



A Primer on Alzheimer's Disease and the Brain - National Institute on Aging



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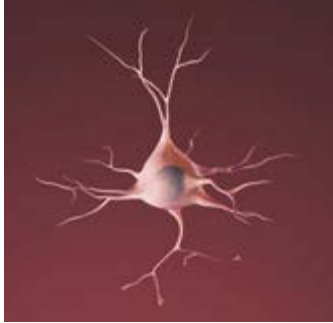
The healthy human brain contains tens of billions of neurons, specialized cells that process and transmit information via electrical and chemical signals. Most neurons have three basic components: a cell body, multiple dendrites, and an axon. The cell body contains the nucleus, which houses the genetic blueprint that directs and regulates the cell's activities. Dendrites are branch-like structures that radiate from the cell body and collect information from other neurons. The axon is a cable-like structure that extends from the other end of the cell body and transmits messages to other neurons.

The function and survival of neurons depend on several key biological processes:

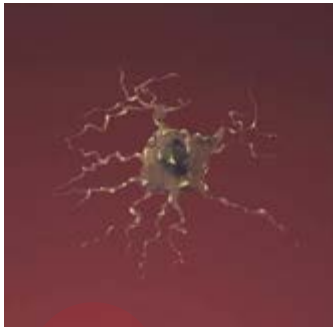
- **Communication.** When a neuron receives signals from other neurons, it generates an electrical charge that travels down the length of the neuron's axon to a specialized structure called the synapse, where the axon comes into close contact with the dendrites of another neuron. At the synapse, chemicals called neurotransmitters are released and move across a microscopic gap to one of the dendrites of another neuron. There, each neurotransmitter molecule binds to a specific receptor molecule, like a key fitting into a lock, and triggers chemical or electrical signals within the dendrite that either stimulate or inhibit the next neuron's activity. Each neuron's axon can make connections with the dendrites of many other neurons, and each dendrite can receive connections from many axons. In fact, scientists estimate that in this brain cell communications network, one neuron may have as many as 7,000 synaptic connections with other neurons.
- **Metabolism.** This term encompasses all chemical reactions that take place in a cell to support its survival and function. These reactions require chemical energy in the form of oxygen and glucose, which is supplied by blood circulating through the brain. The brain has one of the richest blood supplies of any organ and consumes up to 20 percent of the energy used by the human body—more than any other organ.
- **Repair, remodeling, and regeneration.** Unlike many cells in the body, which are relatively short-lived, neurons have evolved to live a long time—more than 100 years in humans. As a result, neurons must constantly maintain and repair themselves. Neurons also continuously remodel their synaptic connections depending on how much stimulation they receive from other neurons. Neurons may strengthen or weaken synaptic connections, or even break down connections with one group of neurons and reestablish connections with a different group of neurons. In addition, a number of brain regions continue to generate new neurons, even in adults. Remodeling of synaptic connections and the generation of new neurons are thought to be important for learning, memory, and possibly brain repair.

Neurons are the cells responsible for transmitting messages between different parts of the brain, and from the brain to the muscles and organs of the body. However, the brain contains other cell types as well. In fact, glial cells are by far the most numerous cells in the brain, outnumbering neurons by at least 10 to 1. Glial cells (of which there are several varieties) surround neurons and play critical roles in supporting neuronal function. For example, glial cells help protect neurons from physical and chemical damage and are responsible for clearing foreign substances and cellular debris from the brain. To carry out these functions, glial cells often act in collaboration with blood vessel cells, which in the brain have specialized

features not found in blood vessels elsewhere in the body. Together, glia and blood vessel cells regulate the delicate chemical balance within the brain to ensure optimal neuronal function.



Healthy neuron



Dying neuron

How Does Alzheimer's Disease Affect the Brain?

While the brain may shrink to some degree in healthy aging, it does not lose neurons in large numbers. In Alzheimer's disease, however, damage is widespread as many neurons stop functioning, lose connections with other neurons, and die. Alzheimer's disrupts processes vital to neurons and their networks, including communication, metabolism, and repair.

At first, the disease typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and the hippocampus. It later affects areas in the cerebral cortex responsible for language, reasoning, and social behavior. Eventually, many other areas of the brain are damaged, and a person with Alzheimer's becomes helpless and unresponsive to the outside world.

What Are the Main Characteristics of the Brain with Alzheimer's Disease?

Many changes take place in the brain of a person with Alzheimer's disease. Some of these changes can be observed in brain tissue under the microscope after death. The three abnormalities most evident in the brains of people who have died with the disorder are:

- **Amyloid plaques.** Found in the spaces between neurons, plaques consist predominantly of abnormal deposits of a protein fragment called beta-amyloid. Beta-amyloid is formed from the breakdown of a larger protein called amyloid precursor protein (APP). Beta-amyloid comes in several different molecular forms. One of these, beta-amyloid 42, has a strong tendency to clump together. When produced in excess, beta-amyloid 42 accumulates into plaques. Scientists used to

think that amyloid plaques were the primary cause of the damage to neurons seen in Alzheimer's. Now, however, many think that unclumped forms of beta-amyloid, seen earlier in the plaque formation process, may be the major culprits. Scientists have not yet determined if plaques are a cause or a byproduct of Alzheimer's disease.

- **Neurofibrillary tangles.** Found inside neurons, neurofibrillary tangles are abnormal clumps of a protein called tau. Healthy neurons are internally supported in part by structures called microtubules, which help guide nutrients and molecules from the cell body to the axon and dendrites. Researchers believe that tau normally binds to and stabilizes microtubules. In Alzheimer's disease, however, tau undergoes abnormal chemical changes that cause it to detach from microtubules and stick to other tau molecules, forming threads that eventually clump together to form tangles. The tangles disrupt the microtubule network and create blocks in the neuron's transport system. Abnormal tau may also cause blocks in synaptic signaling. As with beta-amyloid, some scientists think that other, smaller forms of abnormal tau may cause the most damage to neurons.
- **Loss of neuronal connections and cell death.** In Alzheimer's disease, the synaptic connections between certain groups of neurons stop functioning and begin to degenerate. This degeneration may be due to the abnormal deposits of beta-amyloid and tau. When neurons lose their connections, they cannot function properly and eventually die. As neuronal injury and death spread through the brain, connections between networks of neurons break down, and affected regions begin to shrink in a process called brain atrophy. By the final stage of Alzheimer's, damage is widespread, and brain tissue has shrunk significantly.

Amyloid plaques, neurofibrillary tangles, synaptic loss, and cell death are the most striking features of the Alzheimer's brain when it is viewed under the microscope after death. However, scientists are now realizing that many other cellular changes occur in the brain during the Alzheimer's disease process. For example, glial cells show abnormalities, as certain populations of glial cells begin to swell up and divide to produce more glial cells.

The Alzheimer's brain also shows signs of inflammation, a tissue response to cellular injury. (See Inflammatory and Immune Responses in Alzheimer's and Brain Aging .) In addition, brain blood vessel cells as well as brain neurons show signs of degeneration. Some of these other cellular changes likely occur in response to neuronal malfunction, and many of them could contribute to neuronal malfunction. (See Astrocytes and Blood Vessels in Aging and Alzheimer's Disease .)

What Causes Alzheimer's Disease?

In some rare cases, people develop Alzheimer's in their late 30s, 40s, or 50s. This form of the disease, called early-onset dominantly inherited Alzheimer's disease, always runs in families and is caused by a mutation in one of three genes that a person has inherited from a parent. An NIA-funded clinical study is underway to identify the sequence of brain changes in this form of early-onset Alzheimer's, even before symptoms appear. (For more about the Dominantly Inherited Alzheimer's Network study, see [Supporting Infrastructure and Initiatives](#) .)

For more information about early-onset Alzheimer's, view this [webinar video](#) , which discusses research in families in Colombia, South America. The webinar was hosted by the NIH Fogarty Center as part of its "Brain Disorders in the Developing World" program.

More than 90 percent of Alzheimer's cases occur in people age 60 and older. The development and progression of this late-onset form of the disease are very similar to what is seen in the early-onset form of the disorder. The causes of late-onset Alzheimer's are not yet known, but they are believed to include a combination of genetic, environmental, and lifestyle factors. The importance of any one of these factors in increasing or decreasing the risk of developing Alzheimer's differs from person to person—even between twins.

Much basic research in Alzheimer's disease has focused on genes that cause the early-onset form of the disease and on how mutations in these genes disrupt cellular function and lead to the disorder. Scientists hope that what they learn about early-onset Alzheimer's disease can be applied to the late-onset form of the disease.

Perhaps the greatest mystery is why Alzheimer's disease largely strikes people of advanced age. The single best-known risk factor for Alzheimer's is age, and studies show that the prevalence of the disease dramatically increases after age 70. Research on how the brain changes normally as people age will help explain Alzheimer's prevalence in older adults. Other risk factors for Alzheimer's may include cardiovascular disease, diabetes, depression, and certain lifestyle factors such as being physically inactive.

How Is Alzheimer's Disease Diagnosed?

Clinicians use a number of tools to diagnose "possible Alzheimer's dementia" (dementia that could be due to another condition) or "probable Alzheimer's dementia" (no other cause of dementia can be found). Some people with memory problems may have mild cognitive impairment (MCI), a condition that may lead to Alzheimer's disease. People with MCI have more memory problems than normal for people their age, but their symptoms are not as severe as those seen in Alzheimer's. Importantly, not all people with MCI go on to develop Alzheimer's disease, and some may even recover from MCI and regain normal cognition. This recovery may happen if MCI is due to a medicine's side effect or temporary depression, for example.

Tools for diagnosing probable Alzheimer's disease include a medical history, a physical exam, and tests—preferably over time—that measure memory, language skills, and other abilities related to brain

functioning. Information provided by family members or other caregivers about changes in a person's day-to-day function and behavior also help in diagnosis. Currently, the most definitive diagnosis of Alzheimer's is made after death, by examining brain tissue for plaques and tangles. However, in specialized research facilities such as NIA's network of [Alzheimer's Disease Centers](#), clinicians may also use brain scans and biomarkers found in blood and cerebrospinal fluid to help diagnose Alzheimer's dementia in people, who may or may not be participating in a clinical trial.

Early, accurate diagnosis is crucial because it tells people whether they have Alzheimer's disease or something else. Stroke, tumor, Parkinson's disease, sleep disturbances, or side effects of medications are all known to affect cognitive function and memory, and some of these conditions are reversible. When Alzheimer's is diagnosed, knowing early on can help families plan for the future, while the person with the disorder can still participate in making decisions.

Researchers are developing tests using biomarkers to detect the disease before memory loss or cognitive impairment is evident. One day these tests could be used in general medical practice.

How Is Alzheimer's Disease Treated?

Only a few medications have been approved by the U.S. Food and Drug Administration to help control the cognitive loss that characterizes Alzheimer's disease. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®, formerly known as Reminyl®) are prescribed to treat mild to moderate Alzheimer's symptoms. Donepezil also is approved to treat severe Alzheimer's. These drugs act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine (a neurotransmitter that helps in memory formation). They maintain some people's ability to carry out everyday activities and may slow down symptoms related to thinking, memory, or speaking skills. They also may help with certain behavioral symptoms. However, they do not stop or reverse the underlying disease process and help some people only for months to a couple of years.

