



Memory Loss and Alzheimer's Disease Backgrounder

Types of Memory

Memory is a recording of one's experience stored in the brain — be it an interesting conversation, a piece of information, a memorable scene, or notable event. There are 3 types of memories differentiated by the time lapse between the experience and the recall of that experience. Each type of memory activates a different area in the brain during recall.

- **Working memory** resides in the frontal lobe and lasts less than a minute. This form of memory is commonly referred to as one's attention span and lasts up to one minute before being erased. Trying to memorize and dial a telephone number that someone just gave you is an example of working memory.
- **Short-term memory** resides in the inside (medial) of the temporal lobe called the hippocampus and entorhinal cortex, and lasts a few minutes to a few weeks before being erased. When you try to recall a conversation or a phone number learned a few minutes to a few weeks ago, these brain areas are activated. Not all of one's moment-to-moment experiences activate short-term memory. Only those experiences that are novel, interesting or those that one intended to remember will sufficiently stimulate nerve cells in the hippocampus and entorhinal cortex to record them.
- **Long-term memory** can last a lifetime though scientists are not yet certain which brain areas are involved in this function. Well-learned facts such as the name of a school one attended as a child are stored as long-term memories.

Dementia and Mild Cognitive Impairment

While a slight decline in a person's overall memory function can be a part of normal aging, a notable or sudden decline is more likely attributable to some underlying medical condition. Depending on the severity of such disease-related memory loss, a patient may satisfy criteria for either mild cognitive impairment (MCI) or dementia. MCI and dementia are not specific diseases, but rather, each represents a "stage" along the continuum of cognitive impairment and both are generally caused by some underlying disease or condition. The dementia stage is further divided into mild, moderate and severe stages as indicated below:



Mild Cognitive Impairment

When cognitive function is impaired by a progressive disorder, the earliest and subtlest stages of impairment are called Mild Cognitive Impairment (MCI). If the cause of MCI is not treated, the condition often progresses until the individual is demented. According to widely accepted definitions, persons with MCI have impairments limited to one category of cognitive function (e.g. memory, judgment, reasoning, executive function) and this impairment does not interfere with performing activities of daily living.

Dementia

The definition of dementia has two elements. The first element requires that one has developed difficulties in two or more areas of complex brain function (cognition) such as the ability to:

- Remember what was recently learned
- Recognize and name objects, such as people or other familiar things



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- Speak sentences that are understandable to others
- Make decisions or judgments about things that are personally important
- Plan, organize and execute simple and complex tasks

The second part of the definition requires that these "cognitive difficulties" affect one's ability to perform the usual routines of daily life.

Causes of Memory Loss

The predominant cause of memory loss is a family of diseases called Alzheimer's Disease and related disorders (ADRD) which includes but is not limited to Alzheimer's Disease, vascular dementia, Parkinson's Disease, Lewy Body disease and Frontal Lobe dementia. Alzheimer's Disease is by far the biggest cause of memory loss and accounts for 60% of dementia cases.

In addition to ADRD, many other conditions cause dementia and memory loss. The tables that follow list the major causes of memory loss, the appropriate treatment and the most likely result of treatment:

Alzheimer's Disease and Related Disorders

Disease	Treatment	Result of treatment
Alzheimer's Disease	Cholinesterase inhibitor and glutamate modulation	Stabilization and sometimes improvement
Parkinson's Disease	Dopaminergic stimulation	Stabilization and sometimes improvement
Frontal lobe dementia	No established treatment	n/a
Vascular disease	Treat risk factors and medication	Stabilization and sometimes improvement

Other Causes of Memory Loss and Dementia

Condition	Treatment	Result of treatment
Anxiety	Anti-anxiety agents	improvement
ADHD	Psycho stimulants	improvement
Depression	Anti-depressants	improvement
Thyroid gland disease	Thyroid hormone	improvement
Diabetes	Anti-diabetics	improvement
Metabolic Encephalopathy	Diagnose etiology and treat	improvement
Alcohol dependence	Alcohol cessation	improvement
Chemical dependence	Al-anon	improvement
Vitamin B-12 deficiency	cyanocobalamin	improvement
Infections- meningitis and encephalitis	IV antibiotics	improvement
Drugs (prescription & over the counter)	Adjust medication	improvement
Fatigue	Diagnose etiology and treat	Improvement (depends on etiology)
Head injury	Cognitive therapy and medication	Stabilization and frequent improvement
Normal pressure hydrocephalus	shunt	Stabilization and sometimes improvement
Cancer and cancer treatment	Diagnose etiology and treat	Insufficient data



