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# yale medicine

## Your entire brain is memory— and your memory is who you are

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# The first things to go

Misplaced keys and forgotten appointments are among the episodic memories that are lost to Alzheimer disease. Yale clinicians and scientists are looking for new ways to predict the disease and find a cure.

By Ashley P. Taylor  Matthew Daley Illustrations

# It was at his maternal grandparents' 50th wedding anniversary

that Chris H. van Dyck, M.D., first noticed something different about his grandfather. The retired Presbyterian minister, then 83, was at the head of the table making a speech to old friends. "He looked like Granddad there, doing his thing. And he was reasonably coherent," van Dyck, then about 20 years old, recalls. Until he'd finished the speech. "I went over to him and said, 'Hello, Granddad,' and he looked at me and said, 'Who are you?' "

That was the summer of 1975, and van Dyck's grandfather was in the beginning stages of Alzheimer disease, an illness that would later claim both of his maternal grandparents, and which van Dyck, a geriatric psychiatrist, would study as the director of Yale's Alzheimer's Disease Research Unit.

Alzheimer disease is characterized by a gradual loss of what, arguably, makes people who they are: their memories. It starts with innocent forgetfulness. "Usually the first thing to go is episodic memory," says Arash Salardini, M.D., co-director of Yale's Memory Disorders Clinic, referring to memories with specific contexts in space and time. "Based on that, you can see what sort of memories usually go first. People misplace things. They forget appointments." People first lose the ability to form new memories, while long-term memories—the sort van Dyck's grandfather was probably recounting at the anniversary—are more resilient. As the disease progresses, people start to lose executive functions: the ability to make and carry out plans. They lose interest in hobbies; they can no longer use the phone, drive a car, or balance a checkbook. Eventually, they can no longer attend to their own basic needs and become dependent on others. In the United States, Alzheimer disease ranks high on the list of diseases people most fear.

After van Dyck's grandfather became ill, van Dyck says, his mother bought her parents a house near her home in northern Vermont so that she could take care of them. As the grandfather's dementia progressed, van Dyck's mother ended up hiring nearly 24-hour live-in care. Almost immediately after his grandfather died, van Dyck says, his grandmother began to show signs of memory loss, too; she died of Alzheimer disease a few years later. Then his mother's second husband, van Dyck's stepfather, got the disease, and his mother cared for him until his death. "She was immersed in Alzheimer disease," van Dyck says. His mother, now 89, shows no signs of dementia.

Though he believes his choice to focus on Alzheimer disease was in part intellectual, van Dyck feels that his family history also nudged him in that direction. "Seeing my mother do heroic work caring for these people was impressive, and showed what that was like for families and the need for treatments."

## A DISEASE THAT DEFIES DIAGNOSIS

In the past, Alzheimer disease could be definitively diagnosed only upon autopsy. Doctors observed two kinds of brain pathologies: large plaques of a protein called beta amyloid crowding the spaces outside neurons, and inside them, what are called neurofibrillary tangles of another protein, tau. An accurate clinical diagnosis relied on the results of memory and neurological tests and ruling out other potential causes of dementia.

Van Dyck began utilizing neuroimaging to study the aging brain. He and Yale colleagues (including Richard E. Carson, Ph.D., director of the Yale PET Center) were among the first to adapt Single-Photon Emission Computed Tomography (SPECT) and positron emission tomography (PET) to visualize molecules in the brain. In conjunction with the Alzheimer's Disease Neuroimaging Initiative (ADNI) of the National Institutes of Health, van Dyck and the Alzheimer's Disease Research Unit have helped to evaluate PET imaging methods to visualize pathological changes in the brain linked to Alzheimer disease.

In the past 10 years, the ADNI consortium, along with other research teams, has demonstrated that PET imaging could be used to visualize beta amyloid in the brains of patients with Alzheimer disease and that markers of beta amyloid could even be seen in people at high risk for the disease before the onset of symptoms. Based on this work, amyloid PET scans are now approved for use in the diagnosis of Alzheimer disease.

For Salardini, PET scanning is an important diagnostic tool, particularly when trying to distinguish Alzheimer disease from other types of dementia. These brain scans have also brought new understanding of the disease itself. Alzheimer disease's hallmark amyloid plaques, researchers have found, accumulate decades before symptoms arise. Using PET scans, doctors are getting better at diagnosing Alzheimer disease and at determining who is at risk for developing it, paving the way toward early interventions.

"You don't want to treat the disease once the manifestations occur and you already have memory loss," says David Hafler, M.D., M.Sc., chair of neurology and neurologist-in-chief at Yale-New Haven Hospital. Instead, you want to use multiple tests to determine who's at risk and "get patients on treatment before they

develop the disease. That's my vision for what we want to do at Yale."

The glitch, however, is that there is no treatment for Alzheimer disease. Yale researchers are trying to change that. One clinical trial is testing a drug that interferes with a chain of molecular events—triggered by beta amyloid—that causes the brain's neuronal connections to break down. Another is testing whether keeping beta amyloid from building up could prevent Alzheimer disease.

