Patience and Patients: Understanding the spectrum of Alzheimer's disease

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Patience and Patients:
Understanding the spectrum of Alzheimer's disease

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About the Speakers

Adrian Ivinson, PhD

Adrian Ivinson, PhD is the founding director of the Harvard NeuroDiscovery Center. Adrian helped develop the vision of an integrated and tightly managed research center engaged in groundbreaking and collaborative research at Harvard Medical School, its affiliated research hospitals, and other leading research groups around the world. From 1993-2000 he held a number of leadership positions at the Nature Publishing Group, including editor-in-chief of *Nature Medicine* and Publisher of the monthly journals. Adrian received his PhD in genetics from the University of Manchester in the UK where his early research career focused on the genetics of single gene disorders. Today he works on collaborative approaches to translational research aimed at understanding and treating neurological diseases, with a particular concentration on genetics, biomarkers, drug discovery, mouse models and bioethics.

Reisa Sperling, MD

Reisa Sperling, MD is a neurologist, specializing in dementia and imaging research, and an Associate Professor in Neurology at Harvard Medical School. Dr. Sperling is the Director of the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital and serves as the Director of the Alzheimer's disease Neuroimaging Program of the Massachusetts ADRC at Massachusetts General Hospital. Dr. Sperling's research is focused on the early diagnosis and treatment of Alzheimer's disease. Her recent work involves the use of functional MRI and PET amyloid imaging to study alterations in brain function in aging and early Alzheimer's disease. She is the Principal Investigator on multiple NIH and Foundation grants to investigate the basis of memory impairment in aging and early Alzheimer's disease, including a new National Institute on Aging Program Project grant – the Harvard Aging Brain Study - to investigate the impact of amyloid on brain aging. She was recently chosen to lead the National Institute on Aging-Alzheimer's Association working group to develop recommendations for the study of "Preclinical Alzheimer's disease". Dr. Sperling also oversees a number of clinical trials of potential disease-modifying therapies in mild cognitive impairment and Alzheimer's disease dementia at the Center for Alzheimer Research and Treatment, and will serve as the Project Leader for the Alzheimer's Disease Cooperative Study A4 multi-center trial proposal – Anti-Amyloid in Asymptomatic Alzheimer's disease.

Ruth Kandel, MD

Ruth Kandel, MD is a graduate of Albert Einstein College of Medicine. She is an Assistant Professor at Harvard Medical School and an Associate in Internal Medicine at Beth Israel Deaconess Medical Center. Dr Kandel, a board certified geriatrician, directs the Memory Disorders Clinic at Hebrew SeniorLife. She has been involved in various research projects that primarily focus on dementia in long-term care residents. Dr. Kandel teaches about Alzheimer's disease both in academic settings as well as in the community.

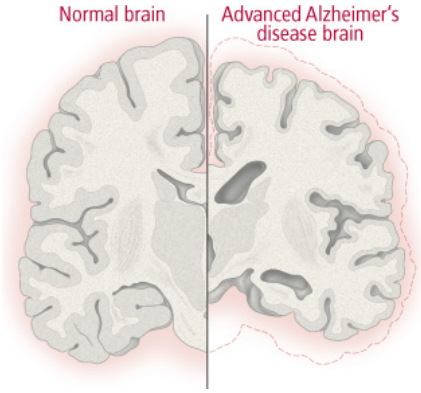
The following content is provided by Harvard Health Publications

What is Alzheimer's disease?

Alzheimer's disease is a degenerative brain disorder that results in memory loss, impaired thinking, difficulty finding the right word when speaking, and personality changes. Its course is marked by a continual loss of neurons (nerve cells) and their connections with other neurons (synapses) that are crucial to memory and other mental functions. In advanced Alzheimer's disease, the dramatic loss of neurons causes the brain to shrink (see Figure). Levels of brain chemicals known as neurotransmitters, which carry complex messages among billions of nerve cells, are also diminished. After the symptoms first appear, people live anywhere from two to 20 years in an increasingly dependent state that exacts a staggering emotional, physical, and economic toll on families.

There is no cure and little that can be done by way of prevention. But early diagnosis is important because drugs are available that may temporarily stabilize or delay worsening of cognitive symptoms, and they work best in the early stages of the disease.

Figure: Brain changes in Alzheimer's disease



The massive loss of brain cells that occurs in advanced Alzheimer's disease causes the brain to wither and shrink, as shown in these crosswise slices through the middle of the brain between the ears. In the Alzheimer's brain, the outer layer (cortex) shrivels up, damaging areas involved in thinking, planning, and remembering. The hippocampus, a structure that plays a vital role in memory formation, is one of the hardest-hit areas.

Reasons for hope

Nevertheless, there are reasons for hope. Promising results of broad-based brain research have made Alzheimer's researchers optimistic about the prospects for improved treatment and prevention. Intense efforts since the 1980s have advanced scientists' understanding of the chemical changes that take place inside the brain. Key discoveries have cleared the way for pharmaceutical companies to start developing compounds that might block the disease's destructive course and cure the patient. There is also hope that scientists will someday create a vaccine to prevent and even treat Alzheimer's disease).

These prospects are exciting, but they're still a long way from providing relief for the estimated 35.6 million people worldwide who currently have Alzheimer's disease. The good news is that science has given health care providers a better understanding of ways to improve the day-to-day lives of people with Alzheimer's. And this growing awareness has produced an increasing number of support groups and community services around the country to alleviate families' isolation and help ease the burden of caring for those with Alzheimer's disease at home.

A surprising history

The medical profession used to consider Alzheimer's disease a rare disorder that struck in middle age. This assumption was based on a report published in 1907 by a German doctor named Alois Alzheimer. During an autopsy, Alzheimer discovered microscopic changes — including abnormal neurons, tangled fibers, and clusters of nerve endings — in the brain of a 51-year-old patient who had died of progressive dementia. The report attracted attention within the medical community, and thereafter, progressive dementia in a person younger than 65 was called "Alzheimer's disease."

Doctors used to believe dementia in people over age 65 was caused by cerebral atherosclerosis ("hardening" of the brain's arteries), and it was labeled "senile dementia." (Senile simply means "old," and dementia is literally "deprived of mind.") But attitudes began to change in the 1970s. Evidence accumulating from autopsy studies suggested that Alzheimer's disease was, in fact, the most common cause of dementia in older persons. The National Institute on Aging was established in 1974, with one of its primary goals to conduct and support research on memory loss.

With the 1984 publication of diagnostic criteria for Alzheimer's and other irreversible dementias, physicians began diagnosing the disease more frequently. Meanwhile, the Alzheimer's Association, founded in 1979, began raising public awareness about the disease.

Warning signs of Alzheimer's disease

Here are some common warning signs of Alzheimer's disease. If you or someone you love is experiencing one or more of the following symptoms, talk to a doctor. The medications used to manage Alzheimer's disease work best in the early stages of the disease, making an early diagnosis significant.

Trouble remembering things. At first, only short-term memory may be affected. The individual may forget an appointment or the name of a new acquaintance. She may also forget where she left things, or she may leave things in odd places (for example, putting her shoes in the microwave). Eventually, long-term memory also is impaired, and the individual may not recognize family members.

Mood or personality changes. Someone who was social and outgoing may become withdrawn. The person may also become stubborn, distrustful, angry, or sad. Depression also often accompanies Alzheimer's disease, bringing such symptoms as loss of interest in a favorite hobby or activity, a change in appetite, insomnia or sleeping too much, lack of energy, and hopelessness.

Trouble completing ordinary tasks. Simple tasks that once caused no difficulty may become much more challenging. For example, a person may forget how to use the oven, lock the door, or get dressed.

Difficulty expressing thoughts. It's common for people with Alzheimer's disease to have trouble with language. The individual may try describing an object rather than using its name — for example, referring to the telephone as "the ringer" or "that thing I call people with." Reading or writing may also be impaired.

Impaired judgment. The individual might have trouble making decisions, solving problems, or planning. For example, he may no longer be able to balance a checkbook or pay bills.

Disorientation. We all know what it's like to be driving and momentarily forget where we're going. But those with Alzheimer's disease may get lost in their own neighborhood. They may also lose track of dates and the time.

Unusual behavior. The individual may wander, become agitated, hide things, wear too few or too many clothes, become overly suspicious, engage in unsafe behaviors, or use foul language.

The growing numbers

The risk of Alzheimer's rises steadily with age. One in eight people ages 65 and older is affected, and nearly half of those who live to age 85 have Alzheimer's.

Of course, Alzheimer's affects a far greater number of people, for it takes a toll on loved ones as well as those with the disease. With the graying of America, Alzheimer's disease is a growing national problem. Today, an estimated 5.4 million Americans have Alzheimer's. If no effective treatment or means of prevention is found, that number could rise as high as 16 million by 2050.

Most people with Alzheimer's disease are cared for at home by spouses or other family members, sometimes for five years or longer. In many cases, this results in financial as well as emotional strain. The burden on society is also high. The estimated yearly cost for Alzheimer's disease is about $183 billion nationally. Aggregate costs of health care, long-term care, and hospice are projected to increase to $1.1 trillion in the United States in 2050.

Is it forgetfulness or dementia?

Regardless of age, everyone experiences occasional episodes of forgetfulness. Many people fear that a growing number of such lapses are a sure sign of Alzheimer's, but there are important differences between simple forgetfulness and dementia (see Table). A third state, called mild cognitive impairment, falls in between normal memory function and dementia. People with mild cognitive impairment are more likely to develop dementia.

Table: Normal aging or dementia?

Physicians often use a chart like this to help differentiate between normal aging and dementia.

Normal aging	**Dementia**
The person remains independent in daily activities.	The person is critically dependent on others for key daily living activities.
The person complains of memory loss but can provide considerable detail regarding incidents of forgetfulness.	The person complains of memory problems only if specifically asked and cannot recall instances when memory loss was noticeable.
The individual is more concerned about alleged forgetfulness than close family members are.	Close family members are much more concerned than the individual is about incidents of memory loss.
Recent memory for important events, affairs, and conversations is not impaired.	Recent memory for events and ability to converse are both noticeably impaired.
The person has occasional difficulty finding words.	The person makes frequent word-finding pauses and substitutions.
The person does not get lost in familiar territory, but may have to pause momentarily to remember the way.	The person gets lost in familiar territory while walking or driving and may take hours to return home.
The individual operates common appliances even if she or he is unwilling to learn how to operate new devices.	The person cannot operate common appliances and is unable to learn to operate even simple new appliances.
There is no decline in interpersonal social skills.	The person loses interest in social activities or exhibits socially inappropriate behaviors.

