Neurobiology of Learning and Memory

Prof. Anagnostaras

Lecture 10:

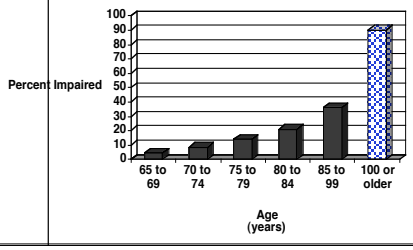
Alzheimer's Disease and Cognitive Decline in Aging

Dementia

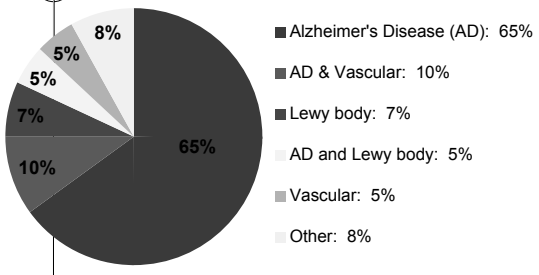
A syndrome characterized by a decline in cognitive functions sufficient to cause impairment in social and occupational performance

Risk of Dementia is Unrelenting with Age

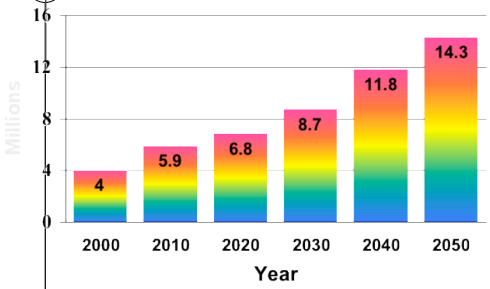
Percentage of Persons with Moderate to Severe Memory Impairment



Causes of Dementia



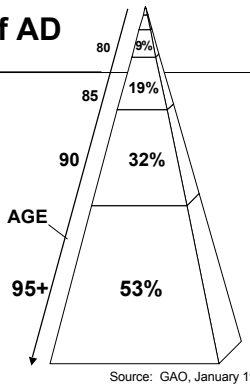
Projected Number of American's with AD



Evans, DA, et al. Milbank Quarterly 68:267-289; 1990.

Prevalence of AD

AGE	%
65	1
70	2
75	5
80	9
85	18
90	32
95+	53



Source: GAO, January 1998

Alzheimer's Disease Outline

Incidence: approx. 4 million Americans

Late onset: 65+ yrs (can occur earlier, but less than 10% of cases do - and in those cases caused by a specific gene mutation)

Women more likely to have it (b/c longer life span)

Can't be diagnosed for certain until death

Terminal disease: live an avg. 8 yrs post-diagnosis

Currently linked to several genes (transgenic mouse models)

The Implications of an Aging Society for AD Prevalence

- **40% of persons turning 65 in 2000 will survive to age 85**
- **30-50% of persons reaching age 85 will have AD**

Source: NEJM, 2000

Overview

- Progressive, degenerative brain disease characterized by
  - Increasing memory loss
  - Other cognitive decline
  - changes in behavior, personality, judgment and ADL's (Activities of Daily Living)
- Most common cause of dementia among people aged 65 or over

AD Characteristics

- **beta amyloid (protein) plaques & neurofibrillary tangles form most prevalently in brain areas assoc. w/memory & cognitive function (entorhinal ctx, hippocampus, frontal ctx, parietal ctx)**
  - **involves death of many cells, but esp. Ach-producing cells in the basal forebrain**
  - **Symptoms: dementia, memory loss, confusion, language loss**
  - **No cure; treat with Ach agonists (help w/early cognitive deficits)**

Ten Early Warning Symptoms

- Memory Loss That Affects Job Skills
- Difficulty Performing Familiar Tasks
- Problems with Language
- Disorientation of Time and Place
- Poor or Impaired Judgment
- Problems with Abstract Thinking
- Misplacing Things
- Changes in Mood or Behavior
- Changes in Personality
- Loss of Initiative