Another type of medication, memantine (Namenda®), is prescribed to treat moderate to severe Alzheimer's symptoms. This drug appears to work by blocking receptors for glutamate, another neurotransmitter involved in memory function. Studies in animals suggest that memantine may have disease-modifying effects, although this effect has not yet been demonstrated in humans.

In addition to these medications, physicians may use other drugs and nondrug approaches to treat behavioral and psychiatric problems associated with Alzheimer's. These therapies address problems like agitation, verbal and physical aggression, wandering, depression, sleep disturbances, and delusions. (No drugs are specifically approved by the U.S. Food and Drug Administration to treat behavioral or psychiatric symptoms in dementia; such use is considered "off-label.")

Researchers are exploring a number of lifestyle factors, from diet and exercise to stress and sleep problems, that may influence the risk of Alzheimer's and age-related cognitive decline. Many studies have indicated links between cardiovascular health and brain health. Physical frailty, diabetes, depression, and cardiovascular disease have been linked to Alzheimer's disease and/or other forms of age-related cognitive decline. Taking steps to reduce the risk of those conditions—through physical exercise, not smoking, limiting intake of high-fat and high-sugar foods, cholesterol and blood pressure control, and maintaining social and intellectual engagement as one ages—may also reduce one's risk of Alzheimer's.

Prevalence of Alzheimer's Disease

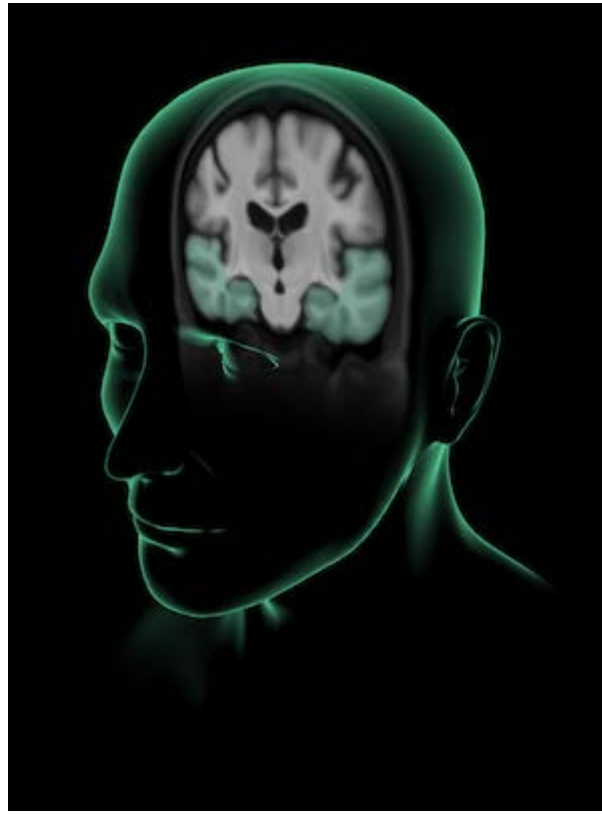
Effective interventions to prevent, delay, and treat Alzheimer's disease are urgently needed. Today, research reports estimate that as many as 5.1 million Americans may have the disorder, and the number is expected to rise as the population ages.

From a public health standpoint, preparing for the human, financial, and societal challenges of Alzheimer's disease requires a clear grasp of the numbers involved—how many people are currently affected by Alzheimer's, how prevalence may vary in different socioeconomic groups, and likely future trends. For example, an important topic for researchers has been to estimate the proportion of the aging population who will develop Alzheimer's disease (as opposed to “normal” age-related cognitive decline) and to describe features that distinguish the two groups.

Outlook for Individuals with Mild Cognitive Impairment

People with mild cognitive impairment, or MCI, have cognitive deficits that are more pronounced than is typical for their age group, but less severe than those with Alzheimer's dementia. While MCI can be a precursor to Alzheimer's disease, it is unclear how many people with MCI will go on to develop dementia.

To address this question, University of Pittsburgh researchers led a study involving nearly 2,000 volunteers age 65 or older living in a western Pennsylvania community (Ganguli et al., 2011). They found that only a small proportion of those who met the diagnostic criteria for MCI progressed to dementia over the course of 1 year; the majority remained stable, and a few even improved.



This image shows areas of brain susceptible to Alzheimer's disease, such as the hippocampus. Courtesy of Paul M. Thompson, PhD, and Arthur W. Toga, PhD, Laboratory of Neuro Imaging, UCLA.

These results differ from previous findings in clinical research settings, perhaps because people who seek clinical diagnosis and care for MCI (either on their own or at the behest of family members) may already be on the way to developing dementia. MCI in the general community may spring from a greater variety of causes that can be treated or managed, such as depression or side effects from medications. The study also showed that MCI is more likely to progress to dementia when a person has specific memory impairment and/or more than one impaired cognitive domain.

Alzheimer's disease has a long "prodromal" phase, during which people begin to experience cognitive changes that herald the onset of the more severe stages of the disorder. To better understand this early stage, researchers at Rush University Medical Center, Chicago, followed for up to 16 years more than 2,000 older volunteers participating in two ongoing studies, the Religious Orders Study and the Rush Memory and Aging Project (Wilson et al., 2011).

They found that the 462 volunteers who eventually developed Alzheimer's showed accelerated decline in multiple areas of cognitive function (memory, visuospatial skills, and perceptual processing) during the 5 to 6 years before receiving a diagnoses of Alzheimer's disease. In contrast, little evidence of cognitive decline was seen in the larger group of participants who remained free of the disease.

This study suggests that declines in cognitive function are detectable well before the onset of Alzheimer's dementia, and that changes in cognition are not an inevitable consequence of aging. Further, it suggests that treatments, once available, may be most effective if started early—underscoring the need for biological and behavioral markers to aid in early detection.

Dementia Among the "Oldest Old"

The oldest old (people age 90 or over) are the fastest growing age group in the United States. University of California, Irvine, researchers studied dementia rates among 395 participants (average age, 93) in the 90+ Study, a large study of a southern California retirement community (Peltz et al., 2011). Each year, more than 8 percent of the cognitively normal participants developed dementia. For those with MCI or other cognitive problems, the conversion rate was as high as 40 percent. The results of this study suggest that the oldest old, particularly those with MCI, have very high rates of dementia and will present a growing public health burden over the next decades.

New Neuropathological Criteria for Alzheimer's Disease

Currently, Alzheimer's disease is usually diagnosed in two ways. The first is by clinical examination of patients, including tests of cognitive abilities such as memory, problem solving, attention, and language. The second is by neuropathological examination after death, in which brain tissue is examined under the microscope for characteristic signs of disease such as plaques and tangles. In April 2011, the clinical diagnostic criteria for Alzheimer's disease were revised for the first time in 27 years by a series of expert panels convened by National Institute on Aging and the Alzheimer's Association. The new clinical criteria incorporate a deeper understanding of Alzheimer's disease, recognizing that the symptoms of the disease develop gradually over many years. The new clinical guidelines describe the earliest preclinical stages of the disease, as well MCI and dementia due to Alzheimer's pathology.

In late 2011, the neuropathology guidelines for Alzheimer's disease—in use since 1997—were similarly updated to reflect advances in diagnosing the disorder in brain tissue. The new guidelines incorporate a new understanding of the relationship between the clinical and neuropathological signs of the disease. In contrast to the old guidelines, the new ones no longer require that individuals receive a diagnosis of dementia while living in order for their brains to be examined for signs of Alzheimer's disease after death. This change reflects the realization in recent years that the brains of many cognitively normal older individuals contain significant amounts of amyloid plaque, which may represent the early stages of Alzheimer's disease.

In the new guidelines, inspection of brain tissue for the presence of plaques and tangles remains central to diagnosis. However, the guidelines now ask pathologists to report in more detail the amounts and locations of plaques and tangles within the brain, and to check for them even in the brains of people who appeared free of dementia while living.

The new guidelines also require that brains be examined for signs of other diseases that may contribute to cognitive decline, such as cerebrovascular disease or Lewy body disease, and which often coexist with Alzheimer's in the brains of older people. Finally, the new guidelines recommend that in research settings, genetic risk markers and new biomarkers be used in conjunction with neuropathological and clinical data to follow the progression of the disease and to study its underlying mechanisms (Hyman et al., 2012).

Understanding the Biology of Alzheimer's Disease and the Aging Brain

Research in 2011 and 2012 offered new insights into how Alzheimer's disease impacts not only neurons, but also brain inflammatory responses, glial cell biology, and vascular function. In addition, because age is the major risk factor for Alzheimer's, increasing attention has turned to the normal, age-related changes in cellular and brain networks.

Neurodegeneration and the Aging Brain

Recent neuroimaging studies have shown that 25- to 50-percent of cognitively normal older adults have significant accumulations of brain beta-amyloid, which may represent an early stage of the Alzheimer's disease process. In a post mortem study led by University of Washington, Seattle, researchers, the brains of many cognitively normal older adults showed signs of other dementia disorders as well (Sonnen et al., 2011).

The researchers obtained post mortem brain samples from more than 300 volunteers who lived on average between 80 and 90 years. They analyzed the tissue under the microscope for signs of three common dementias: Alzheimer's, Lewy body disease, and vascular brain injury from stroke or other vascular disease. Alzheimer's disease was the most common pathology, found in 47 percent of the brains. Vascular brain injury occurred in more than one-third of the volunteers, while 15 percent showed signs of Lewy body disease.

These findings indicate that the brains of a large proportion of cognitively normal older people show accumulations of cellular damage, likely the result of one or more diseases or other factors influencing brain health over the lifespan. Studies like these intensify our interest in how people with such damage in their brains can still enjoy normal cognitive function.

How Tau Pathology May Spread in the Alzheimer's Brain

Neurofibrillary tangles are a hallmark of Alzheimer's disease. Tangles are composed of misfolded forms of the protein tau—a structural change that results in tau clumping into insoluble fibrils that, under the microscope, resemble threadlike fibers. What causes tau to misfold and lose function has long been a mystery.

A University of Pennsylvania, Philadelphia, study using kidney cells suggests a “domino effect” in which misfolded tau causes normal tau to misfold (Guo and Lee, 2011). The researchers found that minute quantities of misfolded tau introduced into cultured cells expressing normal tau caused the tau to form fibrils like those seen in the Alzheimer's brain. In addition, the researchers found that the cells soaked up the misfolded tau from the fluid surrounding them. Assuming that brain cells also take up tau, this study suggests a route by which tau pathology could spread from one neuron to another, as it appears to do in Alzheimer's disease.

As Alzheimer's disease progresses, tau pathology spreads from one brain region to another in a consistent pattern. Tangles appear first in the entorhinal cortex, next in the hippocampus, and then in the cerebral cortex. These brain regions are connected to one another via synapses that create communication networks.

Research groups at Columbia University, New York City, and Harvard University, Cambridge, MA, have now shown that abnormal tau spreads from one brain region to the next by moving across synapses (Liu et al., 2012; de Calignon et al., 2012). Each research group performed similar experiments in which they created experimental mice that expressed mutant human tau only in the entorhinal cortex. As the mice aged, the mutant tau gradually spread across the connected brain regions. As the abnormal human tau appeared in each brain region, it clumped together with normal mouse tau to form tangles and damage synapses.

