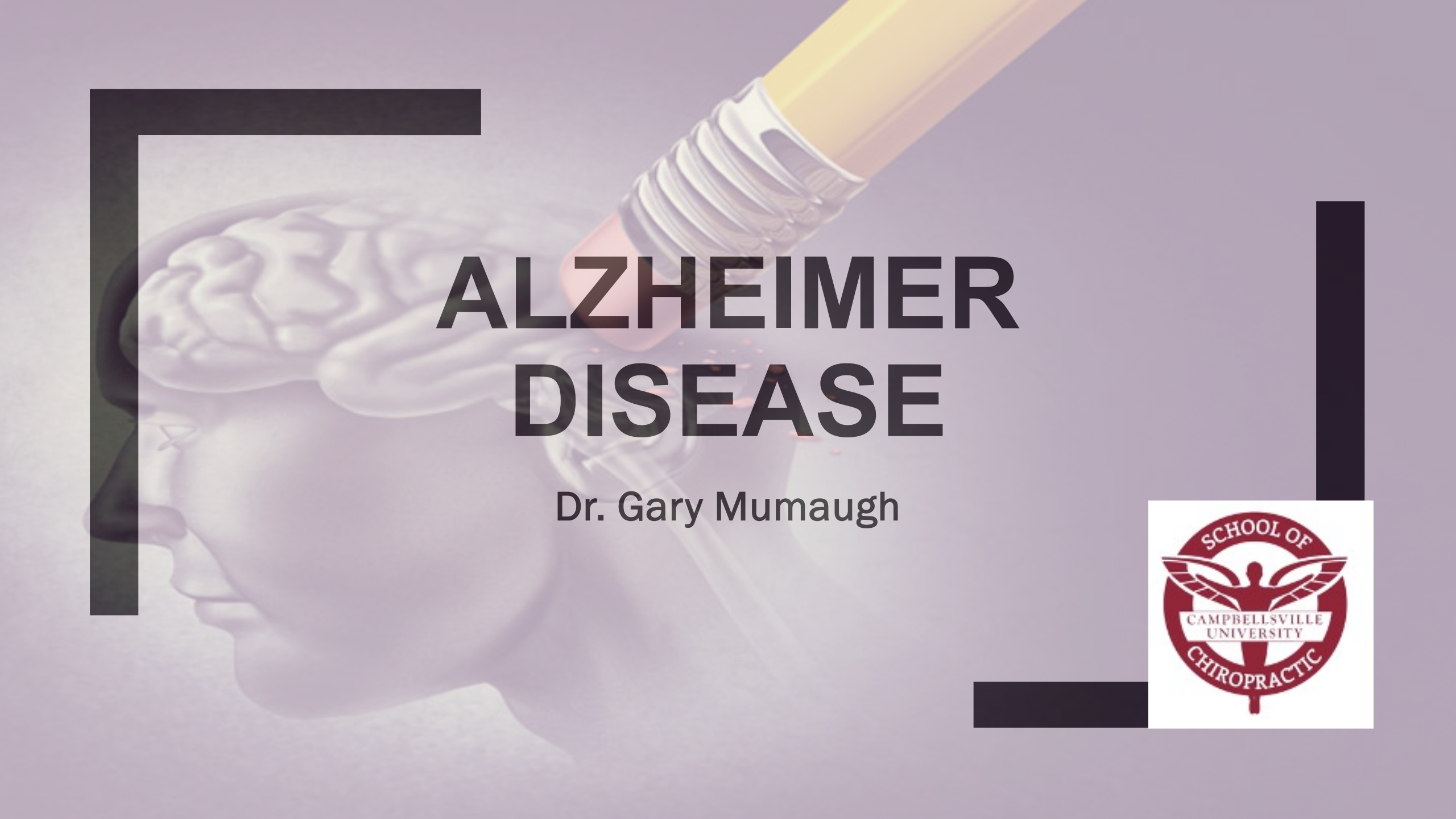
ALZHEIMER DISEASE

Dr. Gary Mumaugh



Introduction

- Alzheimer's disease (AD) is the most common progressive, dementing neurodegenerative disease in elderly, which affects innumerable people each year, and these numbers are likely to further increase as the population ages.
- In addition to the financial burden of AD on health care system, the disease has powerful emotional impact on caregivers and families of those afflicted.

History

- Alois Alzheimer, a German physician, is credited with being the first to describe AD.
- In 1906, Dr. Alzheimer observed a patient, Auguste Deter, in a local asylum who exhibited strange behaviors.
- He followed her care and noted her memory loss, language difficulty and confusion.

- After her death at the age of 51, he examined her brain tissue. The slides showed what are now known as plaques and tangles.
- In 1911, Doctors were using Dr. Alzheimer's research to base diagnosis.
- In the 1960's British pathologists determined that AD was not a rare disease of the young but rather what had been termed "senility."
- In the 1990's researchers identified that the beta amyloid protein was a factor in AD.