Performance on mental status examinations is normal relative to the individual's education and culture.	Performance on mental status examinations is below normal in ways not accounted for by educational or cultural factors.
Source: Diagnosis, Management and Treatment of Dementia: A Practical Guide for Primary Care Physicians (American Medical Association).	

Normal forgetfulness

Normal forgetfulness is neither progressive nor disabling. Such memory problems are likely to surface when you're under stress, fatigued, ill, distracted, or overloaded. Typically, you remember the forgotten information later. Written reminders and other memory-jogging techniques can help you overcome this kind of forgetfulness.

A certain increase in forgetfulness seems to be a normal byproduct of aging and is perhaps a result of changes in the brain that begin around age 50, such as a gradual loss of receptors on brain cells and a decline in certain neurotransmitters. Researchers disagree over how much deterioration is normal.

Memory loss isn't inevitable, though. There are many things you can do to preserve or sharpen your memory, including learning memory-enhancing techniques, reducing stress, and improving your organizational techniques (for example, always writing down appointments or having a designated spot for belongings such as keys and eyeglasses). It's also important to regularly challenge your mind with activities such as reading, doing crossword puzzles, playing chess, or taking classes. Experts believe that these kinds of activities help build and maintain synapses, the small gaps between neurons that enable them to communicate with one another.

Much age-related mental decline is due to poor vision or hearing, cardiovascular disease, diabetes, sleep disturbances, alcohol abuse, depression, or medications. Addressing these conditions can also make a difference. Changes people see in themselves or a relative are far more likely to be signs of some other health problem, not early dementia.

Mild cognitive impairment

Mild cognitive impairment (MCI) is considered a transitional state between normal forgetfulness and dementia. At least one cognitive (thinking) domain — usually memory — is below normal or in decline. When memory is affected, the condition is called amnesic MCI. Although some people with MCI remain stable or even improve, studies show that the majority, especially those with amnesic MCI, eventually develop dementia.

Researchers who examined brain tissue removed during autopsies have provided evidence that certain telltale anatomical changes may underlie this progression. As reported in *Archives of Neurology* in 2006, the researchers found that the brains of people with amnesic MCI have more of the abnormal changes associated with Alzheimer's disease than those of normal people, but the changes were not as extensive as those found in patients with Alzheimer's disease. A 2011 study in the same journal found that a

diagnosis of MCI may be preceded by more than four years of increased cognitive decline, and that the rate of decline may double again after an MCI diagnosis.

MCI becomes more common with age and affects 10% to 20% of people over age 65. A 2007 report in *Neurology* found that people with MCI who also showed signs of anxiety (such as persistent worrying and avoiding social situations) were about twice as likely to progress to Alzheimer's disease within three years compared with people with MCI but no symptoms of anxiety.

A person who has MCI is able to carry on daily activities without difficulty, but a particular subset of cognitive skills may be diminished. In particular, someone with MCI may show some of the following signs:

- increasing difficulty with memory or, in some cases, subtle problems in other cognitive domains, such as language, attention, spatial skills, and problem solving
- confirmation of impairment on neuropsychological tests, often manifesting as difficulty with learning and delayed recall of information compared with others of the same age and education level; in some cases, memory is normal but is less reliable than it used to be.

Still sharp after all these years?

Sometimes, what appears to be a mental problem may simply reflect a slower processing speed. Comparisons of younger and older people's scores on memory, learning, and intelligence tests suggest that mental sharpness declines slightly with age. But whether such comparisons are valid is questionable because timed tests may favor the younger person. The older person's information processing is a little slower: in one study, elderly people took 20 to 40 milliseconds longer than younger people to detect gaps in circles. Thus, the lower scores of older persons may simply reflect a slowing of their responses, not a reduction in their mental sharpness.

People may require more time and effort to learn new information as they age, but once they've learned it, they retain it as well as younger people. In practical terms, slightly slower thinking is not necessarily a disadvantage. It may actually reflect more thorough reasoning and result in fewer mistakes.

Dementia

With dementia, memory loss is severe enough to interfere with someone's ability to function socially and at work. Most common is Alzheimer's disease, which causes 60% to 80% of dementias. Other types of dementia include frontotemporal lobar degeneration, dementia with Lewy bodies, and vascular dementia (which is caused by multiple strokes that interrupt blood flow to the brain). Increasing evidence suggests that more than one type of dementia can be at play. These are some signs of dementia:

- Intellectual function has declined from a previous level.
- The person is aware and alert, which differentiates dementia from delirium.
- More than one type of thinking is affected. In addition to memory, at least one of the following is also impaired: personality, abstract thinking, judgment, use of language, the ability to perform

complex physical tasks, or the ability to recognize objects or people. Known as global cognitive impairment, this characteristic distinguishes dementia not only from forgetfulness but also from such conditions as amnesia (memory loss only) and speech deficits (caused by stroke, for example).

Recognizing the symptoms

Alzheimer's disease usually is not diagnosed in the early stages, even in people who visit their primary care doctors with memory complaints. One reason is that people and their families generally underreport the symptoms. They may confuse them with normal signs of aging. The symptoms may emerge so gradually that the person affected doesn't recognize them. Or the person may be aware of some symptoms but go to great lengths to conceal them.

Recognizing symptoms early is crucial because medication to control symptoms is most effective in the early stages of the disease and early diagnosis allows the individual and his or her family members to plan for the future. If you or a loved one is experiencing any of the following symptoms, contact a physician.

Progressive memory loss

This is the hallmark of Alzheimer's disease. Initially, only short-term memory is impaired, and the person merely seems forgetful. But because short-term memory is essential for absorbing new information, the impairment soon interferes with the ability to interact socially and perform one's work. Long-term memory may be retained longer, often in great detail, but it becomes fragmented as the disease progresses. Toward the final stage, people with Alzheimer's may be unable to recall their own names.

Decline in cognitive abilities

These are the "thinking" activities of reasoning — solving problems, making decisions, exercising judgment, and so on. Impairments of cognitive function can begin subtly as poor performance in an activity the person once did well. Poor judgment and lack of insight can lead to accidents.

Early in the disease, individuals may easily lose track of time; later, their disorientation becomes more pronounced and extends to places and people. The sense of time becomes more distorted as the disease progresses, and people may insist it's time to leave immediately after arriving at a place or may complain of not having been fed as soon as a meal has ended.

Changes in mood and personality

These changes are often the most convincing evidence for families that something is wrong. Apathy is common, and many individuals lose interest in their usual activities. A person may become withdrawn, irritable, or inexplicably hostile.

Depression may also accompany Alzheimer's, partly as a result of chemical changes in the brain caused by the disease itself and partly as an understandable psychological reaction to the loss of mental abilities. Symptoms of depression include loss of interest in previously enjoyable activities, change in appetite that sometimes leads to weight loss or gain, insomnia or oversleeping, loss of energy, and

feelings of worthlessness. People with Alzheimer's, though, seldom have feelings of excessive guilt or thoughts of suicide, which are often symptoms of depression.

Aphasia

This medical term describes an impairment in using and understanding language. Because speaking, writing, reading, and understanding speech involve different areas of the brain and different nerve networks, aphasia can be uneven, with some skills retained longer than others. For example, a person may be able to recognize written words flawlessly and yet fail to comprehend their meanings.

Typically, aphasia begins with word-finding difficulties. Unable to think of the right words, a person may try to cover up with long-winded descriptions that fail to reach the point, or he or she may angrily refuse to discuss the matter further. Substituting a similar-sounding word ("wrong" instead of "ring") or a related word ("read" instead of "book") is common. The person may ramble, stringing phrases together without expressing any real thought, or may forget all but a few words (which he or she may repeat over and over). In many cases, all language abilities are lost as dementia becomes severe, and people become mute.

Agnosia

The ability to process sensory information deteriorates, causing agnosia, a disorder in perception. Unable to comprehend the meaning of what they see, people with agnosia may run into furniture. They may believe a spouse is an impostor, become frightened by ordinary sounds, or fail to recognize their own reflection in a mirror. Agnosia can contribute to inappropriate behavior, such as urinating into a wastebasket.

Apraxia

The inability to perform basic motor skills such as walking, dressing, and eating a meal is known as apraxia. This is quite different from weakness or paralysis caused by a stroke. A person with apraxia has literally forgotten how to perform these activities. Usually, apraxia develops gradually, but in some cases, it begins abruptly. Apraxia may first be evident in fine hand movements, showing up in illegible handwriting and clumsiness in buttoning clothing. Everyday skills like using a phone or switching channels on a TV set may disappear. Eventually the ability to chew, walk, or sit up in a chair is lost.

Behavior problems

Troublesome changes in behavior are a common feature of the disease. Examples include being stubborn, resisting care, refusing to give up unsafe activities, pacing or hand-wringing, wandering, using obscene or abusive language, stealing, hiding things, getting lost, engaging in inappropriate sexual behavior, urinating in unsuitable places, wearing too few or too many clothes, eating inappropriate objects, dropping lit cigarettes, and so on. A particular behavior can disappear as a patient's abilities further deteriorate (for example, verbal abuse declines as aphasia progresses), only to be replaced with new problems.

Catastrophic reaction

A strong emotional response to a minor problem is another symptom of the disease. Catastrophic reactions can involve crying inconsolably, shouting, swearing, agitated pacing, refusing to participate in

an activity, or striking out at another person. The usual triggers include fatigue, stress, discomfort, and the failure to understand a situation. Essentially, a catastrophic reaction is the response of an overwhelmed, frightened person who feels cornered and is trying to protect himself or herself. The behavior is caused by brain dysfunction and is mostly beyond the person's control.

Sundowning

This term refers to behavior problems that worsen in the late afternoon and evening. No one knows exactly why sundowning occurs, though there are several theories. Because people are tired at the end of the day, their tolerance for stress declines, and a minor problem can generate a major outburst. An already confused person may be overstimulated when several people are in the house, dinner preparations are under way, and the television is on. Dim light may also contribute to a person's misinterpretation of visual information.

