

# Alzheimer Disease

Intermediate article

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*Alzheimer disease is the leading cause of dementia among older adults. It results in neurochemical and neuroanatomical brain changes that cause increasing cognitive dysfunction.*

## INTRODUCTION

Alzheimer disease (AD) was first described by Alois Alzheimer in 1907. A German neuropathologist working in Emil Kraepelin's laboratory in Heidelberg, Alzheimer reported a case study of a 51-year-old woman who had psychiatric symptoms and memory problems. Upon her death, Alzheimer noted an abundance of neuritic plaques and neurofibrillary tangles in her brain. Although neuritic plaques had been described previously, Alzheimer was the first to recognize that their presence in large numbers was abnormal, and that the coexistence of the plaques and tangles signaled a previously unidentified disease of the cerebral cortex. This combination of neuritic ('senile') plaques and neurofibrillary tangles is now recognized as the neuropathologic signature of AD.

Alzheimer disease is the most common cause of dementia, accounting for approximately two-thirds of all cases. It is estimated that over 4 million people in the USA have AD, and by the eighth decade of life as many as one in two adults will develop the disease, which is characterized by neuronal changes, neurotransmitter abnormalities and decreased brain volume. These changes underlie cognitive deficits including memory loss, language dysfunction, and visuospatial and temporal disorientation.

## DIAGNOSIS

Dementia is defined as an overall loss of intellectual function severe enough to impede daily activities. It consists of a group of behavioral symptoms

that must occur together; these symptoms can have various etiologies. Alzheimer disease is defined as the presence of memory impairment plus one other area of cognitive dysfunction: language, motor, attention, executive function, personality, or object recognition, according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. The deficits must have a gradual onset, and a continuous (and irreversible) progression. A definitive diagnosis of AD can be made only at postmortem examination by observing the hallmark neuritic plaques and neurofibrillary tangles. Antemortem, the diagnosis of 'probable' AD is given when an individual meets the criteria of the DSM-IV, the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA), and when all other causes of dementia have been eliminated. When made by a trained clinician, this exclusionary diagnosis is accurate in 80–90% of cases.

## INCIDENCE AND PREVALENCE

The incidence of AD increases exponentially with advancing age. At age 70–75 years the incidence of AD is approximately 1% per year, but at age 80–85 years the annual incidence is over 6% per year (e.g. Hebert *et al.*, 1995). Overall, women remain at greater risk of developing AD than men. The prevalence of AD also increases with age (e.g. Fratiglioni *et al.*, 1991), with 30–50% of adults aged 70 years and above having a diagnosis of probable AD.

## NEURONAL CHANGES

Alzheimer disease results in a range of neuronal changes, including cellular dysfunction and death.

Eventually, AD affects nearly all brain structures. Early in the disease, however, some brain regions (e.g. limbic structures) are affected to a much greater extent than others (e.g. the primary sensory cortices).

## Neuropathologic Changes

The hallmarks of AD are neurofibrillary tangles (intracellular) and neuritic plaques (extracellular). These changes reduce the efficiency of neural communication. While normal aging is associated with these neuropathological changes as well, the number of plaques and tangles seen in the AD brain is far greater than in nondemented individuals.

### Neurofibrillary tangles

Neurofibrillary tangles consist of small, paired, helical filaments (i.e. two fiber strands that are twisted around one another). They are found in the cell body and dendrites of neurons, and often appear flame-shaped, with a rounded cell body and a threadlike apical dendrite. They can also have a more spherical shape. Neurofibrillary tangles are composed of hyperphosphorylated tau protein. Typically, tau protein is a soluble component of the cell. When tau is overphosphorylated, however, it becomes insoluble and forms tangles. Because neurofibrils are frequently used for the transport of chemicals that will be made into neurotransmitters, the tangling of these fibrils renders them useless and can prevent neurotransmitter synthesis. Neurofibrillary tangles are not specific to AD, but also appear in other neurological disorders including Parkinson disease, Down syndrome, progressive supranuclear palsy and other forms of dementia.

### Neuritic plaques

Neuritic plaques are dense deposits found outside the brain's nerve cells (extracellularly). They are spherical structures with a dense core of amyloid- $\beta$  protein surrounded by a halo and a ring of abnormal (dystrophic) neurites. The halo component consists of other types of brain cells (astrocytes) and inflammatory cells (microglia). The dystrophic neurites represent dying nerve terminals and are small, threadlike structures consisting of abnormal neuronal dendrites. In addition to these 'typical' plaques, AD brains may also show 'diffuse' plaques, which have a loose accumulation of amyloid- $\beta$  rather than a dense core, and no surrounding dystrophic neurites.