Severe Alzheimer's Disease

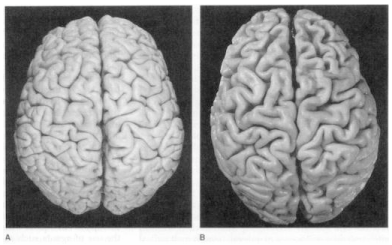
The person cannot:

- Communicate verbally
- Understand words or instructions
- Recognize self in the mirror or pictures
- Recognize family members
- Provide care for themselves

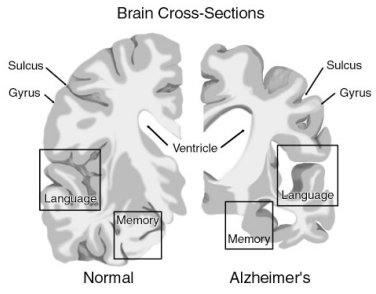
Usually die within 15 years
(4th leading killer of adults)

FAS Test

Alzheimer's Disease

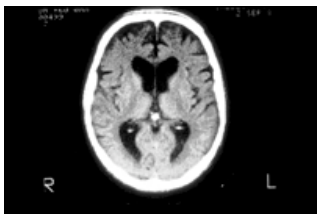


Alzheimer's Disease (degeneration)

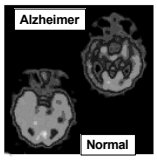


www.ahaf.org/alzdis/about/ BrainAlzheimer.htm

Alzheimer's Disease (MRI)



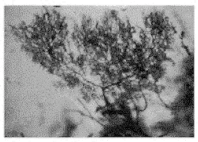
Alzheimer's Disease (PET)



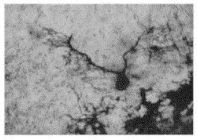
brain scans of a healthy elderly person and a patient with Alzheimer's disease

Alzheimer's Disease (cellular)

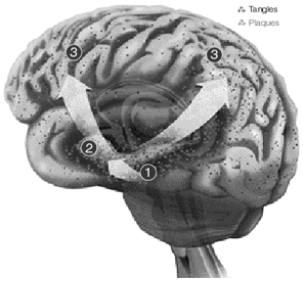
Normal cortex cell



Alzheimer's cell



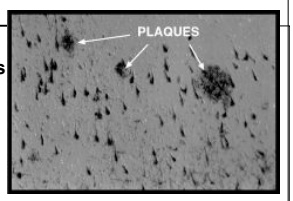
Alzheimer's disease: plaques & tangles in memory areas



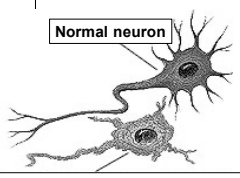
•affects entorhinal ctx (1), then hpc (2), frontal (3), parietal (3) lobes

Alzheimer's Disease (plaques & tangles)

Neurons with external plaques



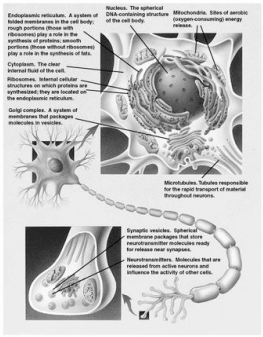
Normal neuron



Neuron with internal neurofibrillary tangles (disrupted microtubules)

Microtubules are "Railroad" for nutrients, NT transport w/i neuron

► The Major Internal Features of a Typical Neuron



Alz Recent Research: Tangles

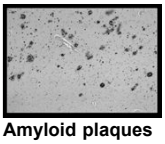
Tau = protein that keeps microtubules ("RR tracks") aligned down length of neuron (tau = "RR ties")

Pts with Alz have problematic tau --> curls & tangles microtubules ("RR tracks in jumble")