Psychosis

Roughly four out of 10 people with Alzheimer's disease will experience psychosis, which is marked by recurring delusions or hallucinations. While this most often occurs in late-onset Alzheimer's and appears to run in families, specific genes associated with it have not yet been pinpointed. The disordered thinking that prompts delusions and hallucinations occurs sporadically, which tends not to be true in other forms of psychosis.

A woman troubled by delusions might call the police to report strangers in the house, talk to herself in the mirror, or talk to people on TV. Hallucinations are often visual — seeing jagged rocks or water where floorboards actually are — but may be auditory (phantom voices), as well.

For more information

This information is prepared by the editors of the Harvard Health Publications division of Harvard Medical School. For more information about Alzheimer's disease, see the Harvard Medical School Special Health Report, *A Guide to Alzheimer's Disease* (Harvard Health Publications 2011) available from www.health.harvard.edu.

How the brain works

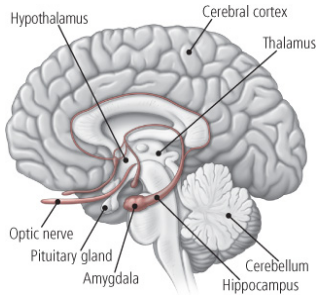
A family often finds it easier to accept the Alzheimer's patient's cognitive problems than his or her behavior problems, which may make a person seem deliberately uncooperative, spiteful, or just plain mean. But both kinds of problems are consequences of the disease. A close look at the brain reveals how memory, intellectual abilities, emotions, and behavior become disconnected in Alzheimer's disease.

A macro view of the brain

Neuroscientist Paul MacLean coined the term "triune brain" to describe what he viewed as the three separate but interconnected levels of the human brain: the brainstem (and cerebellum), the limbic system, and the cerebral cortex. An extensive two-way network of nerves connects these three levels of

the brain. Ongoing communication between the cerebral cortex and the limbic system inextricably links thinking and emotions (see Figure). Each influences the other, and both direct all voluntary action. This interplay of memory and emotion, thought and action is the foundation of each individual's unique personality.

Figure: Inside the brain



In Alzheimer's disease, brain cells die and neuronal connections wither in all parts of the brain, but especially in the hippocampus and the amygdala — important parts of the limbic system that coordinate memory storage and recall — and the cerebral cortex, the seat of higher-level thinking, memory, and language.

The brainstem and cerebellum

Operating at the first level, these two primitive structures control basic survival. The brainstem oversees vital functions such as heartbeat and body temperature, and the cerebellum orchestrates movement.

The limbic system

Nestled deep inside the brain is the limbic system, the second level of MacLean's "triune brain." This wishbone-shaped complex of nerve centers is found in all mammals. The limbic system links emotions and behavior. Stimulating one area of the limbic system produces feelings of anger and aggression, while stimulating another area prompts feelings of pleasure and relaxation. The limbic system is the interface between our animal drives and the constraints of civilization, between irrational impulses and practical decisions, between raw emotions and rational behavior.

The limbic system has another major function: it is central to memory and learning. Although memories are not stored in a single location, discrete structures within the limbic system orchestrate memory formation. Furthermore, these structures process different kinds of memory. The hippocampus, for example, is active in converting information into long-term memory and in memory recall. Repeated use of specialized nerve networks in the hippocampus enhances memory storage, so this structure is involved in learning from both commonplace experiences and deliberate study. In contrast, motor skill learning does not involve the hippocampus and is largely spared in Alzheimer's disease.

Damage to the hippocampus or its nerve connections can cause amnesia (inability to learn and then recall new information). People with amnesia are unable to form new long-term memories, and they forget information soon after they hear or see it. For example, researchers have found that patients

with amnesia can continue doing things like playing checkers as well as they used to (because it was a skill that was acquired over years of practice), but they can't remember the name of their opponent.

But not all experiences in a person's life are etched in memory, nor is it necessary to retain every bit of information. Here, emotions enter the memory process. Some neuroscientists believe the hippocampus helps select which memories are stored, perhaps by attaching an "emotion marker" to some events or information so they are more likely to be recalled.

The amygdala, which sits next to the hippocampus, is concerned with a different magnitude of emotional memory: it comes into play in situations that arouse feelings such as fear, anger, pity, or outrage. Researchers have discovered that memories that have an emotional component are more likely to be retained. But damage to the amygdala can abolish an emotion-charged memory.

The cerebral cortex

The third level of the "triune brain" is the cerebral cortex, commonly called the "gray matter." The cerebral hemispheres contain two specialized regions, one dedicated to voluntary movement and one to processing sensory information. But most of the gray matter is the association cortex. The association cortex is the region of conscious thought: it is where you store memory and language skills, process information, and carry out creative thinking.

A micro view of the brain

Up close, the brain is a web of interconnecting cells called neurons. How these cells communicate and what happens when these cells die form the basis of our understanding of brain disease.

How brain cells communicate

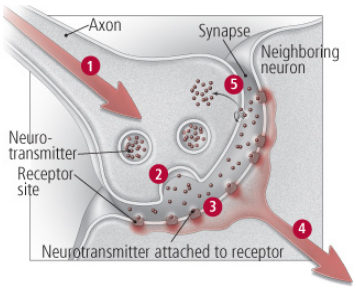
The neuron is the brain's basic unit for processing information. The human brain contains an incredible number of neurons — about 100 billion, give or take 10 billion. The neuron is a unique cell in activity and appearance. It generates both electrical and chemical signals, making it able to communicate quickly with distant neurons. Instead of the compact shape typical of other cells in the body, the neuron is like an oak tree with giant branches stretched out. Each neuron has a body containing a nucleus, one long fiber called an axon, and many shorter branching fibers called dendrites.

The neuron is both a receiver and a transmitter. When a neuron receives a signal, it generates an electrical impulse. This impulse travels through the neuron and down the axon to its end (the axon terminal). The signal is then passed on to other neurons. Viewed under a microscope, neurons look like a dense forest of trees whose branches are so closely intertwined that they appear to touch. But when the details are highlighted with a silver stain, it is clear that each cell is separated from its neighbors by tiny gaps called synapses. Because the electrical signal cannot bridge this space, some other mechanism is required for a neuron to communicate with its neighbors. This is where the neuron's chemical signal comes in.

Stored in the axon terminal are chemical messengers called neurotransmitters. The electrical impulse opens tiny pores in the axon terminal, allowing a supply of neurotransmitters to flood into the synapse

(see Figure). The chemical then attaches to receptors on a neighboring neuron. What happens next depends on whether the neurotransmitter has an exciting or inhibiting effect on the neuron.

Figure: How nerve cells communicate



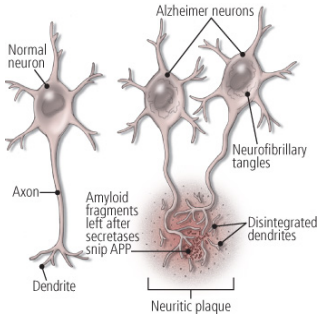
1. An electrical signal travels down the axon of a neuron.
2. The neuron releases chemical neurotransmitter molecules.
3. The neurotransmitter molecules bind to receptor sites on another neuron.
4. The signal is picked up by the second neuron and is either passed along or halted.
5. The neuron that released the neurotransmitter takes back some of the remaining molecules, a process called reuptake.

An excitatory neurotransmitter passes the message on by creating an electrical impulse in the cell that receives it, and the process of electrical-to-chemical signaling is repeated. But if an impulse were to be transmitted to every neuron in the brain, the result would be chaos; much like a power surge can cause a short circuit, neurons firing all at once would cause a prolonged epileptic seizure. To safeguard against this happening, inhibitory neurotransmitters suppress communication to neighboring neurons.

Of the more than 20 chemical messengers discovered thus far, a few are fairly well understood. Several of them are involved in memory, including acetylcholine, serotonin, and dopamine. Many of these neurotransmitters have additional functions; for example, serotonin helps regulate sleep and sensory perception, while dopamine helps regulate movement.

As biological processes go, the speed of thought is rapid (although slow compared with a computer). Electrical impulses in some neurons reach speeds of nearly 200 mph, and transmission from cell to cell takes about a thousandth of a second. In addition, one nerve cell may have more than 1,000 synapses and, with a single impulse, can transmit simultaneously to all its neighbors.

Figure: Plaques and tangles



The brains of Alzheimer's patients contain neurofibrillary tangles inside neurons and clumps of fibers called neuritic plaques outside of neurons. A set of enzymes, called secretases, in the neurons cause plaques to form. The secretases snip pieces from a large amyloid precursor protein (APP), leaving behind fragments of amyloid proteins that snarl and clump with the debris of dying neurons (pieces of dendrites). In contrast to the neuritic plaques, neurofibrillary tangles form within neurons and are composed of aggregates of a different protein known as tau.

When nerve cells die

The tremendous number of neurons and synapses in a normal brain provides a seemingly infinite capacity for processing information, as well as a margin of safety in case some are destroyed. But in Alzheimer's disease, the wholesale destruction of neurons eliminates this safety net, especially in the areas involved in memory and cognition — the association cortex, the limbic system, and their connecting nerve networks. Although research suggests that one day it may be possible to coax new neurons to grow, at this point such a feat is impossible.

Nerve cell regeneration

For decades, the accepted wisdom was that neurons could not regenerate. Scientists used to believe that we are born with a certain number of neurons, and once they die, they are gone forever. But research has turned this theory on its head.

Scientists have discovered that adults do grow new neurons, and that some of this regeneration takes place in the hippocampus, a structure that is devastated by Alzheimer's disease. This hopeful finding raises the possibility of using the brain's regenerative system to replace cells that are lost in diseases of aging, such as Alzheimer's. For example, scientists are looking into ways to recreate brain cells in the cerebral cortex by manipulating precursor cells.

Dr. Jeffrey D. Macklis, professor of surgery and neurology at Harvard Medical School, has shown that under the right conditions, precursor cells, or stem cells, introduced into adult mice selectively migrate into regions of the brain that have degenerated. Furthermore, these cells can grow into neurons that are indistinguishable from their healthy, normal neighbors. Besides offering promise for treating degenerative brain diseases such as Alzheimer's and Parkinson's, this technique for regenerating nerve cells may ultimately be useful for any number of conditions that affect the central nervous system, such as spinal cord injuries.

