Image of the Month

To evaluate the level of atrophy in the brain—which presumably is a surrogate marker for the underlying pathology—researchers have focused on a few regions, such as the hippocampus and entorhinal cortex. These regions are known from histopathologic studies to be affected by Alzheimer disease (AD).

In part, studies have been limited to a few areas because it can be cumbersome and time consuming to outline these regions manually on images. However, "automated computer analysis methods have the ability to go beyond that and look at many different regions together," said Christos Davatzikos, Ph.D., director of the section of biomedical image analysis in the department of radiology at the University of Pennsylvania, Philadelphia.

The ability to use an assessment of brain structure to help determine MCI could be particularly important for high-functioning individuals.

Dr. Davatzikos and Susan M. Resnick, Ph.D., of the National Institute on Aging's laboratory of personality and cognition, along with their colleagues, recently studied 15 elderly individuals with mild cognitive impairment (MCI) and 15 healthy individuals from the Baltimore Longitudinal Study of Aging's neuroimaging substudy. Although the 15 case patients were free of dementia at initial enrollment, they developed MCI over the course of up to 9 years (Neurobiol. Aging 2006 doi:10.1016/j.neurobiolaging.2006.11.010).

Participants in the Baltimore Longitudinal Study of Aging are screened yearly, using a number of tests of mental status and cognitive function.

Diagnosis of MCI was made by consensus based on the results of assessments, including the clinical dementia rating scale.

MCI/AD appears to be a complex process that involves many brain regions. The idea behind this approach was to avoid making a priori assumptions about which regions are affected by AD but rather to look at the entire brain.

"The computer essentially evaluates every region in the brain and gets a number of how much gray matter there is locally in that region," said Dr. Davatzikos. In the next level of analysis, the computer evaluates whether a given combination of these numbers indicates a spatial pattern that is suggestive of MCI—strictly from the perspective of brain structure.

In patients with MCI, the researchers used the MR brain images immediately prior to the diagnosis of dementia, or else the most recent scans for those who had not progressed to dementia; MR brain images used for healthy patients were selected to match the two groups on age and sex. Then the researchers used the MR brain images of patients with MCI to teach the computer what the spatial distribution of gray and white matter looks like in individuals with MCI, said Dr. Davatzikos.

When evaluating a new individual, the computer compares the spatial distribution of gray and white matter of that individual with the patterns of MCI and healthy controls. The computer then determines whether the brain pattern of the new individual more closely resembles that of the MCI patients or of normal individuals.

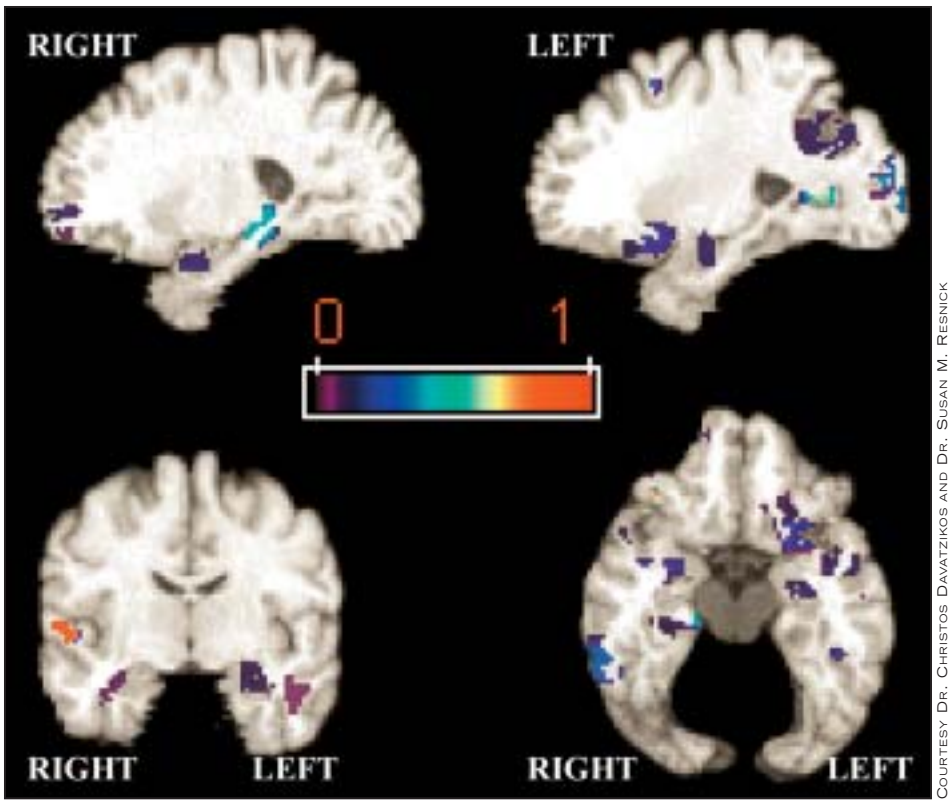
"So basically we took the most recent scans and we said, 'Can you train the computer to recognize the spatial patterns of atrophy that are highly characteristic of MCI?' and we found—with approximately 90% accuracy—that we could do that," said Dr. Davatzikos.

The researchers used the most recent scans to develop the model but then were able to apply it to previous scans and follow brain pattern changes in these individuals longitudinally.

An abnormality score was developed for each individual based on regional tissue distribution and volumetric measurements of specific brain regions.

A positive value (up to 1) indicates a structural pattern resembling MCI, while a negative value (as low as –1) indicates brain structure in unimpaired individuals.