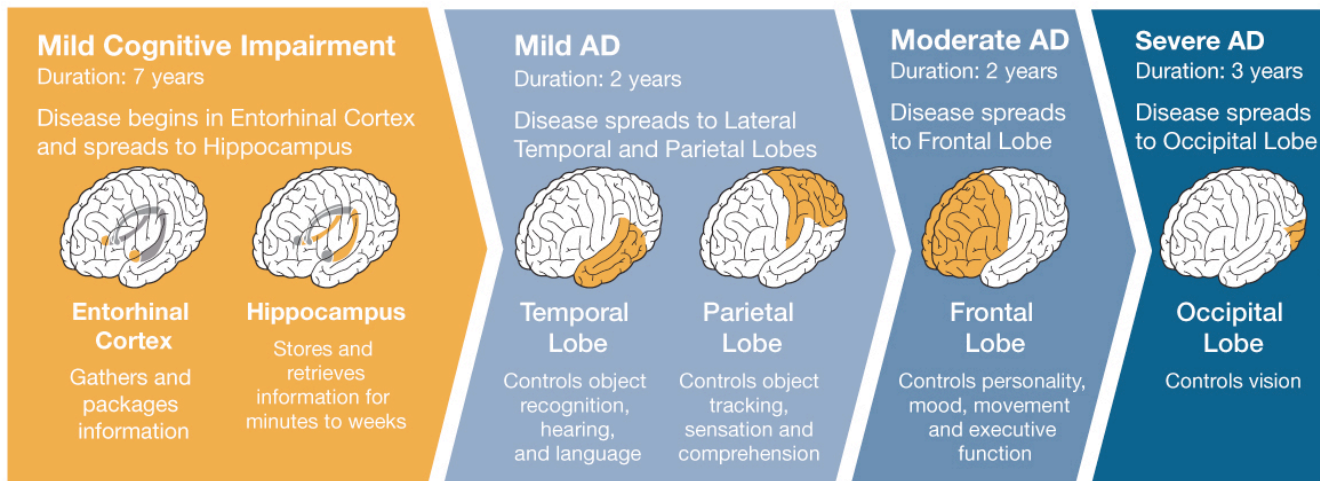
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Alzheimer’s Disease

Alzheimer’s Disease (AD) is by far the biggest cause of memory loss accounting for about 60% of dementia in the USA. First identified in 1906 by the German physician Alois Alzheimer, the disease is characterized by pathological hallmarks of neurofibrillary tangles and accumulations of amyloid plaques.

While AD can begin at ages in the early 50’s, it is primarily a disease affecting those over the age of 65. In 1900 the average life expectancy was 47 years, so AD occurred rarely. Since then, life expectancy in the United States has increased to 77.9 years and with it so has the incidence of Alzheimer’s disease. This disease is now a major economic healthcare problem and is the most common neuronal degenerative disease of aging.

AD is a progressive disease that generally impairs short-term memory in its earliest symptomatic stage and causes mild cognitive impairment (MCI). The subtype of MCI associated with Alzheimer’s disease and loss of short-term memory is called amnesic MCI. Approximately 80% of people with amnesic MCI become demented within 6 years. According to the Mayo Clinic, this progression occurs at a rate of about 15-20% of MCI patients per year compared to a conversion rate for the general population of about 1-2% per year. As such, accurately detecting amnesic MCI enables medical professionals to identify those who are at high risk for AD and to initiate treatment at the earliest appropriate moment.