Alzheimer's leaves two odd types of deposits in these areas. Inside the neurons of an Alzheimer's patient are neurofibrillary tangles, hairlike protein fibers twisted tightly together like yarn. Lying outside

the neurons, near synapses, are neuritic plaques, made up of a protein core called beta-amyloid (also called a-beta or Aß) surrounded by debris from degenerating neurons (see Figure). These two features — neurofibrillary tangles and neuritic plaques — are the distinctive microscopic signatures of Alzheimer's disease.

These tangles and plaques, first described by Alois Alzheimer in 1907, have been the main focus of research for decades, and for good reason: the worse the mental deterioration, the more amyloid and tangles are found in brain tissue. The prevailing view among neurologists used to be that these deposits caused the mental changes in Alzheimer's disease.

However, tangles and plaques are not unique to this condition. Some are found in other dementing disorders, and a few are scattered about in the brains of healthy middle-aged and elderly people. Studies now indicate that dementia in Alzheimer's patients stems from the shrinkage and death of neurons and synaptic loss, and not from the tangles and plaques themselves. What causes this damage is uncertain, but the leading theory is that small fragments of soluble amyloid protein are the toxic factor, triggering a cascade of biochemical events that causes cells to shrink and die. In other words, the body overproduces beta-amyloid or fails to clear this protein away properly, and this sets off a chain reaction that leads to the destruction of nerve cells.

Neuroscientists were able to determine this likely cause for dementia by examining brain tissue from 10 people with normal brain function who died after age 60. All the samples contained about the same number of neurons in an area of the association cortex richly supplied with nerves from the sensory region. For the first time, scientists had a standard for defining how many neurons were "normal" in the human brain. Furthermore, this finding indicated that neuron loss was not a product of normal aging.

Next, the researchers compared the normal samples with brain tissue from 10 people with Alzheimer's and discovered, on average, a 41% reduction in the number of neurons. And the longer dementia had been present, the fewer neurons were found. There was also a correlation with neurofibrillary tangles: people with the greatest neuron loss had more tangles, but loss of neurons was dramatically greater than the number of tangles. The researchers offered "housekeeping" as a possible explanation for this finding: molecules that clear away dead cells in the body eventually removed the tangles.

When they counted neuritic plaques, the researchers found no relationship with neuron loss or disease duration. Although tangles and plaques are still considered the diagnostic hallmarks of Alzheimer's disease, synaptic loss and neuron death correlate best with dementia.

Experts also believe that decreased levels of the neurotransmitter acetylcholine, a chemical that bridges synapses between neurons that affect memory, also contribute to the memory loss of Alzheimer's disease. In the cortex and hippocampus, where this neurotransmitter is needed for memory and learning, the acetylcholine-producing neurons (called cholinergic neurons) are normally plentiful. But of the several types of neurons that can degenerate in Alzheimer's disease, the cholinergic neurons are especially hard-hit. As acetylcholine production falls in the cortex and hippocampus, dementia becomes progressively worse. By the time someone with Alzheimer's disease dies, the cortex may have lost 90% of its acetylcholine.

Other neurotransmitter abnormalities may also be present. Reduced levels of serotonin and noradrenaline have been found in some people with Alzheimer's disease. Imbalances among these and other neurotransmitters could explain why some patients experience sensory disturbances, depression, sleep problems, aggressive behavior, and mood swings.

New diagnostic criteria for Alzheimer's disease

The National Institute on Aging and the Alzheimer's Association has published new guidelines for the diagnosis of Alzheimer's disease. This is the first update since the original guidelines were created in 1984.

The guidelines include several significant changes. First, they describe three disease stages: asymptomatic (preclinical), thinking difficulties (mild cognitive impairment), and dementia (Alzheimer's). This is the first formal recognition of what research has suggested for several years now — that Alzheimer's disease evolves gradually over many years and that physiological changes in the brain occur a decade or more before noticeable symptoms such as memory loss or behavioral changes.

Second, the guidelines propose — for research purposes only — using biomarker tests in conjunction with clinical assessments to determine whether someone might be at an early stage of Alzheimer's. The biomarkers are still being tested, however, and are not meant for routine use in a clinical setting.

Finally, the guidelines emphasize that although Alzheimer's usually involves memory loss, in some cases it will cause other symptoms first — such as difficulty in finding the right words for something or problems seeing the "big picture" in a situation.

Investigators, clinicians, and policy makers are hoping the guidelines will help accelerate research on ways to prevent or at least slow the progression of Alzheimer's. The cost of Alzheimer's — whether measured in terms of human suffering or health care dollars — is already enormous and will only grow further in the years ahead. Currently, five million Americans have Alzheimer's. By 2050, as more baby boomers age and the elderly population increases, as many as 16 million will be affected. Finding a way to delay the onset of Alzheimer's symptoms by five years could — according to one projection — not only help more than half of those at risk for dementia avoid this fate, but also significantly reduce projected Medicare costs for their care.

A long trajectory

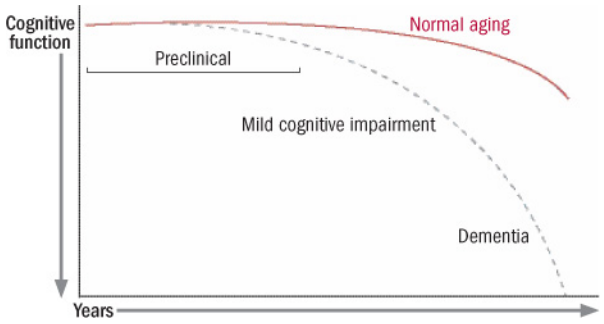
The leading theory about Alzheimer's is that the disease process begins when deposits of beta-amyloid protein collect outside neurons (brain cells), gradually destroying synapses (the connections that enable neurons to receive and communicate information). The next step in the process occurs when neurofibrillary tangles made of tau protein accumulate inside neurons, interfering with normal cell

functions and eventually killing them. As neurons die and synapses wither, brain tissue shrinks in key areas that support memory, language, and other thinking abilities.

But biology is not always destiny. One surprise from brain imaging research is that about 30% of older people have amyloid deposits that might suggest Alzheimer's, and yet their memory and thinking ability remain normal. Although many will develop Alzheimer's later, others are spared.

Multiple factors influence whether someone will go on to develop dementia. Head injury, high blood pressure, diabetes, and obesity all increase the likelihood of progression to dementia, while physical activity, social relations, and keeping mentally active all protect against it. But it is still impossible to predict, on an individual basis, which people with early Alzheimer's pathology will go on to develop the severe memory and thinking problems that characterize the disease. By better delineating the three stages of Alzheimer's disease progression, researchers hope one day to find a way to intervene in the disease process in the people most at risk.

A three-stage process



The preclinical stage of Alzheimer's causes subtle cognitive impairments that resemble those that occur normally with age. Only later does the disease progress to mild cognitive impairment and dementia. (Illustration adapted with permission from Alzheimer's & Dementia.)

Stage 1: Preclinical

The earliest stage of the Alzheimer's disease process is preclinical, when symptoms such as memory loss are absent or so subtle as to go undetected. At this stage, however, pathological changes are probably already under way in the brain.

The section of the guidelines that discusses the preclinical stage of Alzheimer's does not provide diagnostic advice — since there is nothing to diagnose — but instead describes how researchers might use five biomarkers to estimate the chances of whether someone might be at the preclinical stage. Some of the biomarker tests measure beta-amyloid accumulation in the brain, an early sign of Alzheimer's pathology that suggests the disease process has just begun. Others measure tau protein levels in spinal fluid or use imaging techniques to assess brain shrinkage — signs that the disease has progressed to the point where it is damaging neurons.

All of the biomarkers remain investigational, partly because there is no agreement about what findings are in the normal range or when they reach the threshold for abnormality. The recommendations suggest that researchers use biomarkers not only to help determine whether someone might be at the preclinical stage of Alzheimer's, but also to learn what factors might predict a transition to mild cognitive impairment.

Stage 2: Mild cognitive impairment

Mild cognitive impairment is an intermediate state between the normal forgetfulness that occurs with age and the more pronounced memory and thinking deficits that occur in Alzheimer's. Within five years, about half the people with mild cognitive impairment develop dementia — most often Alzheimer's. As many as one-quarter of those with mild cognitive impairment regain normal cognitive functioning in time. The rest remain stable. The guidelines not only outline criteria to determine whether someone has mild cognitive impairment, but also describe how biomarker tests might be used to predict whether they are likely to progress to Alzheimer's.

The foundation of diagnosis is a thorough evaluation to rule out other medical problems that might cause problems in thinking, such as heart disease, stroke, depression, or head trauma. There are no standard neuropsychological tests to diagnose mild cognitive impairment, so clinicians adapt those developed for other purposes. Because other thinking areas may deteriorate in parallel with or even before memory, the guidelines also recommend testing a variety of cognitive functions. The following pattern of findings may suggest mild cognitive impairment:

- *change in cognition*, a deterioration in thinking ability noticed either by the person affected, a loved one, or a clinician
- *impairment of one or more abilities*, including memory, attention, language, and ability to plan
- *ability to function independently*, although perhaps less efficiently or more slowly than before
- *absence of dementia*, based on the criteria described in the next section.

Some clinicians may suggest biomarker testing in a person with mild cognitive impairment if the results could guide treatment or help with life planning. Although some people in this position might not want to know what the future holds, others do — to allow time for making medical and financial plans or enabling participation in research studies.

Stage 3: Dementia due to Alzheimer's disease

Once Alzheimer's has progressed to the point where memory, thinking, and behavior are so impaired that a person is no longer able to function independently, the diagnosis is dementia. Diagnosis of Alzheimer's dementia relies primarily on clinical signs and symptoms, along with tests to rule out other types of dementia or neurological illnesses. The changes in thinking and functioning can be assessed by a clinician and confirmed by a knowledgeable observer, such as a spouse or close friend. Further testing may be necessary to confirm the nature and extent of cognitive impairment.

The criteria emphasize that memory impairment — although the most common initial symptom — may not be the only one. After stroke, delirium, and other possible causes of dementia are ruled out, a diagnosis of Alzheimer's is probable when cognitive or behavioral impairment develops gradually, increases over time, and involves at least two of the following cognitive domains:

Memory. This is the most common problem area and typically involves episodic memory (difficulty learning or remembering new information). In day-to-day life, this might cause someone to misplace personal belongings, repeat the same question or conversation, forget things, or get lost while walking or driving in familiar areas.

