

## Section Editors

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# Alzheimer disease

## What changes in the brain cause dementia?

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When scientists look under the microscope at the brains of very elderly patients who have died, some confusing patterns are seen. Some patients who had healthy memory and thinking show many of the findings often seen in patients with Alzheimer disease (AD). These are called plaques and tangles. This is confusing because plaques and tangles are not always seen in normal patients but are more common in patients with AD. At the same time, some patients with significant dementia have very few of these brain changes. Brain researchers wonder how memory and brain function stay healthy in patients even though their brains show problems seen in AD.

A new study reported by Erten-Lyons and coauthors tries to answer this question (*Neurology* 2009; 72:354–360). They compared the brains of patients with AD to another group that had similar findings under the microscope but had normal thinking and memory. They asked, “What protects those patients whose thinking remains normal?” The investigators looked for differences in the medical histories and brain examinations of these two groups. They also looked at differences in the size of some brain areas using MRI scans that were taken when the patient was living. Along with the MRIs, other changes were considered, like age, sex, and timing of the MRIs. The authors’ idea was that plaques and tangles might be necessary to cause AD, but that there might be some important reasons why some patients did not get AD. They thought that patients with healthy brains might be able to lose some brain function but have enough reserve that these changes did not result in dementia. The authors were also interested in other factors that might show why these patients seemed to be protected.

**WHAT WAS THE MAIN FINDING?** Surprisingly, the two groups were not very different in their medical histories, ages, or education. They looked similar

on an important gene test. In addition, their brain studies did not show more signs of small strokes or other differences that might explain why one group had more memory and thinking problems and the other did not. However, the groups were different when the size of some brain areas was compared. Those people with plaques and tangles who did not show thinking and memory problems had larger overall brain size than the group that had dementia. In addition, the brain structure that is important for new learning and memory, the hippocampus, was also larger in the healthy group. Importantly, these brain size differences were seen even after the researchers carefully considered a number of other factors. These factors included the time between brain MRI and death, age, and number of plaques and tangles in the brain.

### HOW DOES THIS HELP EXPLAIN WHY SOME PEOPLE GET AD AND SOME DO NOT?

The findings are interesting and suggest that there is not a direct link between the presence of plaques and tangles and dementia. It has been long suspected, and proven here, that it is possible to survive into old age without developing dementia, even with many plaques and tangles in the brain. The results raise the important possibility that healthy brain aging requires healthy brain cells and a high number of brain cell connections (synapses). This is consistent with the cognitive reserve idea, which suggests that larger brain size and greater cognitive abilities beginning early in life may be important for later protection against dementia. Whether or not this idea is true, the findings indicate that brain size measurements may show if someone is at risk of developing dementia. Studies like this may point the way toward better prevention of dementia. Finding ways to actively prevent dementia is a very important approach, since our ability to treat AD, once it has started, is currently very limited.

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# About Alzheimer disease

**WHAT IS ALZHEIMER DISEASE?** AD is a progressive neurologic disorder associated with aging. It is common, now affecting more than 5.2 million Americans. AD begins with great difficulty in new learning and memory, which leads to forgetfulness of recent events. AD worsens over time, usually over many years, leading to difficulty remembering new events, problems in finding words and reasoning, difficulty completing normal activities, relying on others to function, and ultimately death.

At autopsy, when the brain of a patient with AD is examined under a microscope, there are abnormal cells and cell structures in the brain, particularly in portions of the brain related to memory. These parts of the brain include the entorhinal cortex and hippocampus. Under the microscope, a researcher is likely to see atrophy, or shrinkage, in this region. There also may be more generalized shrinkage in the outer gray matter or cerebral cortex, resulting in reduced brain weight and visible brain shrinkage. The key diagnostic neuropathologic features of the disease are senile plaques, a buildup of a protein called amyloid. It is surrounded by dead or dying neurons and inflammatory cells. In addition, the other features are neurofibrillary tangles, which are present in significant numbers throughout the memory structures and cerebral cortex. Amyloid of senile plaques are outside the cell. Tangles are intracellular—inside the cell—and are a buildup of an abnormal form of another protein, tau. Tau is in the neurons and neurons are the cells that assist in all brain functions (such as thinking and memory). The presence of neurofibrillary tangles signals an interruption of cell transport properties that are important for neuronal survival and function. This type of interruption leads to synapse contacts and results in weakened communication between cells in the brain.

**WHAT IS COGNITIVE RESERVE?** Cognitive reserve has been suggested as a concept to explain the differences among individuals in coping with the neuropathologic changes, plaques and tangles, of AD. The notion is that the ability of the mature brain to sustain normal function in the face of significant disease or injury is a function of its reserve capacity. The cognitive reserve capacity is set early in

life and gradually declines as the nervous system ages. As individuals age, those with a greater reserve capacity will have a lower risk of dementia than individuals with less cognitive reserve. The impact of brain diseases or injuries will be less apparent in those with a greater reserve capacity, as healthy brain functions are able to accommodate for the cell loss. However, in those where cognitive reserve capacity is low, the effects of the same injury will be more readily apparent as the limited resources available in this situation become expended more quickly.

**WHERE DO WE GO FROM HERE IN APPLYING THESE FINDINGS TO ENHANCE CLINICAL DIAGNOSIS AND TREATMENT?** The challenge presented by these findings is to determine the biologic factors that support larger brain volumes that will protect against cognitive decline. Knowing these factors will assist in the prevention of cognitive decline and in efforts to maintain brain function even if there is brain disease.

Several possibilities can be explored that could affect care. First, some investigators have suggested that larger brain sizes reflect the limits of our inherited hardware. If correct, this suggests that our brain reserve is set early in brain development and that protection against disease during later aging is a result of the proportion of healthy cells to those affected by disease.<sup>1</sup> The goal would be maintaining healthy cellular function throughout life.

However, other investigators believe that it is not necessarily the number of cells people have but rather the activity of specific neural circuits and synapses, and the efficient use of alternative brain networks that play a role in cognitive resiliency. This suggests that habits or lessons learned early in life may help to keep the brain active and healthy into old age. This highlights the importance of keeping the brain active.

Still another idea is that despite what we inherit and how we use these capacities, environmental factors may hinder cell death and influence the development of AD symptoms. This hypothesis focuses more on cell mechanisms and suggests that there are many events that lead to clinically expressed symptoms of AD. These events can possibly be changed, turned on or delayed, by factors such as high educa-

tion, exercise, nutrition, and absence of cerebral vascular disease.

It is possible that all of these are correct. Good cognitive function may be related to starting capacity and continued efficient neural processing, but it may also be due to inherited genes and how these genes are changed by other health conditions, lifestyle habits, and other factors. Because many of the factors suggested to enhance cognitive resiliency are also important for cardiovascular and cerebrovascular health, attention to healthy diet and lowering cardiovascular risk conditions, such as controlling weight, blood pressure, and diabetes, will be important for

both heart and brain health. The treatment for AD will depend on uncovering the cellular mechanisms responsible for the expression of dementia and the early memory symptoms. Plaques and tangles are a part of the story but may not be the entire picture.

**FOR MORE INFORMATION** For more information, see your local chapter of the Alzheimer's Association or go to [www.alz.org](http://www.alz.org)

#### REFERENCE

1. Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep* 2004;4:374–380.

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## **Alzheimer disease: What changes in the brain cause dementia?**

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