In AD patients, the MCI stage lasts approximately 7 years and then progresses to mild, moderate and severe Alzheimer’s. During the MCI stage of the disease, impairment is limited to the entorhinal cortex and hippocampus and the cognitive function that is impaired is learning and short-term memory. Therefore, tests of short-term memory and learning are most sensitive in identifying the earliest onset of Alzheimer’s disease. As the disease progresses, it spreads throughout the brain impairing additional brain lobes and the function associated with those lobes.

Diagnosis of Alzheimer’s Disease

Early and accurate diagnosis of Alzheimer’s disease enables families and patients to plan for their future while the patient can still be involved in the decision making process. The NINDS-ADRDA diagnostic criteria for Alzheimer’s disease are more than 90% accurate for identifying all stages of the disease allowing physicians to make confident diagnoses of “Probable Alzheimer’s Disease”. This diagnostic process includes:



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Medical history – this should query for initial symptoms that characterize specific dementing disorders. Examples include family history of dementia, risk factors for Alzheimer's disease, visual hallucinations, loss of balance and marked fluctuation in level of alertness or confusion, marked reduction in speech or marked change in personality or behavior, and short-term memory loss.

Laboratory tests – these should be done to diagnose and treat other possible causes of mild cognitive impairment or dementia such as Vitamin B12 deficiency and thyroid disease.

Brain imaging – this should be done to identify hemorrhage, stroke, hydrocephalus, tumor, and degenerative disorders with selective patterns of atrophy. In Alzheimer's disease, the entorhinal cortex and hippocampus in the medial aspect of the temporal lobe are the first cortical areas to show neuronal pathology and cell loss. Therefore, hippocampal atrophy that is greater than that of the remaining cortical areas is virtually diagnostic of Alzheimer's Disease, particularly if the atrophy is not explained focal ischemia, hydrocephalus, a long history of poorly controlled seizures, tumor or focal trauma.

If the patient is in the mild cognitive impairment (MCI) stage then an MRI is needed to detect subtle amounts of atrophy. If a patient has very early stage impairment, a PET scan in addition to an MRI may be required. Decreased tissue activity, identified by PET scan, precedes structural abnormalities, identified by an MRI, by two or more years. However, if the patient is demented, then the amount of atrophy is usually substantial and a CT scan of the brain is adequate to detect selective atrophy, particularly if a spiral CT scan is done with coronal cuts.

Treatment of Alzheimer's Disease and Its Efficacy

Contrary to the notion that current AD treatments are ineffective, timely intervention with appropriate mediations can have substantial benefits and, in some cases, can delay disease progression for several years. Combining pharmacologic treatments with a balanced diet, regular physical exercise, routine social stimulation, and a well-informed caregiver is widely documented as the most beneficial approach.

Today there are five FDA-approved medications for treatment of AD (e.g. Cognex® (tacrine), Aricept® (donepezil), Razzadyne® (galantamine), Exelon® (rivastigmine) and Namenda (memantine) all of which have shown positive treatment outcomes in long-term studies. While the overall efficacy of these medications on a treated population is statistically unimpressive, a percentage of individual patients respond well to treatment, especially when intervention begins early in the disease process and the therapeutic regimen is carefully sustained.

Cholinesterase Inhibitors

Cognex® (Tacrine), Aricept® (donepezil), Razzadyne® (galantamine) and Exelon® (rivastigmine) belong to a class of medications called cholinesterase Inhibitors. Cholinesterase inhibitors increase the availability of acetylcholine, an important transmitter that helps control mood, behavior, memory and other cognitive abilities. Acetylcholine is markedly reduced in AD, Parkinson's disease, Lewy body disease and many other dementing disorders.

Cholinesterase inhibitors also appear to slow the production of beta amyloid. Published five-year data on Exelon®, four-year published data on Razadyne® and three-year published data on Aricept® all show that AD progression can be delayed by 50% or more.

Glutamate Receptor Modulators

Namenda® (memantine) belongs to a class of medication called glutamate receptor modulators. Glutamate is the transmitter for 75% of all neurons in the gray matter on the surface of the brain (cerebral cortex). Excessive amounts of glutamate are released in a wide variety of brain disorders, including stroke, Parkinson's disease, multiple sclerosis, traumatic brain injury, and probably AD. The excessive release of glutamate triggers certain suicide genes in neurons to cause their self-destruction. Namenda® blocks this self destruction plus allows normally released amounts of glutamate

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to exert their proper function in brain communication. Namenda® may also block neurofibrillary tangle formation (a hallmark of AD pathology) to delay AD progression.