These studies demonstrate one mechanism by which Alzheimer's pathology can spread from one brain region to another. They also suggest a possible target for therapies that might delay or prevent disease onset and progression.

Mitochondrial Dysfunction in Alzheimer's Disease

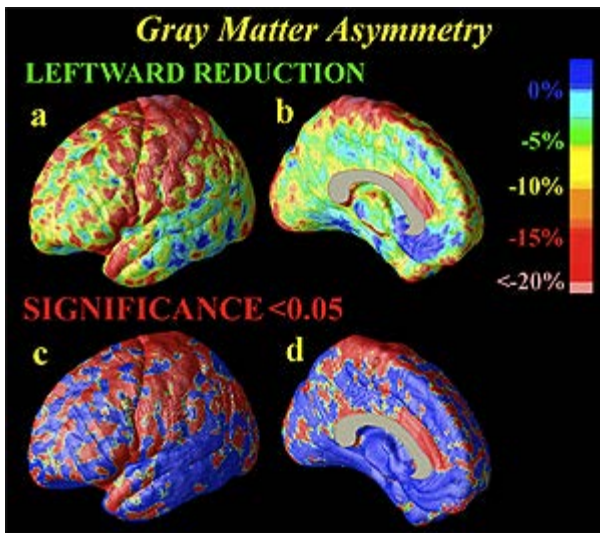
Mitochondria are the "powerhouses" of the cell, generating the energy needed to function and survive. In Alzheimer's disease, abnormal levels of beta-amyloid damage brain mitochondria, leading to neuronal dysfunction. A team led by investigators at Columbia University, New York City, found that beta-amyloid interacts with mitochondria by binding to a mitochondrial enzyme called ABAD (beta-amyloid-binding alcohol dehydrogenase) (Yao et al., 2011). Treating Alzheimer's model mice with a peptide that blocks beta-amyloid binding to ABAD improved mitochondrial function and also alleviated the mice's memory deficits. This study strongly implicates mitochondrial beta-amyloid as a critical player in the development of Alzheimer's disease.

Synapses depend on nearby mitochondria to generate the energy needed for proper functioning. A study led by Harvard University, Cambridge, MA, researchers showed that abnormal forms of tau disrupt this process (Kopeikina et al., 2011). In mice expressing a mutant form of human tau, neurons lacked the mitochondria needed for proper functioning; similar abnormalities were seen at autopsy in people diagnosed with Alzheimer's. The researchers also found that tau does not have to form thread-like fibrils to disrupt mitochondria from delivering energy to synapses. Rather, reduced levels of normal tau in mouse models are enough to disrupt the process.

Working Memory Loss in Normal Aging

Working memory is the ability of the brain to store and manipulate information over brief periods of time. It is critical to tasks of daily living such as planning dinner and keeping the list of ingredients in mind while pulling them out of the refrigerator. Many of the cognitive changes experienced by normal adults (forgetfulness, distractibility, reduced efficiency in carrying out tasks) result from declines in working memory. Research now shows that multitasking impairs working memory performance, especially as we age.

University of California, San Francisco, researchers used functional magnetic resonance imaging scanning to study brain networks in younger and older adults who were asked to perform a working memory task (Clapp et al., 2011). The researchers then intentionally distracted the participants during the task. Both younger and older adults redirected their brain networks from the assigned task to the interruption. However, unlike younger adults, older adults failed to disengage their attention from the interruption and failed to reestablish functional connections with the memory network originally engaged in the task. The inability to disengage from distraction is likely to impact a wide range of life activities, particularly in the information age, which requires increasing organizational skill to deal with even basic needs such as medical care and paying bills.



These images of the hemispheres of the brain show that Alzheimer's disease appears to damage the left side of the brain more than the right side. In fact, this composite image of the brains of older people shows about a 15 percent loss of volume in the left hemisphere of the brain. Significantly, this area plays a critical role in language, and people with Alzheimer's often experience significant declines in their ability to use and process language.

Courtesy of Paul M. Thompson, PhD, and Arthur W. Toga, PhD, Laboratory of Neuro Imaging, UCLA.

To understand the cellular changes underlying age-related decline in working memory, researchers from Yale University, New Haven, CT, studied rhesus monkeys. Like humans, they may develop problems with working memory in their senior years (Wang et al., 2011). The researchers showed that this loss is tied to changes in a specific network of neurons in the prefrontal cortex, the brain region responsible for working memory. In younger animals, these prefrontal cortex neurons continue to fire in response to an environmental signal after the signal is removed. However, with age, the researchers found, the firing rates of these neurons declined steeply.

Taking the experiment a step further, they found that the decline could be reversed in the monkeys by directly delivering drugs to the brain that inhibit cyclic AMP, an intracellular signaling molecule. The beneficial response suggests that declines in age-related working memory may be reversible. One of the cyclic AMP inhibitors used in this study, guanafacine, is already approved by the U.S. Food and Drug Administration to treat high blood pressure. A pilot clinical trial is now underway to see if this medication can improve working memory in cognitively normal older people.

Brain neurons have a remarkable capacity to remodel their connections with other neurons in response to changes in the environment. This phenomenon, known as "synaptic plasticity," is critical for memory processes and for behavioral adaptation to changes in the environment. However, Mt. Sinai Medical Center, New York City, researchers found that in rats, the remodeling capacity of neurons diminishes with age in the prefrontal cortex, a brain region involved in learning and memory (Bloss et al., 2011).

When young rats experienced 3 weeks of behavioral stress, neurons in their prefrontal cortex responded by retracting and/or reshaping their dendritic spines. In contrast, the dendritic spines of middle-aged and aged rats did not remodel during stress. Since the prefrontal cortex plays a central role in working memory, loss of synaptic plasticity in this brain region may contribute to age-related loss of working memory function.

Astrocytes and Blood Vessels in Aging and Alzheimer's Disease

Neurons do not function in isolation, but in close collaboration with blood vessels and glial cells, which support and

protect brain cells. Like neurons, glial cells and blood vessels show changes in structure and function in both Alzheimer's disease and normal aging. These changes can impair healthy brain function.

Astrocytes, a type of glial cell, are star-shaped cells that surround and help regulate, support, and protect neurons and blood vessels. One of many critical functions astrocytes perform is to secrete growth factors that stimulate neurogenesis, or the birth of new neurons. Recognizing that neurogenesis declines as the brain ages, researchers at Rosalind Franklin University, Chicago, studied how aging impacts astrocytes (Bernal and Peterson, 2011).

They found that astrocytes in the brains of aging rats showed signs of structural changes similar to those seen during mild brain inflammation and decreased levels of neuronal growth factors. Importantly, the brain regions in which these astrocyte changes were seen included parts of the hippocampus, where new neurons are generated. These findings indicate that decreased availability of astrocyte-derived growth factors may contribute to age-related declines in neurogenesis.

Another important function astrocytes perform is to protect neurons against damage by free radicals. Free radicals are highly reactive molecules that can build up inside cells due to aging or other factors and cause cellular damage, a condition known as "oxidative stress." Astrocytes protect neurons from oxidative stress by generating antioxidants, molecules that neutralize free radicals and render them harmless.

University of Michigan, Ann Arbor, researchers exposed cultured mouse astrocytes to beta-amyloid, which causes oxidative stress in neurons (Garg et al., 2011). Beta-amyloid disrupted astrocyte antioxidant production pathways and simultaneously interfered with the astrocytes' ability to protect neurons against beta-amyloid toxicity. These results suggest the possibility of developing Alzheimer's disease therapeutics by enhancing astrocyte antioxidant production pathways.

Researchers are interested in finding out how physical exercise may influence cognitive health into late age. University of Kentucky, Lexington, researchers showed that exercise benefits aging glial cells (which support and protect neurons), blood vessel cells, and neurons (Latimer et al., 2011). The researchers compared the brains of middle-aged female mice with and without access to exercise wheels. (Mice provided with exercise wheels tend to run on them without encouragement.) After only 6 weeks, the exercising mice showed significant reductions in markers of glial and blood vessel cell aging compared with the sedentary mice.

Inflammatory and Immune Responses in Alzheimer's and Brain Aging

The Alzheimer's disease brain shows signs of ongoing inflammation, a tissue response to cellular damage. In the short-term, inflammation helps neutralize and flush out harmful substances. However, the inflammatory response may damage tissue if it goes on for too long. A University of California, Irvine, study suggests that chronic inflammation contributes to neurodegeneration in Alzheimer's disease (Kitazawa et al., 2011).

The researchers treated Alzheimer's model mice with an antibody that blocks Interleukin 1, a molecule that promotes inflammation and is abnormally elevated in people with Alzheimer's. Blocking this molecule not only reduced inflammation, but also decreased tau and beta-amyloid levels and improved cognition in the mice. These findings indicate this molecule may be a target for developing interventions to treat Alzheimer's disease.

A University of Rochester, NY, study suggests that the APOE gene increases Alzheimer's disease risk by setting off an inflammatory response that leads to breakdown of the blood-brain barrier, a specialized filter that allows blood-vessel cells in the brain to prevent harmful substances in blood from entering the brain (Bell et al., 2012). In transgenic mice that either lacked the apolipoprotein E (APOE) gene or had the APOE ϵ 4 allele (the allele that increases Alzheimer's risk), the blood-brain barrier breaks down, brain blood vessels begin to leak, toxic proteins

enter the brain, and neurons degenerate.

The researchers found that the critical factor causing blood-brain barrier breakdown in the transgenic mice was an inflammatory protein called cyclophilin A (CypA). Both APOE ϵ 2 and APOE ϵ 3 genes can keep CypA production in check, but mice with the APOE ϵ 4 gene lacked this ability. However, inhibition of the CypA pathway partially reversed neurodegeneration in the transgenic mice, suggesting this pathway as a therapeutic target. Importantly, no beta-amyloid accumulation was seen in the transgenic mice, which suggests that inflammation and blood-barrier breakdown may precede beta-amyloid accumulation in the Alzheimer's disease process.

One function of microglia cells is to clear away cellular debris. Microglia cluster around beta-amyloid plaques but do not digest them efficiently unless they are "activated" by signaling molecules that promote brain inflammation. Researchers at Cornell Medical College, New York City, studying microglia in mouse tissue asked how activation enables microglia to digest beta-amyloid. They found that unactivated microglia can engulf beta-amyloid fibrils and deliver them to lysosomes, the cellular organelles responsible for protein digestion (Majumdar et al., 2011). However, these lysosomes are not acidic enough to allow digestion unless they are exposed to a proinflammatory signaling molecule. This finding suggests that agents that regulate the acidity of microglial lysosomes may offer a potential therapeutic approach for Alzheimer's disease.

