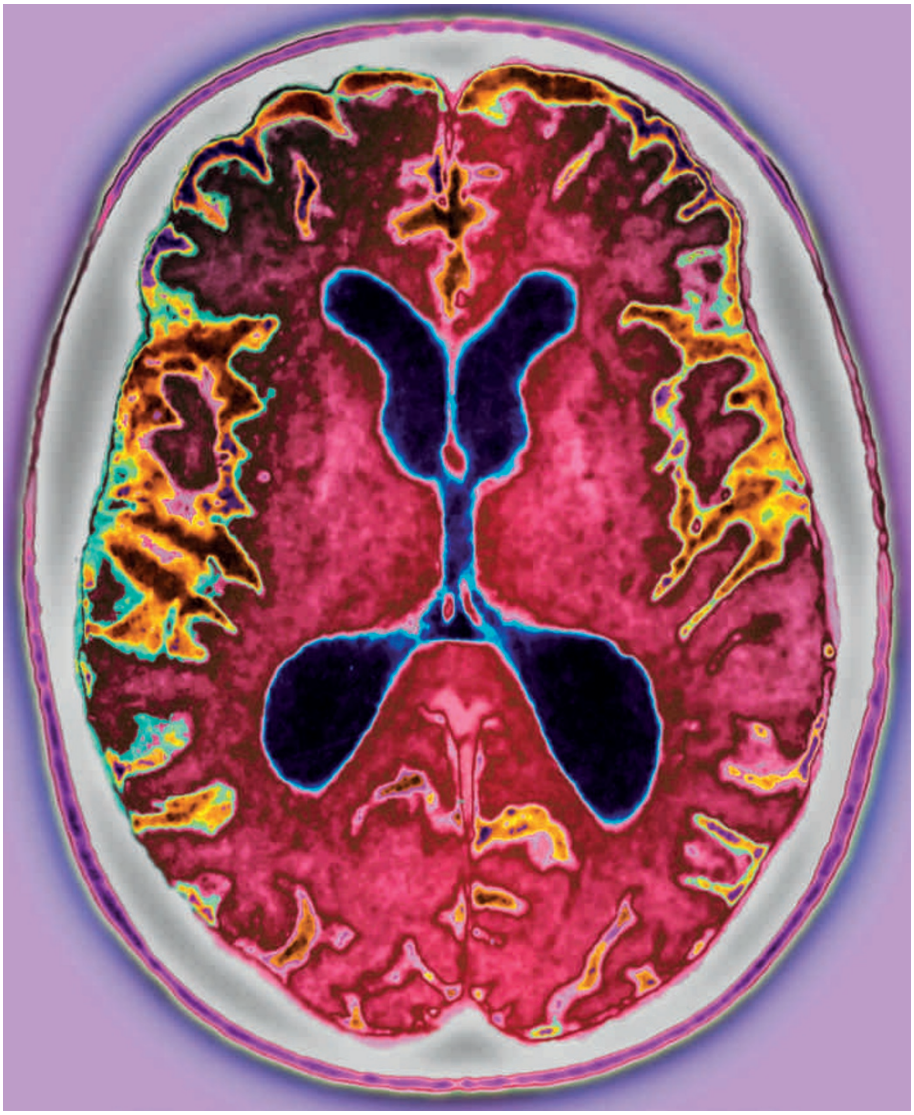

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Orange and blue indicate deterioration in the brain of a 65-year-old Alzheimer's patient.

ALZHEIMER'S DISEASE

Mapping the brain's decline

Imaging the brains of Alzheimer's patients provides insights into the way this insidious disease progresses.

BY SARAH C. P. WILLIAMS

All the memory and cognition tests indicated that the 87-year-old man had Alzheimer's disease, and his brain scan lit up with yellows and reds. The colours were thought to show the presence of tau tangles, the clumps of proteins in the brain that have been linked with Alzheimer's, but the accuracy of the scan had never been verified in humans. So it was filed away. Two weeks later, the man — a participant in a study by Philadelphia, Pennsylvania-based Avid Radiopharmaceuticals — died from an unrelated cause. When his brain was autopsied, researchers found not only amyloid plaques, giving a definitive diagnosis of Alzheimer's disease, but tau tangles in all the same places that lit up in the scan. For the first time, the accuracy of the scan — a form of *in-vivo* tau imaging — had been confirmed.