### HALLMARKS OF ALZHEIMER DISEASE

On a molecular level, Alzheimer disease is characterized by the build-up of beta amyloid. Although neuroscientists still aren't sure what it does, the beta amyloid peptide is part of the healthy brain, where it "gets made and rapidly cleared," explains Stephen M. Strittmatter, M.D., Ph.D., Vincent Coates Professor of Neurology, professor of neurobiology, and director of the Yale Memory Disorders Clinic. In patients with Alzheimer disease, however, beta amyloid takes abnormal forms. Fibers clump together outside neurons to form the disease's iconic plaques. But it's a third type of beta amyloid, in which several copies of the protein come together to form what are called oligomers, that researchers suspect is a culprit in Alzheimer disease. Unlike plaques, which are stuck in place, the oligomers can float around in the brain, interacting with—and possibly destroying—neurons.

According to research from the Strittmatter lab, these beta amyloid oligomers damage synapses—the connections between neurons—creating gaps in the brain's communication system. Beta amyloid doesn't damage neurons directly—it starts a domino chain of molecular events that shrivels synapses. In mice with Alzheimer disease-like symptoms, the Strittmatter lab found that using a drug to block one of the proteins in this chain, called Fyn kinase, halted the damage and allowed both synapses and memory to bounce back. To see whether these results carry over to humans, van Dyck is testing the drug (saracatinib) in a nationwide clinical trial for people with mild symptoms.

Another clinical trial is testing whether an antibody that binds to beta amyloid and removes it from the body could prevent Alzheimer disease from developing in the first place. When tested on Alzheimer disease

SIDEBAR PHOTO, HAROLD SHAPIRO

# Yale designated research center by NIH

In a vote of confidence, the federal government has designated Yale as an Alzheimer's Disease Research Center (ADRC)—the medical school will receive funding from the National Institutes of Health to compile and analyze data on Alzheimer disease patients. The designation comes with a five-year grant of more than $1.5 million per year that will support many facets of Alzheimer disease research, including basic research, collection of clinical data, community outreach, and education. The Alzheimer's Disease Research Unit, the Yale Memory Disorders Clinic, and the Dorothy Adler Geriatric Assessment Center already provide excellent care to Alzheimer disease patients. The grant will allow these groups to synthesize their information and resources, thereby fostering greater knowledge and advancing potential treatments, says Stephen M. Strittmatter, M.D., Ph.D. (in photo, at left), the Vincent Coates Professor of Neurology, professor of neurobiology, and director of the Yale Memory Disorders Clinic, and principal investigator of the ADRC grant from the NIH. He and Chris van Dyck, M.D. (in photo, at right), director of the Alzheimer's Disease Research Unit, co-direct the Yale ADRC; Arash Salardini, M.D. (in photo, center), co-director of the Memory Disorders Clinic, is its assistant clinical director. "The ADRC is composed primarily of people at Yale who were previously carrying out separate tasks. Through the new center they now work as a team in the sense of meeting together, sharing ideas and reagents, and coordinating studies across the translational research scale," Strittmatter says.

As the search for a treatment continues, the number of Alzheimer disease cases—an estimated 5.3 million Americans in 2015, according to the Alzheimer's Association—continues to grow as the population ages.

Arash Salardini //

> "Almost everybody who has amyloid deposition beyond a certain amount will get Alzheimer disease, and almost nobody without amyloid deposition has Alzheimer disease."

patients, the overall finding was that the antibody (solanezumab) did not work. In a subset of patients with mild dementia, however, the drug slowed disease progression by about a third, van Dyck says.

This finding prompted researchers to ask, as van Dyck puts it, "What if you go milder than mild, all the way to preclinical, presymptomatic? Maybe it's a question of intervening before too much brain damage is done." The study is testing that hypothesis in patients 65 or older who are cognitively normal but who have abnormally high levels of beta amyloid, as measured by PET scans. In the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study, which is still enrolling participants, half the patients receive monthly intravenous infusions of the drug and half receive a placebo. The study is "blind"—neither researchers nor participants know who receives the drug. At the end of the three-year study, a second PET scan for beta amyloid will show whether the drug prevented the protein from accumulating, and "unblinding" the results will reveal whether the treatment prevented memory loss.

Whether or not removing beta amyloid from the brain proves effective in preventing Alzheimer disease, it is emerging as a key predictor of risk for the disease and crucially, one that shows up long in advance of disease symptoms. "Almost everybody who has amyloid deposition beyond a certain amount will get Alzheimer disease, and almost nobody without amyloid deposition has Alzheimer disease," says Salardini, adding that such a build-up can begin 20 years before symptoms emerge. One day, van Dyck predicts, screening for Alzheimer disease using amyloid PET scans may be as routine as getting a colonoscopy. "That is the kind of paradigm we're talking about," he says. "We don't even want to wait until people have lost a bunch of gray matter; we'd like to be able to intervene at an earlier stage." But an earlier, more accurate diagnosis will be most valuable only when there's a treatment. Without a treatment, there's no way to act on an earlier diagnosis.

"If we had an intervention that could save people, [PET scanning] would just so obviously pay for itself," van Dyck says, noting that insurance doesn't usually cover the scans. "The cost of a PET scan would be trivial when you compare it to, besides the individual costs, just the sheer economic costs to society."

Strittmatter is optimistic that research will lead to possible treatments, and he believes that the partnership between the new Alzheimer's Disease Research Unit and the NIH will advance that research.

"I think that research that is going on is opening new doors. We have to find out which one will make a difference for people." */yale medicine*

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