In a set of transfusion experiments that involved old and young mice, researchers from Stanford University, Palo Alto, CA, showed that factors in the blood of young mice can rejuvenate the brains of old mice (Villeda et al., 2011). The old mice subsequently showed more youthful levels of neurogenesis (birth of new neurons) in the hippocampus, a region of the brain important to learning and memory. In contrast, the young mice showed reduced neurogenesis and developed learning and memory deficits. The researchers identified a factor in the blood of old mice that was responsible for squelching neurogenesis in the young mice: the immune system protein eotaxin, which plays a role in allergic responses. This study shows that age-associated declines in neurogenesis may be reversible.

New Techniques for Studying Alzheimer's Biology

Much of our current understanding of Alzheimer's disease biology comes from studies in mouse models. However, monitoring disease development in mice typically requires time-consuming behavioral tests and/or post mortem analyses of brain tissue. University of California, San Francisco, researchers used a new method called "bioluminescence imaging" to rapidly and noninvasively monitor disease progression in the living brains of Alzheimer's model mice (Watts et al., 2010). The new imaging tool tracks disease-related changes in brain astrocytes, the star-shaped cells that help support brain health. Astrocytes increase in number and express more of a gene called glial fibrillary acidic protein (GFAP) in Alzheimer's disease.

To study this process, the researchers created a line of Alzheimer's model mice in which part of the GFAP gene was attached to a fluorescent "reporter" gene, a gene that produces a fluorescent protein. They monitored GFAP levels by fluorescence imaging. As the mice aged, their brain astrocytes accumulated fluorescent protein that correlated closely with that of brain beta-amyloid plaque accumulation. The use of this technique should facilitate the testing of Alzheimer's therapeutics in mouse models.

The use of animal models for Alzheimer's disease research has been useful but difficult, in part because mouse cells do not behave like human cells. For example, unlike humans, mice modeled to develop amyloid plaques do not exhibit tau tangles, a hallmark of human disease. Promising studies, however, have developed new human cellular models for studying Alzheimer's biology.

Through the use of genetic engineering techniques, University of California, San Diego, researchers created neurons from cultured skin cells of people with familial Alzheimer's disease (Israel et al., 2012). Compared to neurons made from skin cells of cognitively normal volunteers, neurons made from Alzheimer's volunteers showed Alzheimer's-

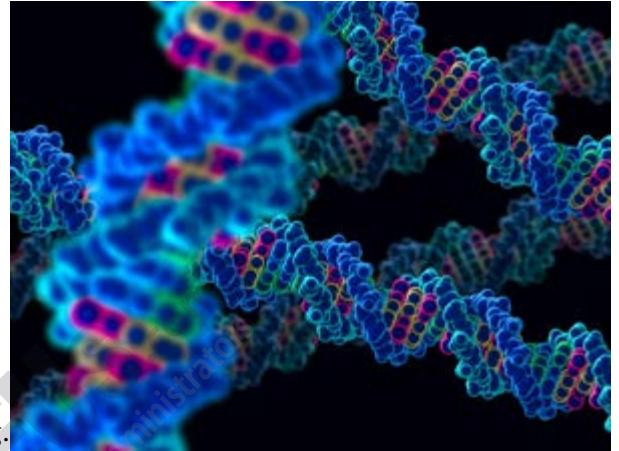
like features, including high levels of abnormal tau as well as beta-amyloid. In addition to development of this important model, the researchers found evidence that both tau and amyloid pathology may result from abnormal processing of amyloid precursor protein (APP) but develop along different pathways. This finding is of considerable clinical significance, as it suggests that drugs targeting beta-amyloid may not improve tau pathology.



The Genetics of Alzheimer's Disease

Age is the best known risk factor for Alzheimer's disease. Most people with Alzheimer's do not start showing symptoms until age 65 or older. However, in rare cases, people develop Alzheimer's disease much earlier, between the ages of 30 and 60. This "early-onset" form of Alzheimer's always runs in families. It is caused by a mutation in one of three genes inherited from a parent that cause abnormal proteins to be formed.

Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP); a mutation on chromosome 14 causes abnormal presenilin 1 to be made; and a mutation on chromosome 1 leads to abnormal presenilin 2. Scientists know that each of these mutations plays a role in the breakdown of APP, a protein whose precise function is not yet known. This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of the disease.



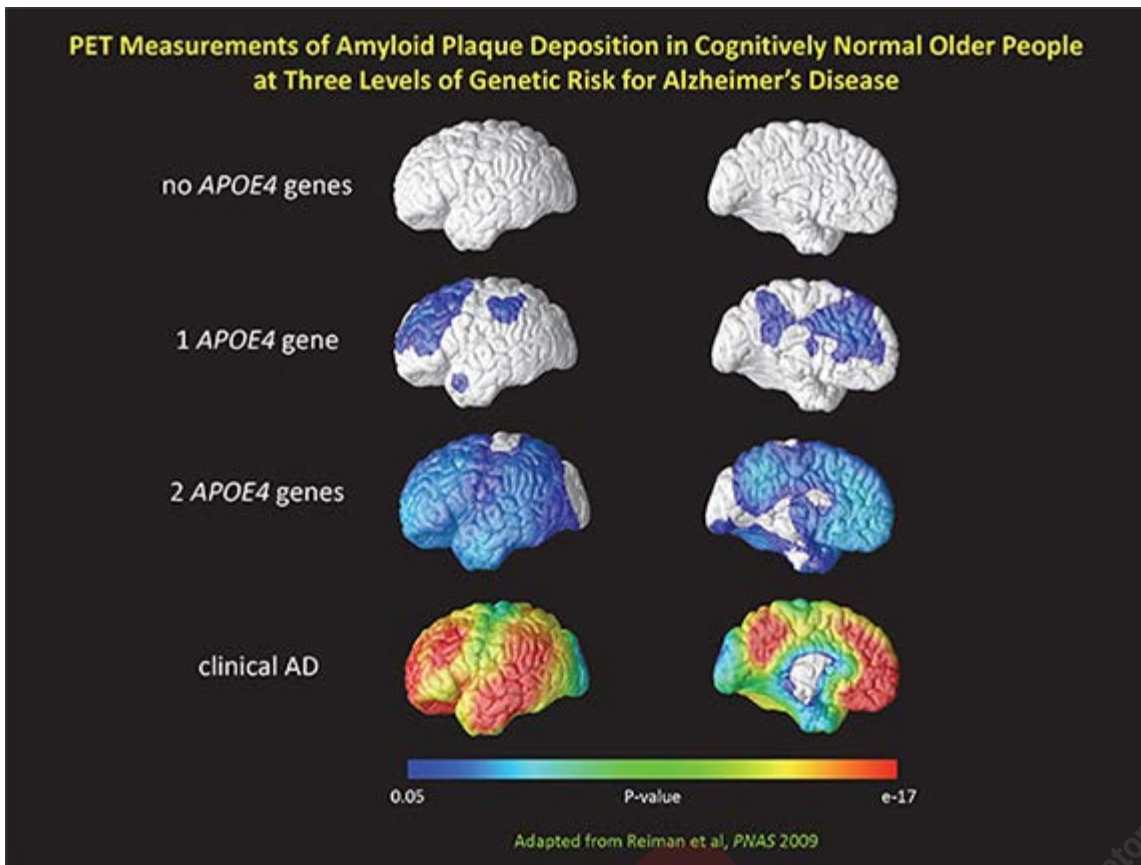
The more common "late-onset" form of the disease typically occurs after age 65. While no single gene mutation is known to cause this form of Alzheimer's, evidence of a hereditary component is mounting. Environmental and lifestyle factors may also contribute to the risk of developing late-onset Alzheimer's.

The apolipoprotein E (APOE) gene is the strongest genetic risk factor identified to date for late-onset Alzheimer's. This gene, found on chromosome 19, comes in three different forms, or alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The APOE $\epsilon 2$ allele is the least common form, found in 5 percent to 10 percent of people, and appears to reduce risk. The APOE $\epsilon 3$ allele, the most common form, is found in 70 percent to 80 percent of the population and appears to play a neutral role in the disease. The APOE $\epsilon 4$ allele, found in 10 percent to 15 percent of the population, increases risk for Alzheimer's disease by three- to eight-fold, depending on whether a person has one or two copies of the allele. The APOE $\epsilon 4$ allele is also associated with an earlier age of disease onset.

APOE $\epsilon 4$ is called a risk-factor gene because it increases a person's risk of developing the disease. However, inheriting an APOE $\epsilon 4$ allele does not mean that a person will definitely develop Alzheimer's. Some people with one or two APOE $\epsilon 4$ alleles never get the disease, and others who develop Alzheimer's do not have any APOE $\epsilon 4$ alleles.

Researchers are working hard to identify many other genes that may influence risk for late-onset Alzheimer's. Those doing genome-wide association studies (GWAS) have identified a number of genes in addition to APOE $\epsilon 4$ that may increase a person's risk for late-onset Alzheimer's. Using high-throughput analytical approaches and a large number of DNA samples, researchers have now confirmed six new risk-factor genes: PICALM, CLU, CR1, BIN1, MS4A4, and CD2AP.

Scientists will continue to identify and study other risk-factor genes, including known candidates SORL1, CD33, EPHA1, ABCA7, and TREM2. In addition, scientists are looking for genes that protect against the disorder. These discoveries help to uncover the cellular pathways involved in the disorder and lead to new avenues for therapeutic approaches.



These images show increasing levels of amyloid plaque deposition in cognitively normal adult groups (average age, 63) at three levels of genetic risk for Alzheimer's disease, as well as in a group of people diagnosed with Alzheimer's dementia. Courtesy of Banner Alzheimer's Institute.

New Functions for Alzheimer's Genes: Synaptic Plasticity

While we know that the APP, presenilin, and APOE genes are involved in regulating brain beta-amyloid levels, researchers are investigating other roles they may play in Alzheimer's disease. For example, these genes may influence synaptic plasticity, the ability of synapses to weaken or strengthen connections to other synapses—a function critical to learning and memory.

For example, researchers at the University of Washington, Seattle, found that the presenilin 1 (PS-1) gene regulates a form of synaptic plasticity known as “homeostatic scaling” (Pratt et al., 2011). Homeostatic scaling is a mechanism that protects brain cells by preventing groups of neurons from altering their firing patterns too drastically in response to changes in the environment. Neurons from Alzheimer's model mice with a PS-1 mutation failed to show homeostatic scaling when tested in tissue culture, and this abnormality appeared unrelated to defects in beta-amyloid processing. This suggests that deficits in homeostatic scaling could contribute to the development of Alzheimer's disease in people with PS-1 mutations.

The ApoE protein binds to several different receptors in the brain, including ApoE receptor 2 (ApoEr2). ApoEr2 is known to promote synaptic plasticity and memory formation in mice, but how it does so is unknown. Georgetown University, Washington, DC, researchers showed that in rodent brain tissue, ApoEr2 increases the number and promotes the stability of dendritic spines and synapses, structures that are important to learning and memory (Dumanis et al., 2011). It does this in part by regulating the assembly of a complex of proteins involved in constructing dendritic spines, dynamic structures that appear and disappear depending on how much synapses are

stimulated.

Understanding the mechanisms by which ApoE2 promotes synapse formation may provide insights into how the APOE ϵ 4 allele increases risk of Alzheimer's and age-related cognitive decline.