Executive function. This type of thinking includes planning, reasoning, judgment, and problem solving. Impairment of executive function might manifest as difficulty with finances, failure to appreciate safety risks, or inability to organize meals.

Visuospatial ability. This refers to the ability to interpret visual information and see how objects fit into surroundings. Impairments in visuospatial ability may manifest in many different ways, such as trouble recognizing familiar people, or the inability to find objects such as eating utensils (even when in plain view).

Language. Impairments in this domain might show up as hesitation in speaking, problems coming up with the right word, or spelling errors.

Behavior and personality. Uncharacteristic changes in behavior and personality include agitation, apathy, mood swings, obsessive or compulsive behavior, or socially unacceptable behavior.

Protective measures

So far, all "disease-modifying" drugs aimed at slowing Alzheimer's have failed. But these drugs have been tested mainly in people with advanced Alzheimer's — and experts in the field think that this may be too late in the disease process to make a difference. They hope that the guidelines will enable researchers to better identify people at a much earlier stage of Alzheimer's and then conduct carefully controlled studies of drugs and other interventions.

The results of such studies will not be available for years. In the meantime, people concerned about reducing their risk of Alzheimer's would do well to focus on maintaining overall physical health, especially when it comes to their heart and blood vessels. Researchers have long recognized that heart disease increases risk for Alzheimer's and vascular dementia (the type that develops when arteries to the brain get clogged). In recent years, they've learned that heart disease acts synergistically with early Alzheimer's brain changes, multiplying and compounding the damage.

People who want to protect themselves against Alzheimer's therefore are wise to follow the usual advice for preventing heart disease. This includes eating a healthy diet, maintaining normal blood sugar and cholesterol levels, exercising regularly, not smoking, and reducing stress levels. There is no guarantee that healthy living will slow or prevent Alzheimer's, but it can't hurt — and it will certainly help improve overall health in the process.

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Caregiving — Day-to-day challenges and beyond

In the 2006 movie *Away from Her*, Fiona, a woman with Alzheimer’s disease portrayed by Julie Christie, says, “Half the time I wander around looking for something, but I can’t remember what it is. Everything is gone.” This movie and several others reveal compelling yet painful portraits of people diminished by the disease. But the roles of the caregivers in these films — spouses and adult children, as is often the case in real life — are perhaps even more poignant. They realize and reflect upon all that is “gone” even more acutely.

Alzheimer’s disease has a profound emotional impact on the family. Fear, denial, anger, resentment, guilt, embarrassment, and grief are all normal reactions. Getting a diagnosis can be an overwhelming experience, and when the diagnosis is uncertain, the family may feel suspended between hope and despair. It’s important that family members not succumb to inaction because, as difficult as it may seem, several important issues should be addressed as soon as possible.

But the day-to-day challenge of caring for a person with Alzheimer’s disease often proves the most difficult and demanding aspect for loved ones, who most often are family members but also may be friends or neighbors.

Explaining the condition

What should you tell someone who has Alzheimer’s? Most experts say if the person asks what’s wrong, you should be honest; knowing that the problem is a disease, not “insanity,” is often a relief for the person affected. Telling someone who has not asked may be helpful, particularly if the person appears troubled about his or her condition. Generally, it’s best for the physician to explain the diagnosis. New information doesn’t always “stick,” however, so don’t be surprised if someone with Alzheimer’s continues to ask what’s wrong. In such cases, you can offer a reassuring but brief explanation.

You may also need to talk to family and friends. People with Alzheimer’s disease often look quite healthy in the early stages of disease, and people outside the household may be unaware that anything

is wrong. But it's important to tell other family members and friends about the diagnosis as soon as possible for two reasons. First, they need to know both that any unusual behavior is caused by disease, not by "craziness" or "meanness," and that they'll need new ways of responding as the person's cognitive abilities decline. Second, you and any other caregivers need emotional support and practical help from others.

Alzheimer's disease in the movies

A number of films have featured characters suffering from Alzheimer's disease:

The Savages (2007). In this tragicomedy, Laura Linney and Philip Seymour Hoffman play siblings suddenly faced with caring for their estranged father with dementia.

Away from Her (2006). Julie Christie was nominated for an Oscar for her portrayal of a woman with Alzheimer's disease who voluntarily enters a nursing home so that she will not burden her husband of 45 years.

The Notebook (2004). Based on a novel by the same name, this movie begins with an old man (James Garner) reading from a notebook to his wife (Gena Rowlands), who is in a nursing home with Alzheimer's disease. The notebook — and most of the movie — describes their youthful romance.

Iris: A Memoir of Iris Murdoch (2001). This film tells the true story of novelist Iris Murdoch's deterioration into Alzheimer's disease, based on the book *Elegy for Iris*, by John Bayley, her partner of 40 years. Judi Dench and Kate Winslet (who portray Iris in her elder and younger years, respectively) both received Academy Award and Golden Globe nominations for their performances.

Coping with daily challenges

The abilities of someone with Alzheimer's can fluctuate from day to day, or hour to hour, which makes the caregiver's job all the more difficult. Often, the person's abilities wax and wane for the same reasons that a healthy person's abilities fluctuate: fatigue, anxiety, discomfort, or medications.

Equally confusing may be a seeming inconsistency in an individual's abilities. He or she may be able to perform a complex task, but not a simple one. Family members may suspect the person is not trying hard enough or is being deliberately uncooperative when, in fact, the uneven loss of abilities is explained by the disease process itself.

Some techniques can improve the quality of life for both patient and caregiver. For example, by breaking an activity into simple steps and talking the person through it one step at a time, you can turn a complicated task such as getting dressed into a manageable one.

Decisions about driving

One of the first questions many families ask is whether people with Alzheimer's disease should stop driving immediately. If the person is only mildly impaired, the answer may not be simple. Some advocates for the elderly believe that driving privileges should not be taken away until a person becomes an unsafe driver. The problem is trying to determine when a person is unsafe before an accident occurs.

Driving requires a complex interaction of eyes, brain, and muscles, as well as the ability to solve problems quickly. A person may appear to drive well until an unexpected situation occurs. The complicated stops, starts, and zigzags of city traffic can cause someone with Alzheimer's to panic or freeze with indecision. A University of California study found that the driving skills of people with mild Alzheimer's were significantly poorer than those of other elderly people, including those with some other forms of dementia.

The person's general behavior in other situations should alert the family as to when safety behind the wheel is questionable. People who exhibit poor judgment, inattentiveness to what's going on around them, clumsiness, and slow or inappropriate reactions certainly should not drive.

A tactful approach that preserves the person's self-esteem may work. Some people agree to stop driving if another reason is given — for instance, the car needs repair or the license or registration has expired. Another option is a road test with a driver's rehabilitation specialist, who can offer an independent assessment of safety.

Be aware that in some states, doctors have a legal duty to report unsafe drivers and drivers with certain medical problems to the state department of motor vehicles. It may not be necessary to go to such lengths. People with Alzheimer's disease sometimes take seriously a written prescription from a physician that says, "Do not drive." If all else fails, you may need to seek advice from a lawyer or an official with the Department of Public Safety in your state. Procedures vary, but generally, a driver's license can be suspended on the basis of a physician's written statement. If nothing else works, you can sell the car.

Bright lights, less dementia?

A unique study offers another strategy for improving symptoms of dementia. People who have dementia often have a diminished ability to track or react to day and night transitions. Both light from the environment and the hormone melatonin are necessary for normal circadian rhythm (the 24-hour sleep-wake cycle).

Researchers studied 189 residents in 12 assisted-care facilities, most of whom had dementia. Some residents received doses of bright light between 9 a.m. and 6 p.m., some took supplements of melatonin or placebo pills, and some received both treatments. A fourth group received no treatment. Almost all of the participants completed at least a year of the study.

People in the facilities with bright daytime lighting appeared to have less progression in their dementia. They had 53% less of a decline in physical function scores, and 5% less decline in memory test scores, compared with the average decline at dimly lit facilities. Patients exposed to bright light were also 19% less likely to develop depression during the time of the study.

People who took melatonin without bright light frequently complained of depression and were more likely to become socially isolated. This suggests that melatonin alone is not useful. However, when melatonin and bright light exposure were combined, depression rates were not higher than expected, and after several months of use, sleeping patterns seemed to improve. There was longer uninterrupted sleep, less frequent episodes in which residents were up out of bed at night, and somewhat less agitated behavior, according to researchers, who reported their findings in *JAMA* in 2008.

For people with dementia and for their caregivers, the use of bright lights is a simple, safe change. It may be helpful to combine light therapy with melatonin for people who have difficulty getting to sleep or staying asleep. These findings could improve the quality of life for people with dementia and ease strain on those who care for them.

Special precautions for wanderers

Keeping an individual with Alzheimer's disease safe is a heavy responsibility. The most dangerous and distressing behavior is wandering. A person might get up at night to dress or cook, for example, or leave home at any hour. Wandering may be more purposeful than it sounds, possibly prompted by deep-seated memories of work, chores, or hobbies, or a longing to return to a past home. Inability to control this behavior is often a family's main reason for deciding to place a loved one in a nursing home.

Simple measures to prevent off-site wandering often work well for a time. The Alzheimer's Association recommends these steps:

- Install slide bolts at the top or bottom of doors.
- Place warning bells on doors.
- Camouflage doorknobs by covering them with cloth of the same color as the doors. Consider childproof knobs, too.
- Camouflage doors by painting them the same shade as surrounding walls.

- Create a two-foot black threshold in front of doors with paint or tape. (A rug might do the job, too.) This creates the illusion of a gap or hole that a person with limited visual-spatial abilities may be reluctant to cross.

Sometimes, it's not possible to prevent wandering. These additional tips for planning ahead can help:

- Take photographs often, so you'll have a recent photo available to give to police, if needed. Close-ups are best.

- Keep a list of familiar places that the wanderer might go to, such as church or a favored restaurant, job sites, or a previous home. Interestingly, the Alzheimer's Association notes that wandering generally follows the direction of a person's dominant hand — to the right if right-handed, or the left if left-handed.