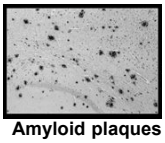
Since neurons can't get nutrients down length of axon…dies

Pin-1 (an enzyme), causes the bending of tau in Alz
SO, block Pin-1 --> block problematic tau?
Still researching…

Alz Recent Research: Plaques



Amyloid plaques in human Alz (70 yrs old)



Amyloid plaques in transgenic mouse

http://www.newsandevents.utoronto.ca/bin1/001220a3.asp

Study of Dementia in Swedish Twins – Concordance Rates

	Monozygotic(%)	Dizygotic(%)
Alzheimer's disease	75	26
All dementias	50	33

781 twins
aged 50 and over
surveyed every three years since 1970's

Source: J Geront, 1997

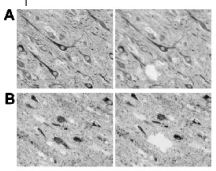
Genetics of Alzheimer's Disease

Several genetic Loci in Alzheimer's Disease:

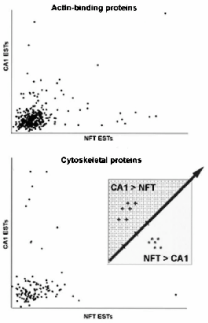
- Chromosome 21 (APP) : Early Onset FAD-6/50 amyloid precursor protein--> amyloid beta
- Chromosome 1 (PS2) : Volga German FAD presenilin2 (? γ-secretase activity)-risk factor
- Chromosome 14 (PS1) : Early Onset FAD presenilin1 (? γ-secretase activity)-40/44
- Chromosome 19: Apo-E4 late onset risk factor apolipoprotein E4+, E3–, E2 lethal
  E4- het = 3x, homo = 15x

Expression profile of AD tangle and normal CA1 neurons (Ginsberg et al, 2000)

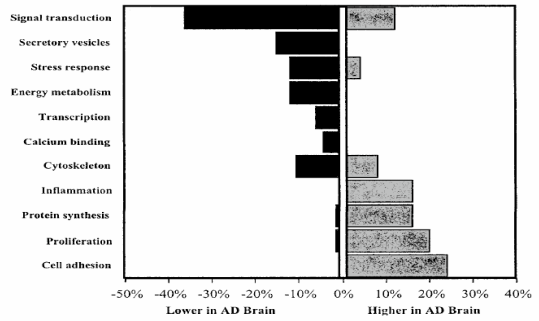
Aspirated non-NFT (A) and NFT-bearing (B) CA1 neurons



Relative expression intensities ➡



Expression of many genes affected in AD (Loring et al, 2001)



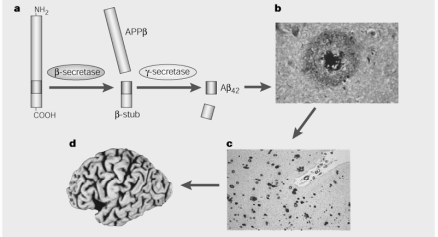
Alz Recent Research: Plaques (cont'd)

•**Plaque vaccine for Alz**

Inject Alz (PDAPP) transgenic mice with beta-amyloid vaccine, can prevent plaques in young-aging mice AND can decrease plaques in mice that already have them

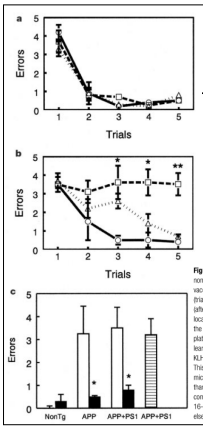
Schenk, D. et al, 1999,Nature 400 (July 8): 173.

