unsafe Driving

These behaviors are signs that a person with dementia may be an unsafe driver:

- Decrease in number of miles driven
- Avoidance of driving in certain situations, such as at night or in the rain
- Recent history of collisions or moving violations
- Aggressive or impulsive personality traits

JUANMONINO/iSTOCKPHOTO