### Patterns of deposition

Neurofibrillary tangles and neuritic plaques show different patterns of accumulation. Early in the course of AD, neurofibrillary tangles are confined primarily within the limbic structures. Neuritic plaques, however, appear throughout the cortex, even early in AD (Arriagada *et al.*, 1992).

### Relation between neuropathology and disease

It is unknown whether these neuropathological changes cause AD, or whether they are epiphenomenal. Nonetheless, there does appear to be a link between the amount of tangles in the brain and the severity of AD. Researchers are now working on therapeutic approaches to reduce the formation of tangles and plaques in the brain, hoping that this reduction will halt, or reverse, disease progression.

### Brain Atrophy

One of the most prominent features of AD is atrophy (shrinkage) of the medial temporal lobe. The entorhinal cortex (a gateway for information into the hippocampus) and the hippocampus are among the first regions affected. These regions lose about 50% of their neurons, a finding that accounts for the shrunken brain tissue. The volume of these regions, measured by neuroimaging techniques, can be used to identify people with early AD, and may even identify individuals with memory impairments who will later develop AD (e.g. Jack *et al.*, 1999). Another region of the brain that shows substantial cell loss early in AD is the nucleus basalis. This region of the ventral forebrain contains many of the brain's cholinergic neurons. Damage to this region reduces neurotransmission in pathways using the neurotransmitter acetylcholine.

As AD progresses the brain changes become more widespread. The ventricles of the brain expand as the surrounding tissue deteriorates. Sulci (the 'valleys' between the brain's folds) widen. Neocortical areas, including temporal and parietal neocortex, show increased atrophy. Eventually nearly all of the brain, including secondary and even primary sensory areas, is affected.

### Neurotransmitter Abnormalities

The damage to the nucleus basalis results in reduced levels of choline acetyltransferase, the enzyme needed for acetylcholine formation. These reductions occur relatively early in the disease, but not all cholinergic pathways are affected equally:

the long-axon cholinergic neurons (e.g. those connecting the nucleus basalis and the cerebral cortex) are particularly vulnerable. Because of the dramatic reduction in cholinergic transmission, the first approved therapies for AD were aimed at increasing the amount of acetylcholine in the brain. Current treatment for AD is administration of acetylcholine esterase inhibitors. Acetylcholine esterase is the enzyme that breaks down acetylcholine into its constituent parts. Acetylcholine esterase inhibitors, therefore, enhance cholinergic neurotransmission by blocking the breakdown of the neurotransmitter. Acetylcholine levels remain higher and can have a longer-lasting effect before being broken down. This therapy, however, provides only a transient increase in memory performance, if any, and has no effect on disease progression.

The minimal effectiveness of acetylcholine esterase inhibitors suggests that acetylcholine deficiency is not the only cause of the cognitive dysfunction in AD. In fact, as the disease progresses, nearly all neurotransmitter systems become depleted. There appears to be much individual variation in the neurotransmitters most affected by AD and the absolute reductions. Estimates, however, suggest that levels of neurotransmitters including noradrenaline (norepinephrine), dopamine and serotonin can show reductions of up to 50% in the late stages of AD.

## GENETICS

Alzheimer disease can be divided into two types: familial (inherited) and sporadic. Familial AD is relatively rare, representing less than 5% of total cases, and typically affects individuals at a younger age than sporadic AD (often before age 50 years, with cases reported of people developing the disease in their mid-20s). Sporadic AD usually has a later age at onset (after age 65 years). Some research suggests that familial and sporadic AD differ not only in terms of age at onset, but also in their cognitive profile. Familial AD may be associated with a more rapid cognitive decline and shorter time to death. It also may be linked to more verbal deficits and fewer visuospatial deficits than sporadic AD (Filley *et al.*, 1986).