- Post emergency numbers in a handy spot.

- Buy identification jewelry engraved with "memory impaired" and the person's name, address, and phone number. Or enroll in the nationwide program MedicAlert + Safe Return, which offers a bracelet or pendant with a toll-free emergency response number that you — or anyone who finds the wanderer — can call 24 hours a day. Response line personnel alert police and a personal contact list.

- A high-tech option uses GPS — the satellite global positioning system — and cell towers to provide an approximate location for a person who might wander. One such system, called ComfortZone, allows family members to check on the patient's whereabouts via an Internet link or by calling a monitoring center. Depending on the level of need, families might request an alert if the person wearing the locator device leaves a specified zone, or they might tap into the system only in case of emergency.

Practical advice for coping with daily routines

Communication

- Use simple phrasing and short sentences, but be careful to avoid talking to the person as if he or she were a child.
- To get the person's attention, begin by using his or her name.
- Be patient. Give someone with Alzheimer's time to complete a sentence or thought, and try not to interrupt.

Bathing

- Use rubber tub mats, tub seats, grab bars, nonslip bath mats, etc. Do not use bath oil or products that make the tub slippery. Put razors and electrical appliances out of reach. Take the lock off the bathroom door.
- Follow the person's old routines as much as possible.
- Prepare everything in advance. Lay out towels, soap, shampoo, and clothes. Have the water ready and at the right temperature before bringing him or her into the bathroom.
- Avoid discussing whether a bath is needed. If the person refuses to get into the tub or shower, be flexible and suggest an alternative. If all else fails, try again later.
- Be calm, gentle, and reassuring. If the person seems disturbed at this invasion of privacy, cover portions of his or her body with a towel.
- Encourage him or her to do as much as possible without hands-on help. Talk through each step.
- Check the skin for rashes and sores. Use powder or cornstarch to prevent chafing, and apply body lotion to dry skin.

Dental care

- Prepare the toothbrush and demonstrate how to brush.
- If the person will not brush and refuses assistance, try a foam applicator or a cloth moistened with mouthwash.

Dressing and grooming

- Avoid shoes with slippery soles, pants or dresses that are too long or full, and long or full sleeves that may catch on doorknobs or furniture.
- Consider the person's past grooming habits, but keep grooming simple to avoid frustration.
- Avoid forcing the person to choose what to wear. Remove clothes that are out of season or seldom worn.
- Try to establish a routine in which you help the person dress at the same time each day.
- Select simple clothing the person can manage easily without assistance. Avoid buttons, hooks, snaps, and ties.
- Lay out clothing in the order that it should be put on.

Mealtimes

- Don't serve food or drink that is too hot. Remind the person to eat slowly and chew each bite thoroughly. If eating nonfood items becomes a problem, keep things like dog biscuits and flower bulbs out of sight.

Safety measures

An environment that's safe for the average family nearly always contains hidden hazards for someone who is mentally impaired. As you try to anticipate safety hazards, look at the world through the eyes of a cognitively impaired person. Conduct a thorough inspection of all areas in and around the house, looking for potentially harmful things that the person with Alzheimer's might misuse or misinterpret.

- Correct hazards that could cause tripping and falling: cluttered areas, extension cords, throw rugs, slippery floors, dim lighting, and uneven surfaces. The route from bedroom to bathroom should be clear of clutter and have night-lights.

- Lower the temperature on water heaters and insulate any exposed hot-water pipes. Block off radiators with furniture or a gate.

- Keep cleaning supplies, insecticides, gasoline, paint, solvents, and medicines out of reach or stored in cabinets with childproof latches. Get rid of poisonous houseplants, and put small items (pins, buttons, etc.) out of reach.

- Hide the stove knobs so the person can't turn on the burners. If you have an electric stove, install a switch that inactivates the burners, or switch off the stove at the fuse box or circuit breaker. If you have a gas stove, ask the local gas company for suggestions on how to disable it. Childproofing knobs may help here, too.

- Make certain that all stairs have sturdy handrails and good lighting. Install a gate at the top of the stairs.

- Install handrails and grab bars in the bathroom. Use a skid-resistant mat inside the tub or shower.

- Lock away all firearms, power tools, sharp knives and scissors, and machinery.

Tips for caregivers and friends

Get organized. Call a family meeting to decide what kind of care is needed and determine who should research it, give it, and help pay for it. Anyone who can't attend in person should try to do so by phone. Try to put aside differences so the focus stays on your loved one's needs. Make a list of what needs to be done and who can do it. While it's helpful to have one person take primary responsibility, everyone should offer to take on specific tasks. In some families, people sign up for tasks and companionship on particular days of the week or month. To help defray costs, one large New England family asked everyone to pitch in monthly on a sliding scale that varied depending on financial ability.

Ask for help. Try to find out whether your loved one already has an informal network of support. Do any friends and neighbors stop by to visit or lend a hand? If you ask them to do so, many people may be willing to help more formally or call you if anything seems amiss.

Offer support — and accept it. If you're not the main caregiver, ask that person how you can help. Offer specific suggestions. For example, could you take over for a weekend, a few weekdays a month, or a much-needed vacation? Could you provide or coordinate certain services, such as housecleaning or transportation to doctor's appointments? If you're the main caregiver, spell out what needs to be done and what sort of help you require. Don't try to do everything yourself "because it's easier." Let other people step up to the plate. When someone offers help, accept it. If no one offers help, ask for it. Write out a list of smaller tasks that people could do, such as cooking an occasional dinner or running errands, and dole these out. Or simply ask others to check off what they can do.

Collect medical information. Keep a well-organized health care binder that includes information on the patient's current ailments, medications, allergies, medical history, specialists seen, and treatments. Add a copy of legal papers (durable power of attorney, health care proxy, living will, etc.), too. The Alzheimer's Association offers a checklist of helpful information for personal health records (www.alz.org/carefinder/support/documents/phr_checklist.pdf). You may wish to organize your personal health record online. The nonprofit American Health Information Management Association also offers useful information on setting up a personal health record at www.health.harvard.edu/learnphr. AARP also offers suggestions for organizing key information and free tools for one such system, which you can find at www.health.harvard.edu/aarptools.

Obtain respite care. Regular respite care from professionals, family, and friends can give you much-needed breaks. Find out if there are any adult day care services available in your community.

Join a real-time or virtual support group. Support groups — face-to-face or online — allow you to talk out frustrations and share helpful ideas with other people in your situation. The Alzheimer's Association, local hospitals, senior centers, or community groups offer support groups, too.

Blow off steam. Post numbers you can call when you're feeling overwhelmed, such as helplines, good friends, and supportive people dealing with similar challenges. Exercise or relaxation techniques may help when you're frazzled, too. Try to carve out regular slices of time to yourself. And set up back-up plans for those precious minutes or hours to help ensure that minor emergencies won't derail you.

Take care of yourself. Eat well, get enough rest and exercise, and pursue activities that bring you pleasure. If it's too hard to find the time, consider getting extra help with some household chores.

Finding help and support

Families often complain that physicians don't adequately explain what they need to know. To avoid feeling isolated, learn everything you can about the disease and about dealing with the person who has Alzheimer's. An excellent place to start is the Alzheimer's Association. It has assembled a wealth of

information from health professionals and caregivers, including practical guides for managing nearly any problem you might encounter.

The Alzheimer's Association organizes family support groups where caregivers share their problems and solutions. The online blogs and message boards are helpful sources, too. The organization also connects families with community resources, including adult day care programs (many of which are specifically geared toward patients with dementia) and in-home respite services.

Caregivers often try to shoulder the burden alone because they are too shy, proud, exhausted, or afraid to seek help. All too often, they wear themselves out and become depressed or ill. Caring for someone with Alzheimer's is a major undertaking that is beyond the resources of a single person. It's essential that you care for yourself by getting away from your responsibilities from time to time.

If you're becoming depressed, seek professional help. You also need to recognize your own limits. The time may come when you can no longer provide in-home care and must move the person to a long-term residential care facility.

One woman's story: Caring for a mother-in-law with Alzheimer's

Florence was 77 years old when she was diagnosed with Alzheimer's. She lived with her son Glenn and his wife Kathy for seven years before moving to a nursing home and then, after several years, to a specialized Alzheimer's care center. It wasn't until then that the couple realized the benefits of the expert care available in a setting specifically geared for patients with dementia. Kathy and Glenn learned some useful tips to manage Florence's cognitive limitations without upsetting her, as Kathy explains below.

One approach we learned was to use "lie-lets." For example, Florence wondered why she hadn't heard from her sister, someone she was very close to. Rather than saying, "Don't you remember? Mabel died eight years ago," I simply and matter-of-factly explained that Mabel was on vacation in Florida and said she'd call as soon as she got back. This misinformation would ease Florence's anxiety and restore her equilibrium about the matter. Sometimes Florence would say that she wanted to go home. Instead of saying, "I'm sorry, you can't go home," we would tell her that we couldn't take her home that evening but would try to make arrangements to do so within the next few days. Most of the time, she'd forget her worry or request in a few hours or days. Trying to drill the truth into people with Alzheimer's is upsetting to them, and what's worse is that once they forget the truth, those upset feelings remain, but without a clear cause, which can be even more disturbing.

Before Florence went into the nursing home, we went through her old photographs and I asked who each person was and if she could remember the occasion. I made notes in the album, so Glenn and I could later recreate the scene for her. Some of the photos stuck with her — for example, a wedding cake she'd made — and it was something she would show to people with pride.

My relationship with Florence was a caring one, but often difficult even when she was healthy. When she first went into a nursing home, it was hard to accept that she'd reached a point where others could do a better job of caring for her than I could. The burden of caring for someone with dementia can take a toll, but I was surprised at the full weight of my grief when she died. In an odd way we became more attached during this very tough time.

The other advice I'd offer is to realize that sometimes, you just can't make it better. Just do the best you can to make your loved one know you're present and available.

HarvardMedicine

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As Time Goes By

Our brains make, hold, and lose memories in response to changes wrought by age

by Ann Marie Menting
Harvard Medicine Magazine, Autumn 2008

All we do is based on a memory. Each thought, each movement, each conversation draws upon the library of life that is nestled within our brains. From the moment of our birth until the moment we die, our brains, with their billions of neurons and trillions of neuronal connections, gather, package, and store the sensory information transmitted by our eyes, ears, nose, and skin so that we may access and apply it to the physical, intellectual, and social demands of the world we inhabit.