Searching for New Alzheimer's Genes

During the past 3 years, scientists have identified a number of new candidate risk genes for Alzheimer's by comparing the genomes of people with the disease to those without it. A method for identifying genes and relating them to cell function and cellular pathways is to search for genes that show different expression patterns (i.e., genes that are activated to a greater or lesser extent) in the brains of people at high risk versus low risk of Alzheimer's. Such genes may or may not directly influence the risk of Alzheimer's, but their expression levels may serve as markers of the disease process and provide insight into disease mechanisms.

Researchers at Albert Einstein College of Medicine, New York City, identified early gene expression "signatures" in the brains of young individuals at high risk for Alzheimer's (Conejero-Goldberg et al., 2011). The researchers compared gene expression patterns in brain tissue donated for autopsy by volunteers who had died relatively young (average age, 42) from causes other than Alzheimer's. Volunteers were identified as being at either high risk or low risk of developing Alzheimer's based on whether or not they carried copies of the APOE ϵ 4 allele.

The researchers identified 70 genes that were expressed at significantly higher or lower levels in the brains of the participants at high risk for Alzheimer's compared with those at low risk. Many of those genes are involved in biological pathways previously shown to play a role in the disease, such as mitochondrial function and regulation of calcium levels in the cell. Interestingly, however, none of the genes identified is known to be involved in beta-amyloid processing.

This study identifies new sets of genes that may be involved in the Alzheimer's process. In addition, because the gene expression differences were evident long before beta-amyloid accumulation typically begins in Alzheimer's, it raises the possibility that beta-amyloid accumulation results from other cellular changes that begin earlier in the disease process.

Down Syndrome and Alzheimer's Disease

Down syndrome is a set of mental and physical symptoms that result from having an extra copy of chromosome 21. While symptoms of Down syndrome can range from mild to severe, typically they include slower-than-usual mental and physical development, including impaired language skills and problems with learning and memory.

A striking feature of Down syndrome is that almost all people with the disorder eventually develop Alzheimer's disease. Moreover, they develop it much earlier than is typical for the general population, with Alzheimer's-like pathology (plaques and tangles) appearing by age 40 and clinical symptoms apparent by age 50.

This fact suggested to scientists that the biology of Down syndrome and Alzheimer's disease might be linked in some way. The key link turned out to be the APP gene. The APP gene encodes the precursor to beta-amyloid protein, which is the main component of amyloid plaque. The APP gene lies on chromosome 21, and people with Down syndrome carry an extra copy the gene. The APP gene is also mutated in certain forms of early-onset Alzheimer's disease that can occur at people in their 30s, 40s and 50s. In both Down syndrome and early-onset Alzheimer's disease, abnormalities of the APP gene lead to accumulation of beta-amyloid.

The life expectancy of individuals with Down syndrome is increasing in developed countries. With that comes increased risk for Alzheimer's and unique challenges in treatment and diagnosis in this population. For example,

Alzheimer's disease drugs used in the general population, such as memantine and donepezil, are not effective in people with Down syndrome, so alternative therapies are needed. Additionally, diagnosing mild cognitive impairment (MCI) and Alzheimer's disease in people with Down syndrome is challenging as other, ongoing cognitive limitations may mask symptoms.

Now, a research team led by investigators at New York State Institute for Basic Research in Developmental Disabilities, New York City, may have identified a new, genetics-based test for diagnosing MCI and Alzheimer's in people with Down syndrome (Jenkins et al., 2010). They used blood samples to measure the length of telomeres, the regions found at the ends of chromosomes that act to prevent chromosome ends from fraying and sticking to one another. The scientists discovered that people with both Down syndrome and MCI or Alzheimer's had shorter telomeres than did people with only Down syndrome.

Because measuring telomere lengths proved highly sensitive and specific, doing so could prove to be a useful biomarker for early stages of dementia in people with Down syndrome, and inform treatment decisions early in the course of disease for these individuals.



Assessing Risk Factors for Cognitive Decline and Dementia

Age and genetics are the best known risk factors for Alzheimer's disease. While these factors are beyond our control, we may be able to influence other risk factors involved in age-related cognitive decline and dementia. Scientists are exploring whether or not lifestyle choices, such as exercise, or certain medical conditions, such as high cholesterol, high blood pressure or diabetes, can influence risk for cognitive decline or dementia (see [Testing Therapies to Treat, Delay, or Prevent Alzheimer's Disease](#)). For instance, recent research has examined the role played by sleep-disordered breathing—or sleep apnea—in the risk for age-related cognitive decline.

A person's early life history can also influence Alzheimer's disease risk. For example, studies in 2011 added to an increasing body of evidence that more years of high school and college education are associated with reduced risk of cognitive decline in old age, and that more years of education may be particularly protective for certain socioeconomic groups (see [The Influence of Education and Health Disparities and Alzheimer's Disease](#)).

Sleep-Disordered Breathing

Sleep-disordered breathing (SDB), or sleep apnea, is a disorder primarily characterized by frequent pauses in breathing during sleep, which leads to frequent arousals from sleep and reduced blood oxygen level (hypoxemia). SDB affects up to 60 percent of older people and is associated with daytime drowsiness and increased risk of cardiovascular disease.

A study led by researchers at University of California, San Francisco, found that SDB also increases the risk of cognitive impairment in older women (Yaffe et al., 2011). The researchers assessed cognitive performance and indices of disrupted sleep, as well as measures of disordered breathing and hypoxemia, in nearly 300 women (average age, 82) who participated in the Study of Osteoporotic Fractures, over a period of 5 years. They found that women with SDB were almost twice as likely to develop mild cognitive impairment (MCI) or dementia compared to women free of the disorder.

The study suggests that the key factor leading to diminished cognition was oxygen deprivation, rather than the arousals from sleep. Treatment of sleep apnea with continuous positive airway pressure (CPAP) devices or supplemental oxygen might help prevent or delay cognitive decline in older adults.

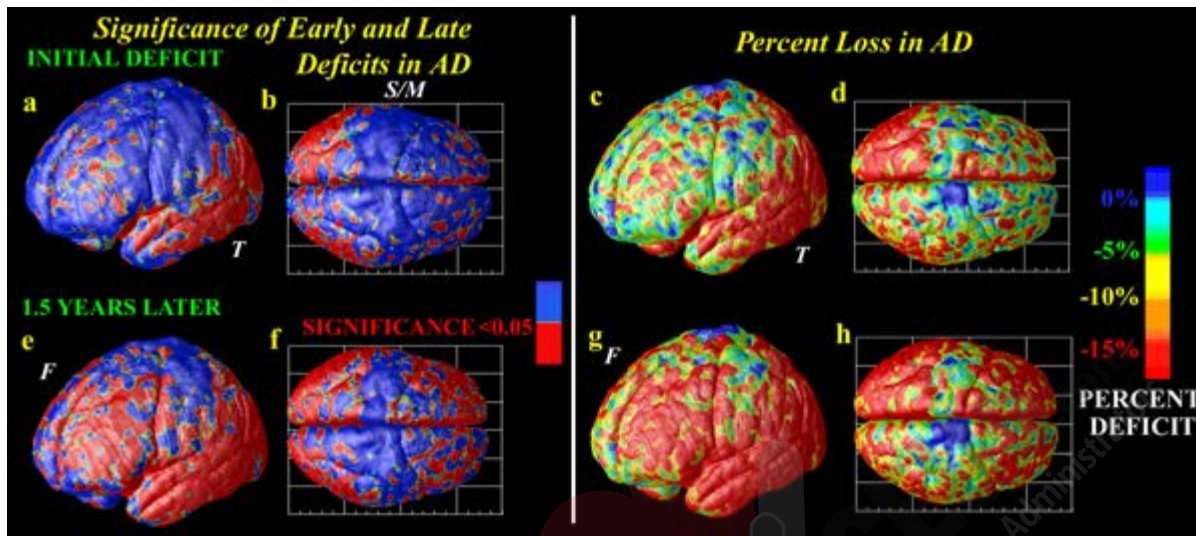
Indeed, there is some clinical evidence for the benefits of CPAP treatment in Alzheimer's disease. A pilot clinical trial led by researchers at George Mason University, Fairfax, VA, is underway to assess whether oxygen supplementation can delay cognitive decline in people with MCI and sleep apnea.

The Influence of Education

Higher educational attainment and larger brain size have been linked to reduced Alzheimer's disease risk. Some researchers believe that education and brain volume are measures of "cognitive reserve"—the ability to use brain networks more efficiently or to recruit alternative networks in the face of brain

degeneration and/or better overall health of brain neurons.

In a study led by researchers at the Washington University, St. Louis, education and brain volume also impacted the speed at which cognitively normal people with early signs of Alzheimer's pathology progressed to symptomatic cognitive impairment (Roe et al., 2011). The team followed nearly 200 people aged 50 or older. All were cognitively normal at the start of the study, but some had elevated levels of tau in their cerebrospinal fluid, believed to be a biomarker of Alzheimer's. Within that group, higher levels of education and greater brain volumes predicted slower progression to cognitive impairment over the next 3.3 years. This study supports the idea that educational level and brain volume are important predictors of rate of progression to Alzheimer's.



*Left: **Early and Late Deficits in Alzheimer's (a and e).** These composite images represent the loss of gray matter—brain regions where neurons and dendrites are found—over 1.5 years in the brains of people in their 70s diagnosed with Alzheimer's disease. Image a shows a mix of blue and red, but over 18 months, the increase in red in image b indicates the brain atrophy that is typical of Alzheimer's disease.*

*Right: **Percent Loss in Alzheimer's (c and g).** This composite image of the brains of a group of older people with Alzheimer's shows many brain regions experiencing about a 15 percent loss of volume. This loss occurs as the color red, which signifies less volume, and increases dramatically from image c to image g 1 year later.*

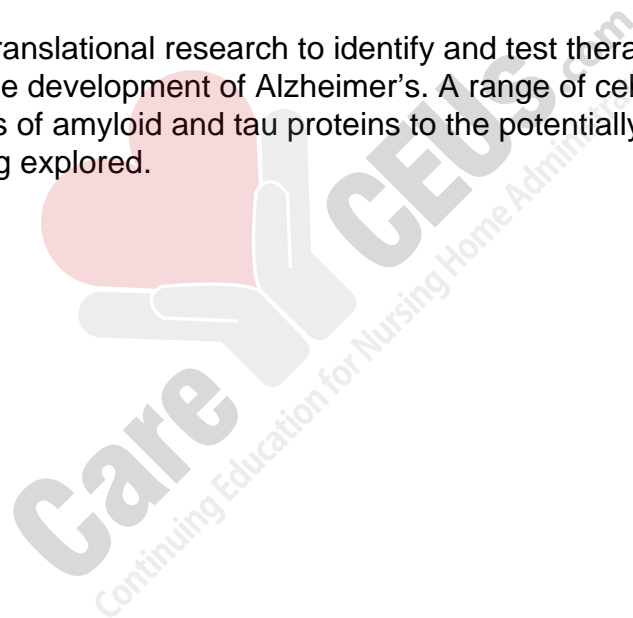
Courtesy of Paul M. Thompson, PhD, and Arthur W. Toga, PhD, Laboratory of Neuro Imaging, UCLA.