### Familial or Early-onset AD

Familial AD is linked to mutations in three genes: those coding for presenilin 1 (PS-1) on chromosome 14, presenilin 2 (PS-2) on chromosome 1, and amyloid precursor protein (APP) on chromosome 21 (Table 1). These mutations are causative: a person

**Table 1.** Molecular genetics of Alzheimer disease

AD Group	Chromosome	Gene	Protein
Familial AD, onset 50s	21	APP	Amyloid
Familial AD, onset 40s	14	PS1	Presenilin 1
Familial AD	1	PS2	Presenilin 2
Late-onset AD	19	APOE	ApoE $\epsilon$ 2, $\epsilon$ 3, $\epsilon$ 4

AD, Alzheimer disease.

who has one of these genetic mutations will develop AD. Familial AD is inherited following an autosomal dominant pattern. This pattern means that if one parent has this form of AD, each offspring has a 50% chance of developing AD. Interestingly, all of these mutations appear to have a common effect: increased production of amyloid- $\beta$  peptide (A $\beta$ ) 42, the main constituent of the amyloid plaques in the AD brain. The peptide is part of a larger precursor protein (APP), which can be cleaved (cut apart) in two different places, leading to the formation of two types of amyloid- $\beta$ , one with 42 amino acids (A $\beta$ 42) and one with 40 (A $\beta$ 40). The first type appears to be more likely to form plaques in the brain than A $\beta$ 40; it may also be the more toxic form, and its presence may lead to neuronal death. Researchers are now working on ways to reduce the amount of A $\beta$ 42 formed from APP, in the hopes of stopping the formation of amyloid plaques, and perhaps also preventing further clinical decline.

### Sporadic or Late-onset AD

Sporadic AD probably has a multifactorial basis, including possible genetic and environmental influences. Although there are no causative mutations, there is a major genetic susceptibility factor. A gene that encodes apolipoprotein E (ApoE) is found on chromosome 19 (see Table 1). Everyone has this gene: it is essential for carrying cholesterol in our bloodstream. The gene has many alleles (or forms); the most common ones produce the ApoE variants  $\epsilon$ 2,  $\epsilon$ 3 and  $\epsilon$ 4. One allele is inherited from each parent. Being homozygous for the  $\epsilon$ 4 allele (i.e. having two  $\epsilon$ 4 alleles) is associated with an increased risk of developing AD (Saunders *et al.*, 1993). Being homozygous for the  $\epsilon$ 2 allele, in contrast, is associated with a reduced likelihood of developing AD. The allele is not predictive of AD, however; individuals without an  $\epsilon$ 4 allele can develop AD, and those who are homozygous for the  $\epsilon$ 4 allele can remain unaffected by AD. The ApoE

alleles are thought to influence the development of late-onset AD in about one-third of the population. Dozens of other genetic risk factors have been suggested, but their roles have been researched less thoroughly than the role of ApoE.

Sporadic AD is also associated with other, nongenetic risk factors. The greatest risk factor is advanced age. One well-researched correlation is with decreased estrogen levels (e.g. Paganini-Hill and Henderson, 1994). It is believed that the reason women are at greater risk of developing AD than men is because of the postmenopausal drop in estrogen levels. Taking estrogen after menopause appears to decrease the likelihood of developing AD, though it does not seem to alter its progression in those who already have the disease. Head injury is another risk factor for AD. Particularly when unconsciousness has occurred, it increases the likelihood of developing AD, and more severe injury is associated with greater risk (e.g. Guo *et al.*, 2000). Head injury as far back as early childhood appears to influence the rate of AD development later in life.

## ANIMAL MODELS

Animal models of AD can provide insight into the genetics, pathological progression and treatment of AD. Several transgenic mouse models have been created with the objective of clarifying the role of genetic factors. Researchers have engineered mice that express genes implicated in AD, such as those coding for APP, the presenilins and tau; for reviews see Janus and Westaway (2001), van Leuven (2000) and Duff and Rao (2001). The characteristic pathologic findings in these mice differ depending on the genetic alterations. Transgenic mice created by introduction of APP develop neuritic plaques, and show deficits in learning and memory; however, they do not develop neurofibrillary tangles, which are the other neuropathological hallmark of AD. Transgenic mice created by inserting human tau genes develop abnormal clumping of tau filaments (neurofibrillary tangles), as well as neuronal degeneration, but do not develop neuritic plaques. Mice engineered to express PS-1, in contrast, do not display abnormal pathology or cognitive impairment, but do show elevated levels of A $\beta$ 42 (the peptide associated with plaque formation). These models, therefore, provide insights into the contributions of genes implicated in the development of familial AD. Transgenic mice can also be used to examine whether and how genetic risk factors (e.g. expression of ApoE  $\epsilon$ 4) influence disease progression.