New Treatments in Pipeline

There are many AD treatments in clinical trials including Flurizan® (Myriad, Inc.) which is likely to be FDA-approved in 2009. Flurizan belongs to a class of selective amyloid lowering agents (SALA). By reducing beta-amyloid production (another hallmark of AD pathology), SALA not only promises to improve various cognitive and functional abilities, but also appears to markedly delay AD progression.

Facts about Mild Cognitive Impairment

- Mild cognitive impairment (MCI) is a relatively recent term, used to describe people who have impairment in one cognitive function (such as memory loss, orientation, judgment) but do not actually have dementia. (Source: Mayo Clinic)
- Amnesic MCI is a subtype of MCI that describes impairment in memory loss. It affects up to 75% of MCI patients and is often associated with Alzheimer's disease. Approximately 80% of people with amnesic MCI develop Alzheimer's disease within 6 years. (Source: Mayo Clinic)
- It is estimated that 3-19% percent of the population has mild cognitive impairment. (Source: Gauthier S. et al. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262-70)

Facts About Alzheimer's Disease

- Approximately 4.5 million Americans currently have Alzheimer's disease. (Source: Alzheimer's Association)
- The number of Americans with Alzheimer's disease will continue to grow. By 2050 the number of Americans with Alzheimer's disease will be between 11.3 million to 16 million. (Source: Alzheimer's Association)
- 1 in 10 Americans have had a family member with Alzheimer's disease and 1 in 3 have known someone with the disease. (Source: Alzheimer's Association)
- Worldwide, approximately 24 million people have been diagnosed with Alzheimer's disease. (Source: Alzheimer's Disease International)
- Worldwide, the number of people with Alzheimer's disease is projected to nearly double by 2040 to 81 million people. (Source: Alzheimer's Disease International)
- In the U.S, only 9,000 physicians are certified to practice geriatrics. To adequately care for the aging population, the U.S. needs 20,000 geriatric specialists now and 36,000 specialists by 2030. (Source: Alliance for Aging Research)
- Up to 95% of diagnoses do not occur until the disease has progressed to the moderate stage, many years after the first symptoms. (Source: Gifford, D.R. and Cummings, J.L., *Neurology* 52, 24-7, 1999)
- While there is no cure for Alzheimer's disease, timely intervention and treatment can delay the progression of the disease by more than 50%. (Source: Farlow, M.R. and Lilly, M.L., *BMC Geriatr*. 5(1):3, 2005)
- Age is the greatest risk factor for Alzheimer's disease. One in 10 individuals over 65 and nearly half of those over 85 has Alzheimer's disease. (Source: Alzheimer's Association)



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- Alzheimer's Disease is the 4th leading cause of death among adults in the U.S.. Typical life expectancy is 8-10 years from the onset of symptoms although some people have lived with the disease for 20 years or more. (Source: Alzheimer's Association)
- The annual direct and indirect cost of caring for those with Alzheimer's disease in the United States is more than \$100 billion. (Source: Alzheimer's Association)
- Alzheimer's Disease is the 3rd most expensive disease in the nation, after heart disease and cancer, with an average lifetime cost per patient of \$174,000. (Source: Alzheimer's Association)
- Medicare costs for beneficiaries with Alzheimer's disease are expected to increase 75 percent, from \$91 billion in 2005 to \$160 billion in 2010; Medicaid expenditures on residential dementia care will increase 14 percent, from \$21 billion in 2005 to \$24 billion in 2010. (source: Alzheimer's Association)
- Average Medicare costs for an Alzheimer's patient are \$13,000 a year compared to \$4,500 a year for older Americans without the disease. (source: Alzheimer's Association)
- Alzheimer's Disease costs American businesses more than \$61 billion annually, including \$36.5 billion in lost productivity of employees who are caregivers. (source: Alzheimer's Association)

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