Developing New Treatments for Alzheimer's Disease

The prevalence of Alzheimer's disease is expected to rise with the aging of the population, increasing the urgency of developing new treatments. Drugs currently to treat Alzheimer's include cholinesterase inhibitors and memantine, both of which help support neurotransmitters important to memory function. These drugs provide symptomatic relief and may slow symptoms of cognitive decline for some people for a limited time. But they neither halt nor reverse disease progression because they do not target the underlying molecular pathways believed to be involved in Alzheimer's.

Translational research is a multidisciplinary, multi-step process that uses basic science discoveries to develop medicines or other interventions that improve health. The process of discovering and developing drugs for neurological disorders like Alzheimer's is extremely challenging and expensive. It takes 10 to 15 years from the discovery of a new therapeutic target until a new drug reaches the market, with an average cost of about \$1.8 billion (Paul et al., 2010).

Intensive efforts are underway in translational research to identify and test therapies that interfere with a variety of processes involved in the development of Alzheimer's. A range of cellular and molecular pathways, from abnormal deposits of amyloid and tau proteins to the potentially protective roles played by growth-factor molecules, are being explored.



Reducing Beta-Amyloid

Beta-amyloid is generated from its precursor protein, APP, by the enzyme gamma-secretase. It is thought that drugs that inhibit this enzyme could reduce beta-amyloid accumulation. However, gamma-secretase is also involved in processing another protein, Notch, which has many critical biological functions—so drugs that completely block gamma-secretase activity carry a high risk of negative side effects.

Rockefeller University, New York City, researchers may have found a way to sidestep this problem (He et al., 2010). They discovered a new brain protein, called gamma-secretase activating protein (GSAP), which specifically promotes gamma-secretase binding to APP but not to Notch. Moreover, they showed that GSAP's activity can be inhibited by an anti-cancer drug, imatinib. Imatinib reduced beta-amyloid production by 40 to 50 percent both in tissue samples and in Alzheimer's model mice, while having no effect on Notch processing. This result suggests that inhibiting GSAP offers a promising approach for lowering beta-amyloid levels while avoiding toxic side effects.

The gene APOE is linked to late-onset Alzheimer's disease. It produces a protein called apolipoprotein E (ApoE) that plays a critical role in the accumulation and clearance of beta-amyloid in the brain. Recent studies have suggested that increasing, rather than decreasing, human ApoE levels may be a promising therapeutic approach. However, a study by Washington University, St. Louis, researchers found that increasing human ApoE levels in a mouse model of Alzheimer's made the pathology worse (Kim et al., 2011). Mice with twice the amount of human ApoE developed more severe beta-amyloid plaque loads, and their brains contained higher numbers of activated microglia (a sign of brain inflammation like that seen in people with Alzheimer's). These findings suggest that strategies to decrease ApoE levels in the brain could be explored as a prevention or treatment of Alzheimer's disease.

Targeting Tau

Researchers are developing therapies that target tau, the protein involved in tangle development. Tau plays a key role in stabilizing microtubules, the protein rods that help transport molecules and other specialized components within neurons. Loss of that function is thought to contribute to the pathology seen in Alzheimer's and other neurodegenerative diseases.

A microtubule-stabilizing drug, paclitaxel, had previously been found to improve symptoms of neurodegeneration in a mouse model of tau disease, but it was difficult to deliver the drug to the brain. University of Pennsylvania, Philadelphia, researchers analyzed a series of other microtubule-stabilizing agents, and identified several that could penetrate the brain and stabilize brain microtubules when administered to mice (Brunden et al., 2011). The drug discovery strategy reported in this study could lead to new agents for treating Alzheimer's disease.

Supporting Neurogenesis

Allopregnanolone is a hormone recently shown to promote neurogenesis, reduce brain pathology, and improve cognition in Alzheimer's model mice. A team led by University of Southern California, Los Angeles, researchers assessed the effectiveness of allopregnanolone treatment in Alzheimer's model mice at different stages of disease progression (Chen et al., 2011). Hormone treatment was most effective in promoting neurogenesis and reducing brain pathology when initiated during the early stages of the disease, before beta-amyloid plaques began to form and before declines in neurogenesis. This study suggests that in humans, allopregnanolone treatment may have the most benefit for patients in the earliest stages of the disorder.

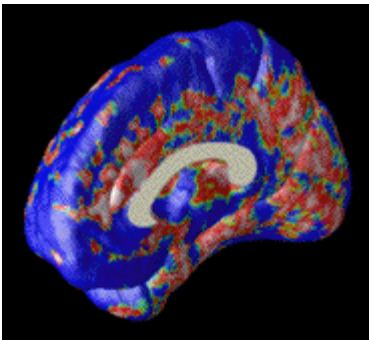


Advances in Detecting Alzheimer's Disease

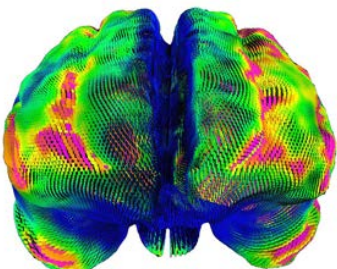
Many researchers believe that treatments for Alzheimer's are more likely to be effective if initiated early in the disease. It is now thought that Alzheimer's-related changes in the brain can begin years, or even decades, before cognitive impairment becomes evident. Researchers are developing methods to detect these changes at their earliest stages. These efforts are designed to determine who is at the highest risk for Alzheimer's so that possible treatments can be tested more rapidly and effectively, as well as to improve diagnosis in clinical practice to better serve patients and their families.

Brain Variability and Alzheimer's Disease

It can be challenging to identify whether changes in brain structure, such as a loss of volume, are part of normal cognitive aging or caused by Alzheimer's disease. Scientists are using advances in brain imaging to gain insight into the variability of the aging brain. Knowing the normal range of variation in brain volume in specific brain regions may one day help researchers identify abnormalities that may signify disease onset.



This composite image of the Alzheimer's brain shows how the structure of certain brain regions can greatly vary between individuals while other regions are less variable. For example, the color pink indicates brain regions that vary the most from one person to another. This area of the brain is important to language.



This image indicates by color the variability of the human brain. Areas in blue are regions that do not differ much from person to person, but yellow and red indicate brain regions that vary greatly between individuals. This knowledge is important as researchers need to know whether the differences they find in an individual's brain are normal for that region or a sign of abnormalities, such as Alzheimer's disease.

Courtesy of Paul M. Thompson, PhD, and Arthur W. Toga, PhD, Laboratory of Neuro Imaging, UCLA.

Genotyping is a major tool for risk assessment, and tests of insulin resistance may also help predict Alzheimer's risk. Scientists are currently exploring three main approaches to early diagnosis: measurements of biomarkers in cerebrospinal fluid (CSF), brain imaging, and standardized clinical tests of memory and thinking abilities to determine cognitive health. Through the National Institute on Aging (NIA)-led Alzheimer's Disease Neuroimaging Initiative (ADNI) and other studies, these efforts are already showing some success, and scientists are beginning to explore the use of biomarkers and brain imaging in combination to predict disease risk. (See [Supporting Infrastructure and Initiatives](#) for more on ADNI.)

In addition, a growing body of research suggests that other early symptoms, including changes in sensory and motor function, may precede memory changes in Alzheimer's.

Genetic Markers

The apolipoprotein E $\epsilon 4$ genotype is the strongest known genetic risk factor for late-onset Alzheimer's disease. Given that mild cognitive impairment (MCI) is often a precursor to Alzheimer's, past studies have produced surprisingly mixed results as to whether the $\epsilon 4$ allele also confers increased MCI risk. This may be because MCI can arise from multiple causes.

To further explore this issue, a team led by scientists at Cornell University, Ithaca, NY, studied nearly 850 people age 70 or older who were cognitively normal or had MCI (Brainerd et al., 2011). The group did not include people with symptoms of cognitive decline caused by stroke and other non-Alzheimer's conditions. They found that those with MCI all met key diagnostic criteria for amnesic MCI (aMCI), the form of MCI that typically precedes Alzheimer's disease, and the $\epsilon 4$ allele was seen at a significantly higher frequency than it was in the cognitively normal participants. This study indicates that the $\epsilon 4$ allele may be a reliable predictor of MCI.

Insulin Resistance and Brain Glucose Uptake

Insulin is a hormone in blood that helps glucose (sugar) to enter cells and be used for energy—also known as “glucose uptake.” Insulin resistance, a condition in which the body has reduced glucose uptake, may lead to diabetes. It may also increase risk of Alzheimer's disease, according to a University of Washington, Seattle, study (Baker et al., 2011).

The researchers used FDG-PET scanning to measure glucose uptake in the brains of 23 cognitively normal older adults (average age, 74) with prediabetes or early diabetes. They found that greater insulin resistance was associated with an Alzheimer's-like pattern of reduced glucose uptake in brain regions important for learning and memory. Compared to healthy individuals, those with prediabetes and early diabetes showed smaller increases in brain glucose uptake during a memory task and also performed more poorly on the task. This study suggests that insulin resistance is a marker of Alzheimer's risk in cognitively normal individuals and is associated with subtle cognitive impairments at the earliest stages of the disorder, even before the onset of MCI.

Cerebrospinal (CSF) Biomarkers

The use of CSF protein biomarkers, such as beta-amyloid, tau, and phospho-tau, has shown great promise for early Alzheimer's disease diagnosis and the selection of at-risk subjects for clinical trials. In people with Alzheimer's, CSF beta-amyloid is decreased, and total tau and phospho-tau are increased compared with older people free of the disease. In this study, a team led by investigators at The Johns Hopkins University, Baltimore, analyzed CSF biomarker data from ADNI for nearly 200 people with aMCI (Okonkwo et al., 2011). They found that abnormal beta-amyloid levels predicted a faster rate of cognitive decline and a greater risk of progression to dementia, but abnormal tau levels did not. This indicates that people with aMCI who have abnormal CSF beta-amyloid levels may be ideal candidates for clinical trials and treatments developed to halt progression.

Imaging the Living Brain

Cortical Thinning

Researchers continue to search for imaging biomarkers (brain changes visible by MRI or other imaging methods) that can predict who will develop Alzheimer's. Scientists at Massachusetts General Hospital, Boston, and Rush University Medical Center, Chicago, identified a "signature" of structural changes in the brains of cognitively normal older people that strongly predicted which of them would develop Alzheimer's (Dickerson et al., 2011). They had previously identified nine regions of the cerebral cortex that thinned out in people with mild Alzheimer's.

In this study of 65 cognitively normal study participants, the researchers identified a subgroup who showed significant thinning in the same cortical areas. They determined that this group was more than three times more likely to develop Alzheimer's dementia over the next 10 years. The cortical thinning signature appears to predict risk for Alzheimer's more accurately than shrinkage of the hippocampus, a more commonly studied MRI biomarker for the disorder.

Beta-Amyloid Imaging

Positron emission tomography (PET) imaging of brain beta-amyloid is increasingly used in research for detecting early stages of Alzheimer's. Pittsburgh Compound B, or PiB, is the radioactive agent commonly used in PET imaging to "light up" amyloid levels in the brain. However, the use of PiB imaging is largely restricted to major research centers due to PiB's short half-life: its signal fades by half within 20 minutes, so it must be made onsite. A team led by researchers at Avid Radiopharmaceuticals reported results with a new beta-amyloid tracer, florbetapir (also known as Amyvid), which has a much longer half-life of 110 minutes (Clark et al., 2011).