Yet, just as our muscles change with age, so, too, do our brains. Small wonder, then, that explorations into how age-related changes affect our brains—and, by extension, the ways we engage with our world—have so captivated researchers, observers, and those who simply hope to keep the old bean keen.

Down Memory Lane

In 1906, the Spanish anatomist Santiago Ramón y Cajal received a Nobel Prize for his "neuron doctrine." Neurons, he said, function as discrete units. Each cell body receives signals from a rootlike array of dendrites and transmits those signals along an axon to the waiting dendrites of other neurons. Researchers later showed that transmissions from axon to dendrites occur across synapses and that neurotransmitters—substances such as dopamine, acetylcholine, and serotonin—help signals jump these clefts.

The idea that neurons form networks that orchestrate our ability to build memories was posited in 1949 by Canadian psychologist Donald Hebb. From his studies of how the brain

commanded behavior, Hebb postulated that when one neuron repeatedly caused another neuron to fire, a type of metabolic bonding occurred. His idea spawned a slogan: Neurons that fire together wire together. This fire–wire partnership, researchers later discovered, results in networks of connected neurons, each a memory trace of a learned experience that expands or modifies other traces.

When functioning efficiently, the more than 100 billion neurons in the adult brain provide access to a phenomenal cache of information. Researchers have found that it is the degree to which our aging, changing brains construct new connections between these neurons—and avoid or minimize the destruction of existing ones—that determines the scope and vitality of these networks.

"The aging process does not appear to be a passive one," says Bruce Yankner, a professor of pathology and neurology at the Paul F. Glenn Laboratories for the Molecular Biology of Aging at HMS. "It instead appears to be a balance between stress and compensation."

One of the leading theories for how the brain confronts age-related changes is the concept of synaptic plasticity. This theory holds that our brains continually remodel themselves, tweaking the number of connections to other neurons so as to embrace new information, eliminate links to unused networks, and reflect new complexities associated with information in other traces.

"Synaptic plasticity truly is an exciting concept because it says the brain is not a fixed structure," says Majid Fotuhi '97, an assistant professor of neurology at the Johns Hopkins University School of Medicine and director of the Center for Memory and Brain Health at Sinai Hospital's LifeBridge Health Brain & Spine Institute. "One cell may have a thousand synapses on it but then something happens—you learn something new—and you might then have a thousand and twenty synapses."

Situations that trigger these types of changes occur constantly. Negotiating a reduction of global carbon dioxide emissions, for example, could trigger synaptic growth. So could preparing dinner.

Let's say you use a particular pot regularly. You know it has a small break in the handle, but it's usable, so you pull it out, fill it with soup, and place it on the stove. After the soup heats, you reach over to pull the pot off the burner. You get burned. A strong signal associated with the pain speeds to your brain, as does the realization that you have touched exposed metal in the handle. Your brain uses this information to establish new connections; you learn to avoid using that pot or to use a potholder when handling it. You have established a memory that, like most memories, helps you function better in your world.

Form and Function

Viewed without its protective bony outer structure or the rugged inner membrane that wraps its mass of cells, the brain's cortex bears an uncanny resemblance to a shelled

walnut. This wrinkled, bisected structure is arguably the most sophisticated area of the brain.

Within each cortical hemisphere is tucked a small structure quite active in memory making: the hippocampus. Shaped like a banana, the hippocampus serves as an active way station for information, holding new material that is needed immediately, sending to storage that which will be held for days or decades, and assisting in the recall of data housed in other cortical areas.

The cortex is involved primarily in declarative memory, which captures the facts and events of our lives and allows for their recall in some tangible manner: the spoken word, a visual representation, a gesture. Declarative memory can be held for a short time, as for a one-time use of a telephone number, or it can be held up to a lifetime. And although synaptic plasticity can help keep it robust, biology and environment do conspire to whittle away at it over time.

A second form of memory, procedural memory, primarily engages noncortical areas of the brain, most notably the cerebellum. Procedural memory involves sequential, coordinated movements, such as those associated with riding a bicycle. Unlike declarative memory, procedural memory is rugged and not easily lost to the passage of time. This form of memory is a product of action, an imprint of repetitive, serial movements that can be acquired only through physical participation.

Adjusting the Volume

Age-related changes to our brains influence the speed with which we can access stored information, the complexity of the neural networks that contribute to those memories, and the level of function of certain cortical areas.

The fetal brain produces cells and connections in quantities that far exceed the numbers that will populate the adult brain. As newborns soak up information critical to functioning within their environment, competitive elimination starts to prune away unused or underused cells. Initially, the neurons and synaptic connections, known collectively as gray matter, are focused on taking in information and learning. By six months, however, researchers have found evidence of declarative memory as infants are able to recall one or more steps in a simple sequence of events within 24 hours of having learned them.

In another three months, infants can recall isolated steps from a sequenced action after as many as five weeks. By 14 months, babies can recall several steps of a multi-step action for as long as four months while 20-month-olds can recall all the steps—and their proper order—after six months.

The robust nature of this progression in behavior mirrors a flurry of development within the structures of the fetal and infant brain. The cells that make up much of the hippocampus form in the first 17 weeks of fetal development and have ordered themselves in the locations they will hold in the adult brain well before birth. Hippocampal synapses

also develop quickly; they are present in the fetus by 15 weeks, ramp up their numbers after birth, and reach adult levels by approximately six months.

Certain subdivisions of the hippocampus are slower to develop. An area known as the dentate gyrus, important in consolidating new information, has about 70 percent of its adult complement of cells at birth and achieves full adult morphology after 12 months. Synaptic development in this subregion also lags that for the hippocampus: Between 8 and 12 months, the number and density of its synapses spike to a level above that supported during adulthood. By age five, selective pruning has decreased the number of connections to that found in adults.

Development in other association areas of the cortex mirrors that of the dentate gyrus. Cortical definition begins around 28 weeks of gestation, with synaptic densities in areas critical to association and storage peaking in infants by age two. Around the same time, the number of synapses in the prefrontal cortex tops out. In the mature brain, this cortical region provides temporary mental workspace, known as working memory, for processing decisions that involve complex behavior and problem solving.

Overall, the number and density of synapses most capable of plasticity increase throughout childhood. By age four, however, increases of this gray matter are outpaced by growth in the volume of white matter, the mass of networked neurons whose axons are wrapped in insulating myelin. Myelinated axons propel information up to a hundred times more quickly than their gray matter counterparts, allowing for quicker access and recall of information. In the brain, the period during which its various regions are most actively pruning, myelinating, and maturing—a period of neural growing pains, as it were—coincides with another period known for its awkwardness: adolescence.

Gear Up

“The cortex of a young person,” says Zaldy Tan, an assistant professor of medicine at HMS and director of the Memory Disorders Clinic at Beth Israel Deaconess Medical Center, “looks like a complicated mass of wrinkled fat tissue, with numerous peaks flanked by valleys. But as the brain ages, its appearance smoothes out; the peaks flatten and the valleys widen.” These topographic alterations are the result of changes to the brain’s volume and cellular material.

The ratio of gray matter to white matter begins to shift from age four through early adulthood. Although the precise reason for this has not been found, neuroscientists speculate it may be twofold: an increase in mature, myelinated regions plus the pruning of less productive gray matter synapses. Researchers even have movie-like evidence supporting this conjecture. In time-lapse sequences of gray matter-to-white matter changes, researchers found that the cortical regions in adolescents mature in an order that echoes behavioral progression. First the primary sensorimotor areas along the frontal-to-occipital axis myelinate, then back-to-front myelination occurs from the parietal lobes to the frontal lobes.

The prefrontal cortex, that working memory reservoir useful in decision-making, is among the last to mature. Part of that maturation involves an increase in the role of dopamine, a neurotransmitter critical to deciphering environmental cues when choosing between conflicting options. Inputs for this chemical increase significantly during adolescence. Exposure to dopamine is thought to contribute to the development of our ability to use ideas to achieve a goal rather than simply acting instinctively in a given situation. In broad strokes this means an adolescent's reflexes and keenness of sight and hearing are honed well before the young person's ability to process complex information is.

Even synaptic pruning, which begins in earnest in childhood, changes focus during adolescence. Pruning in the early brain targets low-performing excitatory synapses that transmit information neuron to neuron, a reasonable approach considering the efficiency with which children and early adolescents need to learn. But by late adolescence, pruning zeroes in on inhibitory synapses, which control the flow of information between neurons. Thus, the developing brain grows in its ability to control not only the speed by which signals travel but also the efficiency of their routes. The result: actions grow nuanced so as to, in a sense, reflect a synthesis of information leavened by learning and experience.

All this upheaval calms by age 30, when the number of cell-to-cell contacts achieves an adult pattern and the number of neuronal connections reaches a near steady state—except among adults who prod their brains to do more.

New Tricks

Normal aging in the brain can mean little notable behavioral change for an adult untroubled by trauma to the head, disease that affects the brain, or excessive stresses, whether from responsibility, diet, or lifestyle. Physiological changes do occur—synaptic connections lessen, the volume of certain cortical areas diminishes, and the production of neurotransmitters decreases. Yet the adult brain may actually be able to compensate for these alterations: Some research indicates cortical regions team up to accomplish work previously done individually.

Researchers looking at cross-sectional behavioral data for individuals between the ages of 20 and 80 have found little to no evidence for accelerated declines in the latter decades for such capacities as processing speed, working memory, and the encoding of new declarative memories.

There is evidence, however, for linear declines in these areas—as well as in spatial ability and reasoning—beginning by age 40 or 50. In one area, speed of processing, several studies have found a 2 percent decline per decade after age 30.

"The decrease in speed of mental processing that is seen with age is not a problem," says Tan. "The brain may become less efficient, but that doesn't mean it also experiences a decrease in absolute memory."

To tease out secrets to healthy brain aging, Tan is mining a 60-year data trove on the health of another organ: the heart.

“Study upon study has shown that physical activity actually decreases one’s risk of cognitive decline with age,” Tan says. “But what has really struck me from my work with the Framingham Heart Study is that healthy aging seems to mean that what’s good for the heartÑa healthful diet, exercise, low cholesterol—is good for the brain, too.”