In addition, animal models can provide clues about the pathological progression of AD. Because

AD appears to occur naturally only in humans, it has not been possible to examine the neuropathological changes in the brain at various stages of the disease. Rather, the samples available have by necessity come at the time of death. While much information can be garnered from analysis of end-point data, animal models provide a means for systematic tracking of pathological changes. Hybridizing mice genetically altered to develop neuritic plaques with those engineered to manifest neurofibrillary tangles, has resulted in a strain of mice showing both of the neuropathological hallmarks of AD. This animal model may be particularly important in contributing to our understanding of how these two neuropathological features relate. Researchers are optimistic that use of such animal models will provide information about the relation between amyloid deposits and tau-containing tangles, and about the role they play in the development and progression of AD.

Animal models will also be important in testing potential treatments for AD. Once researchers have established an animal model that closely approximates the pathological and cognitive characteristics of AD, it will be possible to test the efficacy of treatments on these animals.

## COGNITIVE FUNCTION

The signs of AD develop slowly, and it is often difficult to pinpoint the time of disease onset. Initial symptoms are mild, and can include forgetfulness, passivity, decreased work productivity, word-finding difficulties, and disorientation. As the disease progresses, nearly all aspects of function are affected, including memory, language, attention, vision, audition, and motor control.

## Impaired Capacities

### *Episodic memory*

Impairment of episodic memory – the recollection of events that occupy a specific spatial and temporal context – is typically the earliest and most prominent deficit in AD. Patients have difficulty forming new episodic memories (anterograde amnesia), and this impairment worsens with disease progression. Deficits in episodic memory, including delayed recall of verbal and nonverbal material, are the best way of distinguishing people with AD from healthy older adults (e.g. Locascio *et al.*, 1995). In contrast, however, people with AD remain capable of retrieving some long-term episodic memories. While remote memory is impaired, it

does not show the pronounced decrements seen in the formation of new episodic memories. The loss of retrograde memory (retrograde amnesia) also appears to be temporally graded, with recent memories showing more degradation than remote memories. In fact, the capacity to recollect events from the remote past is often quite resilient in AD. Patients can even become preoccupied with the past, and can confuse their current environment with that of their youth. The degrees of anterograde and retrograde memory deficits are not significantly correlated (e.g. Greene and Hodges, 1996).

The episodic memory deficit is consistent with the neural changes early in AD: brain structures that support long-term memory (medial temporal lobe regions, including the hippocampus) are compromised in early AD, while other regions of the brain are less affected.

### **Emotional memory**

Individuals are often better at remembering emotional compared with neutral information. This emotional memory enhancement effect appears to result from interactions between the amygdala and other regions of the medial temporal lobe, including the hippocampus. Alzheimer disease results in a substantial volumetric reduction in the amygdala, and this amygdaloid atrophy appears to reduce the emotional enhancement effect: people with AD do not show better memory for emotional information than for neutral information (Kensinger *et al.*, 2002) and their ability to remember emotional stimuli appears to correlate with amygdaloid volume.

### **Semantic memory**

Semantic memory – general knowledge about the world – is relatively spared early in AD, but as the disease progresses significant deficits arise. Deficits occur on tasks requiring general knowledge retrieval, word definitions, word–picture matching, or picture naming. It is unclear whether the semantic deficit is related to a breakdown in the structure of semantic memory, to impaired access of semantic information, or to a combined deficit in structure and access.

The extent of the language deficits is useful for assessing the severity of AD (Locascio *et al.*, 1995). Initial deficits include increased ‘tip of the tongue’ effects, reduced fluency scores, and a difficulty with tests requiring confrontation naming. In later stages of the disease, deficits can include forgetting the names of spouse or children, and the inability to recall names of common objects. The progression of semantic memory deficits is associated with the expanding pathological changes of advancing AD:

as perisylvian areas become affected, semantic memory deficits increase.

### **Visuospatial function**

While early AD is associated with some disorientation, visuospatial dysfunction increases with disease progression. In the middle stages of the disease, it is common for patients to become lost while driving their car or on a walk, even when following a route that they have taken on many occasions.

### **Executive functions**

People with AD show deficits in short-term memory and in on-line processing of information (Corkin, 1982). At least some of these deficits may be due to deficits in the ‘central executive’ in Baddeley’s model of working memory. Becker (1988) suggested that AD might have two main deficits: one paralleling that of amnesia, and the other in the central executive. In support of the central executive hypothesis, people with AD have frequently been found to have poor dual-task performance while being capable of performing each component task at a normal level. Baddeley and colleagues also found that dual-task performance declined with disease progression, while single-task performance remained stable.