The researchers analyzed florbetapir-PET images from nearly 30 people who died within several months after their PET scans were done, and they also performed post mortem analyses of the brains to look for Alzheimer's pathology. About half of the group had Alzheimer's confirmed at autopsy. The researchers found a 96 percent agreement in determining the presence of Alzheimer's pathology between the florbetapir-PET images and post mortem results. At this time, florbetapir is approved by the U.S. Food and Drug Administration to help rule out Alzheimer's as a cause of memory and behavior changes.

Acetylcholine is an important neurotransmitter critical to attention and memory. In Alzheimer's disease, brain cells that produce acetylcholine are known to die. Research has shown that as the disorder progresses, neurons lose their stores of choline acetyltransferase (ChAT), the enzyme that produces acetylcholine. The loss of ChAT activity is associated with cognitive impairment. Indeed, University of Pittsburgh, PA, researchers studied the precuneus region, which plays a role in attention and memory.

The researchers found reduced ChAT in the precuneus region at autopsy in people with Alzheimer's but not in those with MCI (Ikonomic et al., 2011). In addition, this decline occurred only after significant beta-amyloid had accumulated in the precuneus. This finding suggests that the window of time immediately following the onset of amyloid accumulation in the precuneus may be a particularly critical period for drugs that enhance acetylcholine production.

Imaging Brain Glucose Uptake

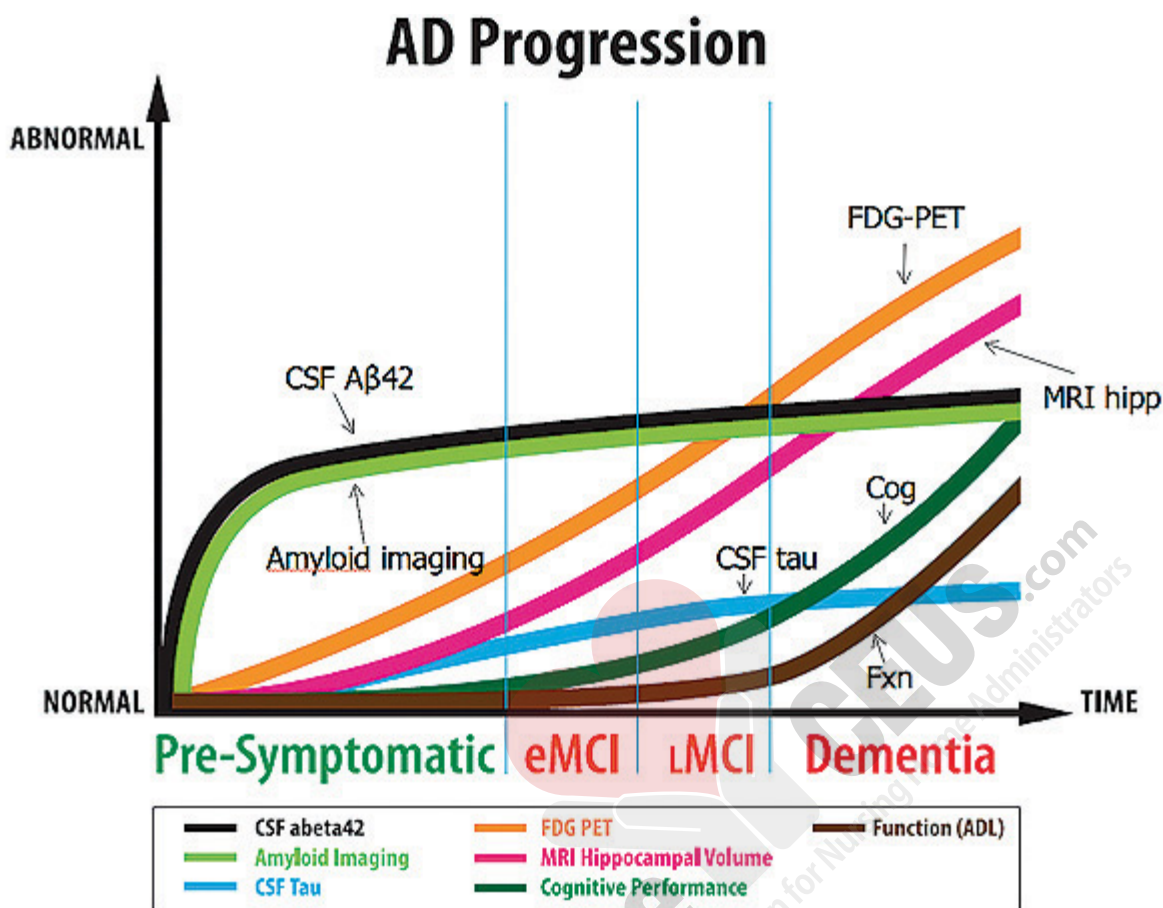
Cognitive tests are frequently used to evaluate new therapeutics in clinical trials. However, a volunteer's performance on a cognitive test may vary depending on the conditions under which the test is administered, and some test results may not accurately reflect their ability to carry out everyday tasks and social activities.

Investigators at the University of California, Berkeley, found that FDG-PET imaging, which measures glucose metabolism in the brain, was a more reliable tool than a commonly used cognitive test for monitoring Alzheimer's progression (Landau et al., 2011). The researchers studied more than 300 volunteers enrolled in ADNI over 2 years. Individuals who had low brain glucose metabolism at the start of the study were more likely to show subsequent cognitive and functional decline. Moreover, statistical analyses indicated that FDG-PET data would be more sensitive than the ADAS-Cog, a cognitive test frequently used for assessing drug treatments.

Combining Genetic, CSF, and Imaging Biomarkers

Researchers are interested in learning how different Alzheimer's biomarkers interact with each other and with genetic factors to predict disease progression. In one study, Alzheimer's Disease Neuroimaging Initiative (ADNI) investigators studied interactions among CSF beta-amyloid levels, gene risk factors (in particular, the APOE ϵ 4 gene), and hippocampal volume loss (Chiang et al., 2011). The study involved nearly 300 older volunteers with normal cognition, MCI, or Alzheimer's.

For all groups, participants who had lower (i.e., abnormal) beta-amyloid levels in CSF at the start of the study showed greater loss of hippocampal volume over a 1-year period. In the MCI group, APOE ϵ 4 carriers showed greater hippocampal volume loss than non-carriers, and individuals with both the APOE ϵ 4 allele and low beta-amyloid showed greater hippocampal volume loss than would be expected from either risk factor alone. These results suggest abnormal beta-amyloid processing may accelerate degenerative brain changes associated with the APOE ϵ 4 allele.



This diagram illustrates how Alzheimer's-related changes in the brain may contribute to disease progression, from normal cognitive aging to early mild cognitive impairment (eMCI) to late MCI (LMCI) to Alzheimer's dementia. The curves represent the sequence in which specific markers may play a role in disease progression. This model suggests that different imaging tools, measurements, and biochemical biomarkers may serve as predictors (measures that predict future change) and outcomes (measures that detect change) at different stages in the transition from normal aging to MCI to dementia. The NIA-led ADNI study is gathering data to test this model.

Courtesy of Paul Aisen, M.D., Alzheimer's Disease Cooperative Study, University of California, San Diego.

Sensory Changes

Loss of the sense of smell (olfaction) is often an early symptom in Alzheimer's disease. Similarly, in mouse models, changes in the olfactory system are an early symptom of degenerative changes. In a study led by researchers at the Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, abnormal network activity was detected in the olfactory bulbs of Alzheimer's model mice as early as 3 months of age (around the time of puberty in mice) and coincided with the first signs of beta-amyloid accumulation (Wesson et al., 2011). The researchers noted these changes occurred before the appearance of beta-amyloid in other brain regions and the onset of cognitive deficits.

Treating the mice with a drug that promotes beta-amyloid degradation reversed the olfactory network abnormalities and restored the mice's ability to detect odors. This study suggests we may be able to reverse the early olfactory impairment that occurs in Alzheimer's, and that more refined methods for testing the olfactory network in humans with increased sensitivity and specificity might help detect the early stages of the disease.

Motor Changes

Declining gait speed may serve as a predictor of cognitive decline in older adults. However, clinicians do not routinely assess gait speed and may have difficulty distinguishing sudden changes from those that occur slowly over time. Oregon Health Sciences University, Portland, researchers reported on the use of an in-home device that monitored gait speed by collecting measurements unobtrusively from infrared motion sensors (Austin et al., 2011). The researchers developed mathematical formulas for analyzing changes in gait speed over time. They also identified parameters associated with a sudden decrease in speed (for example, in a volunteer who suffered a stroke) versus slower decline (in a participant who was diagnosed with MCI toward the end of the monitoring period).

These methods suggest that assessing changes in gait speed might help identify people at risk of cognitive impairment and other adverse health outcomes.



Caring for People with Alzheimer's Disease

Caring for people with Alzheimer's disease presents special challenges, particularly toward the end of life. As the search for more effective interventions continues, it remains critical to improve the care and comfort of people with Alzheimer's, to ease the transitions through the stages of disease and dying, and to provide practical advice and emotional support for often overburdened family caregivers.

End-of-Life Care

Health care transitions—moving between home, nursing care facilities, hospitals, and hospice—in the last months of life can be burdensome and of limited clinical benefit for people with advanced cognitive impairment. A team led by Brown University, Providence, RI, researchers looked at end-of-life transitions among nearly 500,000 cognitively impaired nursing home residents (Gozalo et al., 2011). Of those individuals, almost one-fifth (19 percent) experienced at least one burdensome transition, including a transfer between health care facilities during the last 3 days of life, a lack of continuity of nursing home facilities during the last 90 days of life (i.e., moving from one nursing home to the hospital to a different, unfamiliar nursing home), and/or multiple hospitalizations during the last 90 days of life.

Such transitions can be especially stressful for cognitively impaired people and their families because they are physically difficult, can increase confusion, and often do not address the special needs of person with Alzheimer's, such as assistance with feeding. The researchers suggest that unnecessary transitions from nursing homes to hospitals may be avoidable because nursing homes can effectively treat common complications in residents with advanced dementia, such as pneumonia and urinary tract infections.

Feeding problems are extremely common in dementia and can affect as many as 85 percent of nursing home residents with advanced dementia. Family members and other caregivers often need to make difficult decisions about feeding, such as whether to use a feeding tube, with little guidance or information. A randomized, controlled trial led by investigators at the University of North Carolina, Chapel Hill, tested whether a "decision aid" could help this process (Hanson et al. 2011). The decision aid provided easy-to-understand information about the advantages, disadvantages, and outcomes of different feeding options and discussed the decision-maker's role.

Caregivers and other decision-makers for 256 nursing home residents with advanced dementia received either the decision aid intervention or no intervention. Compared with controls, study participants using the decision aid reported feeling more confident about their decisions and better understood dementia and feeding options. They were also less likely to use feeding tubes and were more likely to have discussed feeding options with a health care provider. These findings suggest that using a feeding-options decision aid may improve decision-making for caregivers of people with advanced dementia.