The boost that cognitive health can get from good cardiac health can be augmented by good social health, according to Robert Waldinger ’78, an HMS associate professor of psychiatry and director of The Study of Adult Development at Brigham and Women’s Hospital.

“There is strong evidence that people who are more connected to others, whether through marriage, friendships, children, or grandchildren, do better physically, cognitively, and emotionally,” Waldinger says. “Loneliness, in fact, is considered a risk factor for aging poorly.”

But with a finely tuned organ such as the brain, little things can mean a lot. Take genes, whose business it is to oversee our molecular world. Several years ago Yankner looked at the genetic signatures of the brains of people whose ages ranged from 26 to 106. He found that certain genes control the formation of new synaptic connections, others respond to age-induced stresses such as the DNA-damaging molecules known as free radicals, and still others are especially vulnerable to DNA damage. An intriguing possibility is that these genetic characteristics may predict the brain’s future.

“We found that gene expression was quite similar among young adults under 40 and somewhat similar among adults over 70,” Yankner says. “But those between 40 and 70 showed a good deal of variability—some looked like the young group, some like the older group. This told us that the aging process that determines how you’re going to fare at age 80 probably begins around age 40 or 50.”

Reserving Space

Barring trauma or illness that would affect brain health, the ability of neurons to ramify remains strong throughout a person’s life. One of the more captivating ongoing investigations of brain health began nearly 20 years ago with a pilot study that looked at healthy aging in residents of a retirement community of Catholic nuns. This largely closed community provided the researchers with a nearly ideal set of participants; the nuns had not only carefully preserved their personal and medical histories but they had also conformed to a documented lifestyle. In addition, the nuns agreed that, after their deaths, their brains would be donated to the study.

The investigators explored these precious donations in the hopes of isolating factors that affected the nuns’ cognitive functioning. They found that cognitive capacity was compromised for women whose brains showed signs of cardiovascular disease, such as brain stroke. But they found cognitive function remained strong for women whose brains

showed little to no evidence of cardiovascular trauma. Perhaps most interestingly, the researchers also found strong cognitive functioning among stroke-free women whose brains showed moderate to advanced Alzheimer's disease. Such brains, they speculated, drew upon reserves that delayed or offset the symptoms of dementia.
Cognitive reserve—the capacity to sustain brain function and to build effective networks that are less susceptible to disruption, including that which accompanies normal aging or even disease—is a growing concept among neuroscientists. While not exactly a 401(k) for your brain, cognitive reserve acquired from a life of active and sustained learning can keep the brain healthier, longer.

"Cognitive reserve is like strength training for your muscles," Fotuhi says. "When you are fit, you can sustain that fitness for a long period of time. There is compelling evidence that synaptic plasticity continues through age 70 and that brain volume can even increase among healthy adults, especially those who enjoy teasing their brains and exercising regularly. The idea that plasticity exists only in children is completely outdated."

Research on the molecular and physical changes that the brain undergoes with time will likely continue to overturn contemporary ideas of how age, disease, and lifestyle affect our ability to gain, maintain, and recall our individual library of memories. That our brains do alter with age is undeniable. But the lens of research increasingly shows us that when good overall health is maintained and brains are kept agile through learning and challenge, life—and memory—can remain rich for a long time. ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.
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What Tangled Webs

People with Alzheimer's disease tend to weave modifications into their memories

by Andrew E. Budson

"Of course I pay my bills each month," my patient said, as the daughter sitting next to him shook her head. Later, while he was under going cognitive testing, she explained more fully: "That's the problem—he remembers doing things he hasn't done. When the electric company shut off his power, we found he hadn't paid any bills for about six months. He swears he paid them all. I worry whether he can keep living alone. He tells me he takes all his medications, but how do I know that's true?"

People with Alzheimer's disease not only fail to remember previously learned information, but they also experience distortions of memory and false memories. Distortions of memory may include simple but critical aspects of daily life. Alzheimer's patients may falsely remember, for example, that they have already turned off the stove or taken their medications, leading them to neglect these tasks.

More dramatic distortions of memory occur when Alzheimer's patients substitute one person in a memory for another, combine two memories, or believe that a long-ago event occurred recently. These distortions may fall under the definition of confabulation—when people fill a gap in their memory with a fabrication they believe to be true.

Sometimes a false memory can be confused with a psychotic delusion or hallucination. A person may claim, for instance, to have recently seen and spoken with a long-deceased family member. Although visual hallucinations are part of Parkinson's disease dementia and dementia with Lewy bodies (dementias that are characterized by parkinsonism, visual hallucinations, and fluctuations), an Alzheimer's patient is usually more likely to suffer from a memory distortion or a false memory than a true auditory and visual hallucination. The same is true for patients who claim that someone has broken into their house and rearranged their belongings. That these symptoms likely represent false memories rather than true hallucinations or delusions has treatment implications, as false memories respond better to memory-improving medications than to antipsychotics.

My interest in memory distortions began with a simple clinical observation: most of my patients with memory problems triggered by mild Alzheimer's disease could not live alone, while most of my patients with memory problems stemming from encephalitis, temporal lobe epilepsy surgery, and other etiologies could live independently. It was clear that something other than simple memory loss was at work in those with Alzheimer's. My discussions with patients and their caregivers soon showed that false memories and memory distortions made the use of routines and reminders more difficult for Alzheimer's patients than for those with memory loss from other conditions.

Bearing False Witness

At Bedford Veterans Administration Hospital in Massachusetts, my colleagues and I began our research into memory distortions by creating false and distorted memories in healthy older adults and then determining whether Alzheimer's patients could use the same mechanisms that the healthy participants used to suppress these false memories. We created false memories by presenting healthy people with a list of words—such as candy, sour, sugar, bitter, taste, honey, heart, and cake—that related to a theme word, which was not itself presented. Study participants were highly likely to falsely remember on free-recall tests and falsely recognize on recognition memory tests the theme word—in this case, sweet. (Even healthy younger and older adults falsely recognize more than two-thirds of such theme words.)

One way to reduce false recognition in healthy individuals was simply to have them repeat the theme word several times. These repetitions helped them recall particular words, thus allowing them to resist the lure of the non-presented yet central theme word. In two studies, we found that repetition allowed healthy older adults to develop specific recollection of words on the list, which in turn reduced their rate of false recognition. Among Alzheimer's patients, however, repetition only helped them grasp the theme of the list, thus leading them to err more often in choosing the theme word, paradoxically increasing their false recognition rate. Another way that healthy individuals

reduced false recognition of related words was by pairing the words with pictures. Although this reduction could simply reflect the fact that pictures are better remembered than words, researchers at Harvard University have shown that false recognition decreases because the stories that form from picture–word pairings are more distinctive, and thus, more memorable.

The basic idea of this heuristic is that some events are so distinctive they would have to be memorable. If you were asked, "Have you killed a fly in your office within the past year?" you might find the answer elusive, because for most people killing a fly is neither remarkable nor distinctive. If instead the question was "Have you killed a snake in your office within the past year?" you would answer confidently, because the memory would have been distinct.

We investigated whether Alzheimer's patients could use this distinctiveness heuristic to reduce their false recognition rates. We experimentally determined that Alzheimer's patients could use the heuristic. Their poor memory, though, limited their ability to reduce their false recognition rate.

In Living Memory

Studying the frequency of memory distortions and false memories in the real world can be difficult. The terrorist attacks of September 11, 2001, though, provided us an opportunity. We contacted Alzheimer's patients and healthy older adults with a phone questionnaire within weeks of the attacks, again three to four months later, and finally one year afterward to evaluate both their memory of and emotions about that day.

Memory distortions were common among all participants, reminding us that a vivid memory isn't necessarily an accurate memory. Even healthy older adults showed a high rate of memory distortions—on average 25 percent—as they misremembered such details as where they were and whom they were with when they first heard of the attacks. Alzheimer's patients showed even less accuracy, with memory-distortion rates approaching 50 percent. In contrast, memory-failure rates—with study participants saying, "I don't know" or the equivalent—were relatively low: 13 percent in the Alzheimer's patient group and only 1 percent in the healthy older adult group. Thus, when it comes to remembering personal information related to national traumatizing events, Alzheimer's patients and healthy older adults are more likely to misremember than to say "I don't know."

We recently conducted several laboratory studies that also have real-world significance. In one of these studies, we first presented Alzheimer's patients and older adult controls with sentences that could be either true or false, followed by a label of true or false. For example, "In New York City, the 53rd Street bus will take you uptown: false," or "It takes 32 coffee beans to make a cup of espresso: true." Interestingly, although the Alzheimer's patients correctly remembered that 69 percent of the true statements were true, the same patients incorrectly remembered that 59 percent of the false statements were true. This finding suggests that if you tell someone with mild Alzheimer's disease that something is false, they

are more likely to remember that it's true. The statement, "The 53rd Street bus won't take you to your sister's house, so take the 67th Street bus instead," for example, will lead an Alzheimer's patient to be more likely to falsely remember that the 53rd Street bus is the correct bus than if the 53rd Street bus had not been mentioned at all. This finding has significant relevance for clinicians and caregivers who need to communicate with Alzheimer's patients.

Brain Storming

To begin to unravel the underlying pathophysiology of these memory distortions in Alzheimer's patients, we elected to test the role that frontal-lobe pathology may play in the disease. We began by examining false recognition in patients with frontal-lobe lesions caused by stroke or tumor resection. We gave these patients and matched control subjects the same related-word lists we had given Alzheimer's patients and found that patients with frontal lesions showed even higher levels of false recognition than the Alzheimer's patients did.

Some of our newer research investigates how the brain forms and retrieves memories. In this work, we use 128 channels of EEG to produce a particular type of neural activity as subjects are shown a picture or presented with a previously studied word. We found that when we average the EEG across 30 or so trials, we can see—in real time—the electrical activity associated with retrieving a memory. These studies have shown that, compared with healthy older adults, people with mild Alzheimer's disease exhibit vastly reduced frontal-lobe activity, thus providing support to the hypothesis that frontal-lobe dysfunction may cause the high levels of memory distortions in people with mild Alzheimer's disease.

An improved understanding of the causes of false memories and memory distortions may lead to behavioral and pharmacological treatments that can decrease their effects. Reducing the effects of these tangled memories may in turn allow patients with Alzheimer's disease to live fuller, more independent lives. ■

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