### **Classical conditioning**

Most forms of nondeclarative memory are spared in AD. One notable exception, however, is seen with delay conditioning, in which the unconditioned stimulus occurs just before the offset of the conditioned stimulus. People with AD are impaired at acquiring a conditioned response (such as an eyeblink in response to a tone). They require more trials to learn this type of relation (e.g. Woodruff-Pak *et al.*, 1996). This deficit is probably not related to damage to the medial temporal lobe because amnesic patients with damage to these structures are capable of acquiring a conditioned response. The deficit is more likely to be related to cholinergic or cerebellar dysfunction.

### **Vision**

Alzheimer disease results in changes in basic sensory and perceptual capabilities. People with AD often have more difficulty perceiving visual stimuli than do nondemented older adults. A significant correlation exists between the severity of perceptual deficits and the extent of cognitive dysfunction (e.g. Cronin-Golomb *et al.*, 1995). It is unclear whether this correlation is causal (e.g. visual deficits could cause poorer performance on a task of

visual memory) or associative (e.g. patients with greater brain atrophy are likely to have both sensory deficits and memory dysfunction). The visual deficits are related to reductions in contrast sensitivity, color perception and discrimination, and visual acuity. The visual dysfunction is probably related to neuropathological changes in primary visual cortices and visual association areas because AD does not appear to affect the retina or optic nerve.

## Preserved Capacities

Despite the range of capacities affected in AD, some domains remain relatively preserved until late in the course of the disease. Most prominently, many types of nondeclarative (implicit) memory are unaffected by early to moderate AD.

### Priming

Priming can be broadly broken down into two subsets: conceptual and perceptual priming. People with AD show a dissociation in performance on these priming tasks: their performance on conceptual priming tasks is impaired, whereas their perceptual priming is normal. This dissociation probably reflects a disproportionate reliance on temporoparietal regions in conceptual priming. Conversely, perceptual priming appears to rely predominantly on occipital lobe regions that are less affected by AD.

### Skill learning

Until the late stages of AD, patients are capable of learning new skills, ranging from motor learning to visual adaptation. The preservation of such learning is likely to be related to the relative preservation of brain regions important for nondeclarative learning, including the basal ganglia and frontal lobe.

## TREATMENT

The treatment of AD consists predominantly of three types of approaches: (a) mitigating noncognitive disorders (psychiatric symptoms such as anxiety or paranoia, sleep disturbance), (b) restoring neurotransmitter function, and (c) protecting neurons from further death. The majority of drugs prescribed to restore neurotransmitter function have been cholinesterase inhibitors. These drugs, however, have had only minimal effectiveness in slowing the disease progression and have not been able to halt or reverse the disease's effects. There is some evidence that antioxidants (vitamin E),

antiinflammatory drugs (ibuprofen), estrogen, and lipid-lowering agents (statins) may be neuroprotective, in as much as they slow the progression of AD. To date, however, there is no evidence that these treatments can slow disease progression in individuals already affected.

## SIGNIFICANCE OF RESEARCH FOR UNDERSTANDING BRAIN FUNCTION

Research into AD has improved our understanding not only of the neurologic disorder but also of brain function. By observing the pattern of spared and impaired functions, researchers have learned that some types of memory (e.g. declarative) are affected by diffuse damage to the medial temporal lobe, while other types of memory (i.e. nondeclarative) remain relatively unaffected. Similar dissociations, such as between preserved perceptual priming and impaired conceptual priming, or between impaired anterograde memory and only moderately affected retrograde memory, have helped to uncover the dissociable neural mechanisms responsible for these cognitive functions. Similarly, the finding of reduced cholinergic function in AD sparked interest in the role of acetylcholine in long-term memory formation. Further research has demonstrated the necessity of the cholinergic system for successful episodic encoding.

By comparing performance in AD and amnesia, researchers have also been able to determine what memory dysfunction in AD is caused specifically by damage to the medial temporal lobe system, and what deficits may be related to neocortical damage (Corkin, 1982). This complementary interaction between neurology, neuropsychology, and neuroscience has allowed simultaneous advancements in the diagnosis and treatment of AD, and in our understanding of brain-behavior relations.

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