In the final stages of Alzheimer's dementia, most people require full-time care in nursing homes. Research has shown significant problems with end-of-life care in nursing homes, including inadequate treatment of chronic and severe pain and high rates of unmet resident needs. In addition, nursing home residents with dementia often undergo stressful and expensive medical treatments in the last months of their lives.



A study led by investigators at Brown University, Providence, RI, showed hospice services can improve the quality of end-of-life care as perceived by family members (Teno et al., 2011). The researchers studied surveys completed by more than 530 family members of demented residents who had died in five different states (Alabama, Florida, Texas, Massachusetts, and Minnesota). Most of the residents had died in nursing homes, and about half of them had received hospice services either in the nursing home or at home. Families of residents who had received hospice services reported significantly fewer unmet resident needs and concerns about the quality of care than families of resident who did not receive hospice services. They also reported a better end-of-life experience for their loved ones.

Medicare and Medicaid payments for people with dementia are estimated to be roughly three times higher than for cognitively normal older people. To understand factors associated with Medicare expenditures for dementia patients, a team led by Columbia University, New York City, researchers followed more than 300 people with advanced dementia in 22 facilities for 18 months (Goldfeld et al., 2011). They found that Medicare expenditures increased near the end of life, largely due to increasing use of acute care and hospice services. This pattern was due in part to people lacking advance directives. Use of a feeding tube and not living in a specialized dementia care unit also raised costs. Roughly one-third of all Medicare expenditures were for hospitalizations.

Hospital transfers are particularly difficult for people with advanced dementia, and most hospitalizations in this group were for conditions, such as pneumonia, that might have been treated as effectively and at lower cost in a nursing home setting. The strong association in this study between lack of a Do Not Hospitalize order and higher Medicare expenditures suggests that advance care planning may be a key step in preventing aggressive end-of-life care and may also reduce Medicare costs.

New Approaches to Dementia Care

Recent years have seen the development of collaborative dementia care models, which integrate and deliver medical and psychosocial interventions in a coordinated way for both people with dementia and their caregivers. University of Indiana, Indianapolis, researchers reported on one novel care program, the Healthy Aging Brain Center. (Boustani et al., 2011).

Part of the Indianapolis public health care program, the Center's program involves several components, including full neuropsychological and medical diagnostic workups at the time of patient enrollment; development of a personalized patient care plan; follow up care through phone and in-clinic assessments, including monitoring of chronic medical conditions (e.g., diabetes, vascular disease); caregiver education that includes training in patient care and self-management skills and help with financial and legal planning; support groups for patients and caregivers; active monitoring and support of the caregiver's emotional and physical health; and facilitation of communication among the patient's care providers.

Within its first year of operation, the Center's staff made more than 500 visits to serve some 200-plus patients and nearly an equal number of caregivers. This report describes how a health care model developed in a research setting can be translated into a practical health care delivery program.

Significantly, even though the Center operates as a special service that supports primary care, the quality of dementia care improved among primary care patients who had at least one visit to the Center—they had fewer emergency room visits and hospitalizations.



Health Disparities and Alzheimer's Disease

Studies and surveys suggest that certain racial, ethnic, and socioeconomic groups may be at greater risk than others for cognitive decline and dementia, and that different groups are vulnerable to different risk factors. Understanding these differences is critical to developing appropriate risk assessments and diagnostic tools and providing the most effective interventions to minimize Alzheimer's disease risk for everyone.

Factors Contributing to Alzheimer's in Minority Populations

Some studies have reported a higher prevalence of Alzheimer's disease among African-Americans and Hispanics compared to non-Hispanic whites. To better understand factors contributing to these observations, a team led by University of Pennsylvania, Philadelphia, researchers studied more than 1,300 people who had been diagnosed with either Alzheimer's or deemed cognitively normal at their initial visit to the University of Pennsylvania Alzheimer Disease Center (Livney et al., 2011). Among these individuals, Hispanics (mostly Puerto Rican immigrants) had an earlier age of onset and greater severity of Alzheimer's symptoms at their initial evaluation. They were also found to have lower average education levels and socioeconomic status than non-Hispanic whites. The Hispanics also suffered more depression than the African-Americans or non-Hispanic whites.

Interestingly, there was no association between the APOE ϵ 4 risk-factor gene and cognitive status in the Hispanic group, in contrast to the strong association seen in the other two groups. African-Americans had a slightly older age at disease onset than non-Hispanic whites. However, both African-Americans and Hispanics had higher levels of cognitive impairment and dementia at their initial clinic visit than did non-Hispanic whites. Reduced access to clinical facilities did not appear to play a role in this disparity. Researchers surmise that the disparity could reflect differing perspectives of African-American and Hispanic family members regarding age-related cognitive decline, or that primary caregivers may lack the knowledge to detect symptoms earlier. These findings highlight some of the factors—from stress to educational levels—that should be considered in future research comparing immigrant and nonimmigrant groups.

A team led by University of Indiana, Indianapolis, researchers studied the incidence of cognitive impairment, no dementia (CIND) and mild cognitive impairment (MCI) in a group of older African-Americans (age 65-plus) in Indianapolis, IN (Unverzagt et al., 2011). "CIND/MCI" is a broad diagnostic category that includes all forms of age-related cognitive impairment, in which people have clinically evident symptoms but do not have dementia.

About 1 in 20 study participants developed CIND/MCI each year during the 5-year follow-up period. These rates are similar to those reported for other groups in the United States and abroad. Age was an important risk factor: among the oldest old (85-plus), 1 in 10 developed the condition every year. Those with a history of depression or head injury were also at greater risk of developing CIND/MCI. Education was a strong protective factor in that people with more years of schooling were at reduced risk.

Rush University, Chicago, researchers studied a very large sample of more than 9,500 older African-Americans and whites to see if educational levels affected health disparities (Barnes et al., 2011). They found that African-American participants with lower levels of education had poorer cognitive function and physical function (leg strength, balance, and walking speed) compared with

similarly educated whites. More years of education were associated with better physical and cognitive health in both groups, and the positive effect of 12 years of education was similar for both groups.



Interestingly, additional years of education beyond high school had a significantly greater positive impact on physical and cognitive health in old age for African-Americans than for whites. Those with the highest levels of educational attainment enjoyed similar levels of cognitive health and physical function in old age. The study suggests that achieving greater levels of higher education in minorities might be helpful in reducing health disparities in old age.

Cognitive testing in minority ethnic groups can be complicated by demographic factors, including cultural background, language differences, and low educational levels. A team led by University of California, Davis, researchers compared the effectiveness of different tests in assessing cognitive decline in a sample of more than 600 Hispanics age 60 and older (Farias et al., 2011).

In this group, the subjects' degree of everyday functional impairment, as measured by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), was a strong predictor of cognitive decline over the next 7 years. The IQCODE is an interview-based questionnaire completed by an "informant," a family member or other person familiar with the study subject, and is available in Spanish.

The researchers found that baseline functional impairment reported by an informant may be a more sensitive indicator of future risk of cognitive decline than neuropsychological tests. Importantly, the informant-provided data are not strongly affected by educational level. In contrast to the results with the IQCODE, the subjects' performance on a verbal memory test was not associated with future cognitive decline when demographic variables were taken into account. This study suggests that informant-based ratings of everyday function, which are easy to collect in clinical settings, are useful for identifying older Hispanic adults at risk of cognitive decline.

Health Disparities and the Burden of Alzheimer's

Almost two-thirds of Americans with Alzheimer's disease are women. Scientists believe that the gender difference in Alzheimer's prevalence results primarily from differences in lifespan. Because Alzheimer's is an age-related disease and women typically live longer than men do, women may simply be more likely to survive long enough to develop the disorder.

However, past research comparing women and men who have already developed the disease suggests that women on average suffer from more severe symptoms than do men. In addition, a recent Mayo Clinic, Rochester, MN, study of a large Minnesota population found that men age 70 to 84 developed MCI, a possible precursor to Alzheimer's, at substantially higher rates than women of the same ages (Roberts et al., 2012). The leaders of that study speculate that the Alzheimer's disease process begins earlier in men than in it does in women, but that women decline more rapidly once the disease process has started.

Gender differences in other health factors may also contribute to the increased risk and/or severity of Alzheimer's disease in women. For example, women have higher rates of depression and anxiety than men and on average get

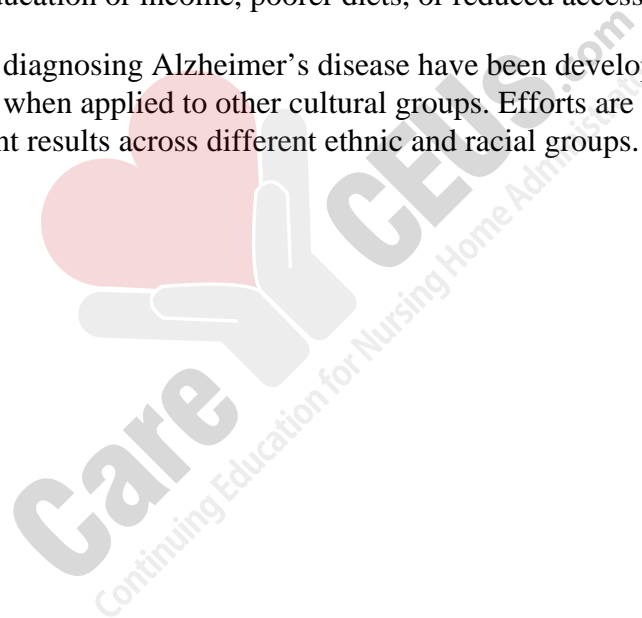
less exercise per week (Carter et al., 2012).

Alzheimer's disease also impacts women disproportionately with regard to caregiving. Women do most of the caregiving for family members with the disorder (more than 70 percent of the unpaid caregivers for people with Alzheimer's and other forms of dementia are women), and they suffer a greater burden of related stress and depression. At the same time, women who themselves suffer from Alzheimer's receive less care and social support than do men with the disorder. Women with Alzheimer's are much less likely to be living with a spouse and, regardless of their marital status, typically receive far fewer hours of care per week from family and friends than do men with the disease.

However, data suggest that husbands who are caregivers show greater physiological risk than do their peers who are not caregivers, with higher rates of obesity, triglycerides, blood pressure reactivity to acute stressors, and poorer immune function. In contrast, such differences are not as great between wives who are caregivers and wives who are not.

A growing body of research suggests that the burden of Alzheimer's disease also varies among different ethnic and racial groups. In many U.S. communities, Alzheimer's disease is significantly more prevalent among elderly African-Americans and Hispanics than among non-Hispanic whites of the same age. African-American and Hispanic individuals may also show more severe symptoms when they are first diagnosed. However, these ethnic and racial differences in Alzheimer's disease prevalence are not consistent from community to community and may result from environmental factors, such as less education or income, poorer diets, or reduced access to health care.

In addition, current cognitive tests for diagnosing Alzheimer's disease have been developed using largely white populations and may be less accurate when applied to other cultural groups. Efforts are underway to develop diagnostic tests that produce consistent results across different ethnic and racial groups. Biomarkers may prove particularly useful in this regard.



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