In the most recent scans, those with MCI had an average abnormality score of 0.26, while those without MCI have an average score of –0.30. In the scans closest to the time of conversion to MCI status (in the eight patients who converted during the study), the average abnormality score was 0.15.



Courtesy Dr. Christos Davatzikos and Dr. Susan M. Resnick

The above image shows the regions in which brain atrophy was evaluated by the pattern classifier to get an abnormality score. The color-coding reflects how much each region contributed to the discrimination between mild cognitive impairment and cognitively normal individuals. Larger numbers indicate a larger contribution.

"On the average, they seem to be halfway between zero—the dividing line—and MCI, and were certainly much closer to MCI than normal individuals," said Dr. Davatzikos.

This indicates that in the year of conversion, the patients who progressed to MCI were already well into the range of abnormal brain structure.

Most of the usual suspects—regions such as the hippocampus, entorhinal cortex, lateral and inferior temporal structures, and anterior and posterior cingulate that have already been identified as playing a role in AD—proved to be important regions in the MCI brain pattern that the researchers developed.

However, some regions known not to be involved in AD, such as occipital cortex, were used by the computer, presumably as normalization factors.

"I think that most of the regions that we found were not actually that surprising," commented Dr. Davatzikos. "The combination of all of these [brain regions] was really what gave the diagnostic accuracy for individuals."

It's also important that "the regions that we found that were involved had been identified in group analyses," said Dr. Resnick.

Dr. Resnick noted that one of the study's strengths is how early patients' mild cognitive impairment was detected, showing the tool's potential for very early diagnosis.

"The people [whose conditions] we're calling 'mild cognitive impairment' in this sample would not really have come to clinical attention," she said.

One advantage of this type of tool is that clinicians typically don't have serial data on patient cognition. Rather, a patient usually comes into the office with a complaint about memory and the clinician has to determine if this is a result of normal aging or a more pathologic process.

The ability to use an assessment of brain structure to help determine MCI could be particularly important for high-functioning individuals, who may have suffered significant cognitive declines by the time they meet clinical criteria for impairment, said Dr. Resnick.

In fact, one participant in this study was considered cognitively normal by clinical measure at the time of the most recent scan. However, when previous scans were evaluated using this method, the patient's abnormality scores rose over time. This patient subsequently died and autopsy revealed moderate AD pathology.

"Although we only evaluated the autopsy results of this one patient who seemed to be an outlier, it shows that the patterns on MRI were more in agreement with the underlying pathology than with the clinical status of the patient," said Dr. Davatzikos.

The study is limited by the small sample size.

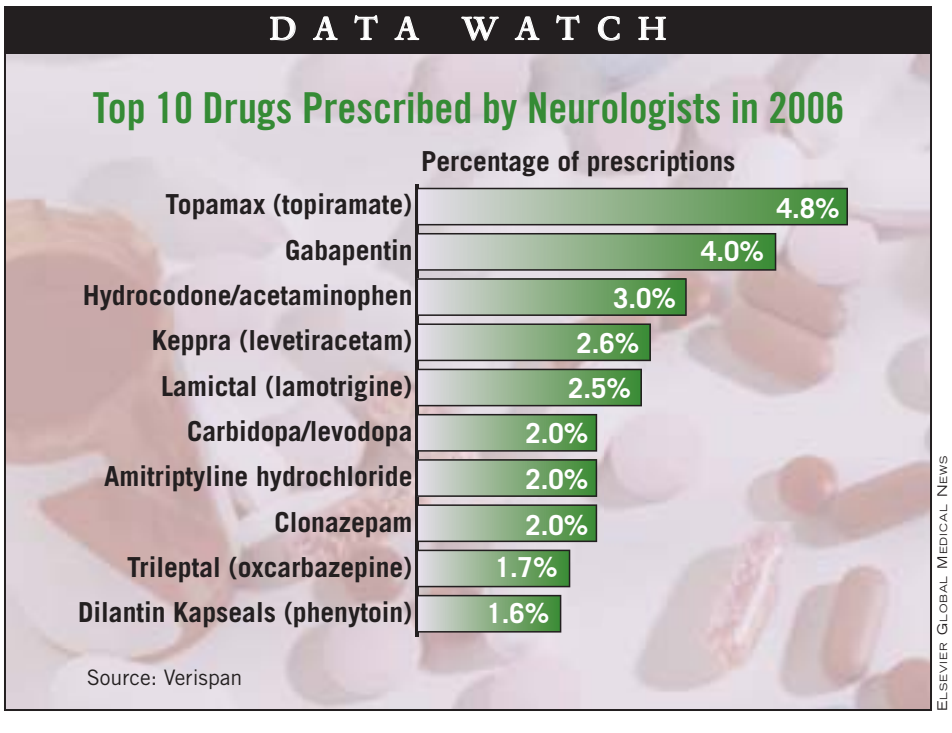
So is this new technique going to solve the problem of predicting which individuals will eventually develop MCI and progress to Alzheimer disease? Probably not. It's unlikely that any one tool or test is going to be able to definitively predict which individuals will develop Alzheimer disease.

"We're talking about risk factors here," said Dr. Davatzikos. "It's like cardiac disease. …It's a collection of information that the clinician then has to evaluate [to] make a decision."

Still, each additional piece of information that can help a clinician identify individuals potentially on the road to Alzheimer disease as early in the process as possible will be essential for making treatment decisions, especially should disease progression–halting drugs becomes available.

—Kerri Wachter

Data Watch



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