Box 1 | **The amyloid hypothesis**

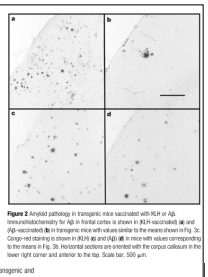


Amyloid-β peptide (Aβ) is derived from a much larger precursor protein, termed amyloid precursor protein (APP), which is cleaved sequentially, first by β-secretase (forming the soluble ectodomain APPβ and the β-stub) and then by γ-secretase (see panel **a** of the figure). Aβ is then thought to self-associate under certain circumstances to form proteinaceous aggregates called amyloid plaques (panel **b**, stained with Bielschowsky's silver stain; panel **c**, stained with anti-Aβ antibody). These plaques occur at a high density in many parts of the brain in patients with Alzheimer's disease (AD) and, on the basis of the amyloid hypothesis, are thought to lead to a broad spectrum of neuropathologies that ultimately result in the neurotoxicity and neuronal death (panel **d**, the brain of a patient with AD showing enlarged sulci) that underlie the symptoms of dementia observed in these patients.

Schenk (2002)



Amyloid-beta vaccine and Memory, Morgan et al., *Nature*, 2000



Pharmacotherapy

- There is no cure yet.
- There are three drugs that AD patient could take to slow the progression.
- They are: tacrine (Cognex), donepezil (Aricept), and rivostigmine (Exxelon).

These drugs are cholinesterase inhibitors

Several new drugs are Ach M1 receptor agonists.

Normal Aging of the Brain

- **Increase in time required to retrieve information**
- **Less able to register and retain new information**
- **Decrease in attention and concentration**

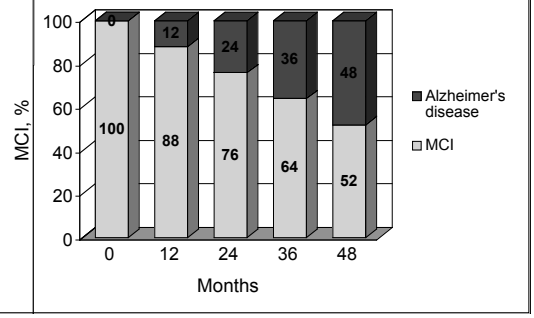
Normal Aging Versus Dementia

- **Minimal memory impairment**
- **Little or no progression of impairment**
- **No functional consequences**

Mild Cognitive Impairment (MCI)

- **Subjective memory complaints**
- **Objective memory impairments**
- **MMSE ≥ 24**
- **No/minor functional impairment**
- **No diagnosis of AD**

Annual Rates of Conversion from MCI to Dementia Over 48 Months



Prevalence of Undetected, Mild Cognitive Impairment – Study Population

Mean age (yrs)	**76**
Female (%)	**58**
Education (yrs)	**16**
Mean MMSE	**28**

	N (%)
Undetected dementia (n = 200)	**22 (11)**
Undetected MCI (n = 179)	**17 (10)**

Source: Hermann, Sager 2002

Summary

Most cognitive impairments in aging due to dementia or pre-dementia

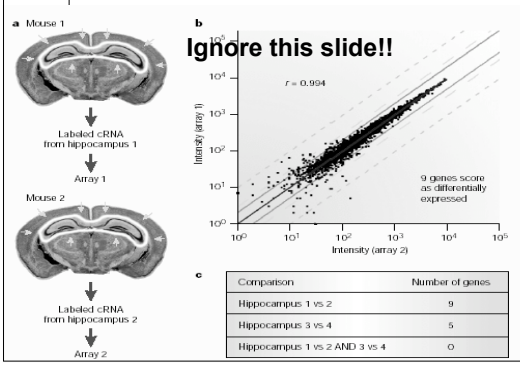
Most dementia is AD

Large heritable component

Large environmental component - e.g., diet

Gene expression among mice of same strain, age, sex, housing [6584 possible genes] (Lockhart & Barlow, 2001)

Ignore this slide!!



Comparison	Number of genes
Hippocampus 1 vs 2	9
Hippocampus 3 vs 4	5
Hippocampus 1 vs 2 AND 3 vs 4	0