Tau imaging isn't the only method being developed to visualize the effects of Alzheimer's disease on the brain, but it's one of the most recent. As these imaging methods improve, researchers hope they will help reveal the underlying causes of Alzheimer's disease, which affects more than 35 million people around the world. Clinicians are hoping the scans will allow them to diagnose patients earlier. And pharmaceutical companies are aiming to develop better drugs, and conduct shorter and smaller clinical trials.

"The point of new imaging is to give you a time-lapse movie of the disease and then see how different interventions change that movie," says neurologist Paul Thompson of the University of California, Los Angeles. "You need to be able to track the spread of the disease in more ways than asking people memory questions."

Scientists know that patients with Alzheimer's disease have a progressive loss of cells in certain areas of the brain, and an increase in two types of protein: amyloid-β, which accumulates to form amyloid plaques; and hyperphosphorylated tau, which forms tangles. But whether tau or amyloid build-ups are causes or effects of the disease is not known. And what other factors are involved remains unclear.

Historically, a tentative diagnosis of Alzheimer's follows a battery of cognitive tests. A definitive diagnosis is only achieved *post mortem* with an autopsy of the brain — a procedure rarely done outside research studies. Since the mid-1990s, clinicians have also been using magnetic resonance imaging (MRI), which shows the loss of brain cells associated with the disease. These scans have shown that the brain begins to change years before symptoms appear.

Nick Fox, a neurologist at University College London, was one of the first to report the changes revealed by MRI up to a decade before the onset of symptoms. For the past ten years he has been involved in a longitudinal study of people with an inherited predisposition for Alzheimer's disease as he explores the early changes to the brain. Comparing MRI scans of individuals over time has allowed him to see which parts of their brain begin to shrink first, and when[1]. "There's a long period of time when people have Alzheimer's disease but typically aren't diagnosed," Fox says.

The MRI scans show that the death of brain cells precedes Alzheimer's symptoms by five or six years. The goal of newer imaging methods is to detect these changes even earlier, and more precisely track disease progression.

BRIGHT SPOTS

Tau imaging uses an experimental form of positron emission tomography (PET). Before the scan, clinicians inject the patient with a tracer molecule called T808 that attaches to any tau protein it encounters — the tracer is what caused the bright spots of yellow and red in the Avid

Radiopharmaceuticals study. But the first PET tracer designed for Alzheimer's disease dates from the early 2000s, when researchers at the University of Pittsburgh unveiled Pittsburgh compound B (PIB), which binds to amyloid[2]. Scientists around the world now use this tracer to track amyloid deposits in clinical trials and research studies. Pharmaceutical companies are looking for amyloid tracers that can be used in imaging studies in the general patient population, not just for research.

The science behind the formation of tau tangles and amyloid plaques is still unclear, however, so not all scientists are convinced that amyloid tracers will be the best way to track the disease. Tau tracers, including T808, are being developed as alternatives, alongside a host of other types of scans. For example, a version of MRI called diffusion tensor imaging can provide detailed images of the connections between parts of the brain and reveal changes to its microstructure. In a study published earlier this year, Fox's team found that such microstructure changes were present in people at high risk of Alzheimer's disease, even when normal MRI could not detect larger structural losses[3].

Other researchers are turning to functional MRI, which shows the areas of the brain that are active during any given task, or when the brain is at rest. They have discovered that a task-free, or resting-state, functional MRI scan reveals alterations in pre-clinical disease, the stage before clinical symptoms[4]. "Even if you only have a basic MRI scanner, you can get a whole handful of these variations of MRI scans in only about 30 minutes," says Thompson.

SEEING RESULTS SOONER

Researchers working to develop scans see their work as a necessary step to improve the way drugs to treat Alzheimer's are studied. "It takes too many participants and too much time to test preventive drugs for Alzheimer's," says Eric Reiman, executive director of the Banner Alzheimer's Institute in Phoenix, Arizona. "We're all interested in developing faster ways to do this."

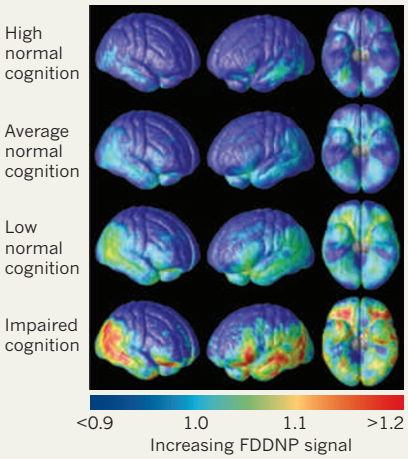
There are many kinds of Alzheimer's disease clinical trials, such as testing drugs or lifestyle interventions, with the aim of preventing disease or treating symptomatic disease. But the primary endpoints are usually the same: measures of cognition, or examinations of autopsied brains. This means that a trial, particularly if it begins before the onset of dementia, can last for decades before reaching an endpoint that shows whether a drug has been successful.

If imaging techniques could provide results sooner, trials could be much less expensive, Reiman says. But the challenge is gathering enough evidence to show that the biomarkers — such as the amyloid or tau PET tracers — are a reliable substitute for measures of actual memory and cognition. "It's a catch-22. You need clinically proven treatments to prove that the biomarkers work," says Reiman. "But the biomarkers will help us develop new treatments much more readily and get them to patients sooner."

One approach, he says, is to focus on populations of people with genetic risk factors for Alzheimer's disease. Testing interventions in such populations requires fewer participants to achieve statistical significance because a higher proportion will develop the disease. So Reiman and his colleagues at Banner have begun working with the US National Institutes of Health and Genentech — a biotech subsidiary of F. Hoffmann-La Roche based in South San Francisco, California — to test an amyloid antibody called crenezumab in an extended family in Colombia that has a genetic mutation leading to early onset Alzheimer's. As well as testing the drug, the scientists are using PET and MRI scans with the latest tracers to track the disease in the participants. They have detected amyloid plaques in family members from around 28 years of age, almost two decades before the typical onset of disease in those without the mutation.

SLIPPING AWAY

Positron emission tomography scans with a tracer (FDDNP) that binds to both amyloid plaques and tau tangles visibly correlate with cognitive decline.



PAUL THOMPSON/UCLA.

GENES AND SCREENS

The latest forms of brain imaging, which provide increased precision and earlier glimpses of disease, along with the decreasing costs of well-established scans, are a boon to pharmaceutical companies looking to test drugs. But they also offer basic researchers a way to find out what causes Alzheimer's.

At UCLA, Thompson heads Project ENIGMA, the world's largest brain imaging study. Scientists based in 20 countries contribute all types of scans of their patients' brains, along with information on the patients' health and genetics. The network, which so far includes more than 26,000 brain images, provides a way to do large-scale automated studies on the specific features of brains from people with Alzheimer's disease or with genetic risk factors for Alzheimer's. "When we pair imaging and genetics, we can screen the brains of certain gene carriers and compare them with non-carriers," Thompson explains. "Then we can ask: what's different about these brains?"

When they looked at one gene known to be a risk factor for Alzheimer's, *CLU*, the ENIGMA researchers discovered that a variant of the gene can damage wiring in the brain when a person is about 20 years old[5]. Thompson says that the variant of *CLU*, which encodes the protein clusterin, "doesn't actually give you Alzheimer's directly, but it gives your brain a punch that makes any second blow harder to deal with."

More recently, researchers found another risk gene for Alzheimer's, *TREM2*, that is prevalent in Iceland[6]. Within five months, Thompson's team had sorted through the ENIGMA scans to find entries that carried the gene variant. They were able to show, in an as yet unpublished study, that the *TREM2* variant speeds up brain cell loss once someone has developed Alzheimer's disease.

As such discoveries progress — linking genetics to structural and functional changes in the brain using automated, high-throughput methods — Thompson hopes that some common molecular pathways will emerge that can help explain dementia. By seeing inside the brain, the scientists can get a clearer picture of what happens during the onset and progression of Alzheimer's.

These latest brain scans are now widely used for Alzheimer's clinical trials and research studies, but they are far from routine in the clinic. A definitive, early diagnosis of the disease can give patients and their caregivers a better idea of the prognosis, but there isn't enough evidence that the results of a scan will change the clinical outcome. It will take an ongoing interplay between better imaging and the development of treatments to change this, says radiologist Clifford Jack, an Alzheimer's imaging specialist at the Mayo Clinic in Rochester, Minnesota. Both sides of the equation — scans with the ability to screen disease, and treatments that slow preclinical disease — will need to be developed first. "At some point, we will develop screening methods and early intervention treatments," says Jack. "Just like with cardiovascular disease today, we can identify people with high blood pressure and high cholesterol, which may not be provoking symptoms, and intervene." Until then, improvements in brain imaging techniques will help scientists working on Alzheimer's disease to better understand this devastating and deadly cognitive decline. ■

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