Auguste Deter 1851-1906

Alzheimer first met his now famous patient, Mrs Deter, on November 26, 1901. She had been admitted the day before to municipal mental asylum in Frankfurt. She was sitting on the bed with a helpless expression. According to the husband, the couple had been harmoniously married since 1873, but he had recently noticed a gradual decline in his wife. Her symptoms began at age 51 years. For 8 months she had been developing progressive changes in her personality. She presented with ideas of jealousy toward her husband, a rapidly worsening memory weakness and pronounced psychosocial impairment; sometimes she felt that someone wanted to kill her and began to shout wildly. At the clinic, she was disorientated to time and place and confused. Over time, her state generally worsened. Her speech became completely unintelligible. In her final year, she was totally apathetic and spent most of her time in bed with legs pulled up.

Epidemiology

- Main cause of dementia > 65 years
- Starting with 0.5% prevalence at 55 yrs., it doubles every five years
  - 60 years -1%
  - 65 years -2%
  - 70 years - 4%
  - 75 years - 8% and so on
- Risk at the age of 80 years is around 15 to 20%
- About 7.7 million new cases of dementia each year.
- A new case detected in every 4 seconds somewhere in world.

Common Types of Dementia

- Alzheimer's Dementia - 50-55% of cases
- Vascular Dementia - 30-35% of cases
- Lewy Body Dementia - 5-7% of cases
- Pick's Dementia - 3-5 % of cases
- Other Dementias - 10-15 % of cases

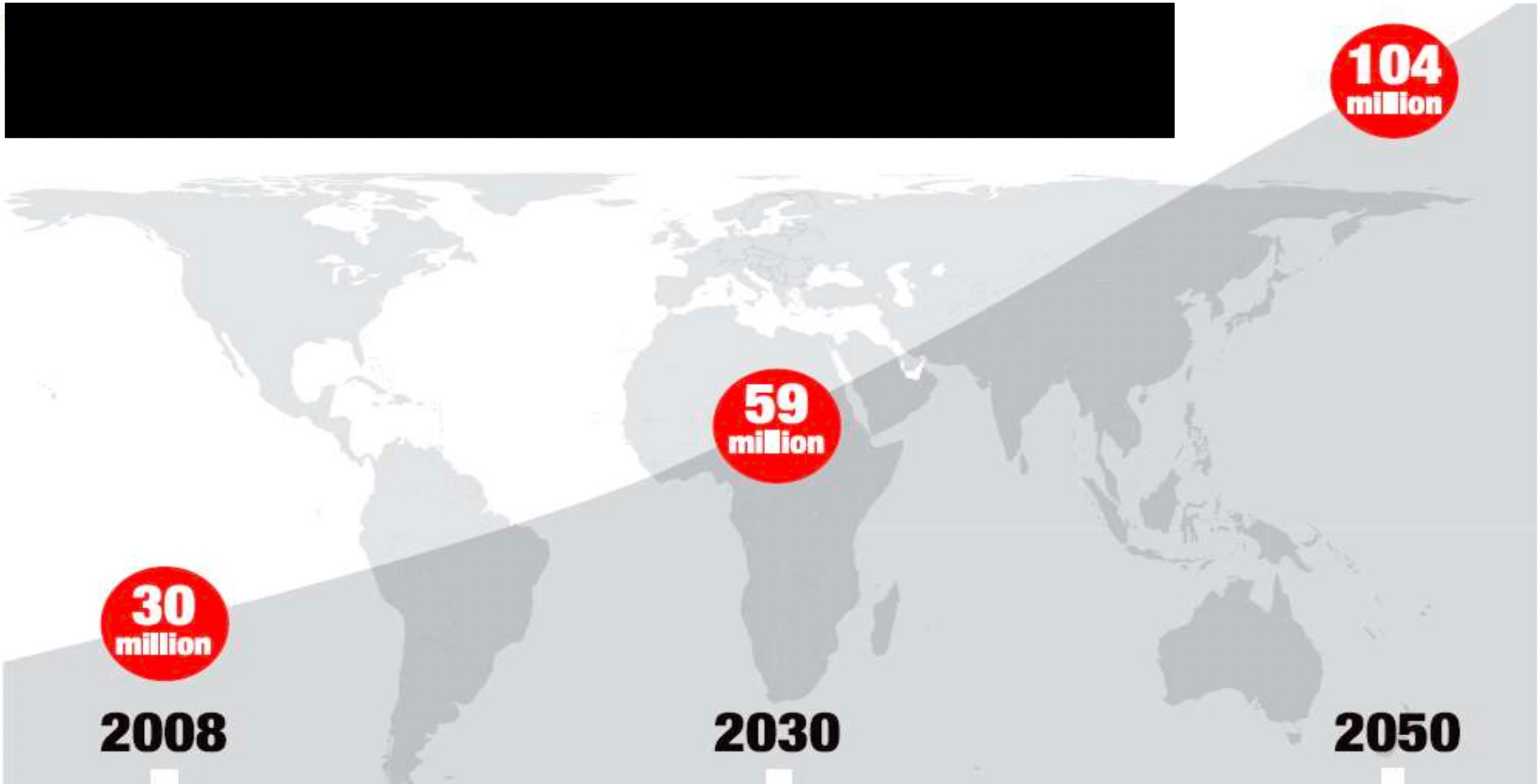
Alzheimer's Is A Type Of Dementia

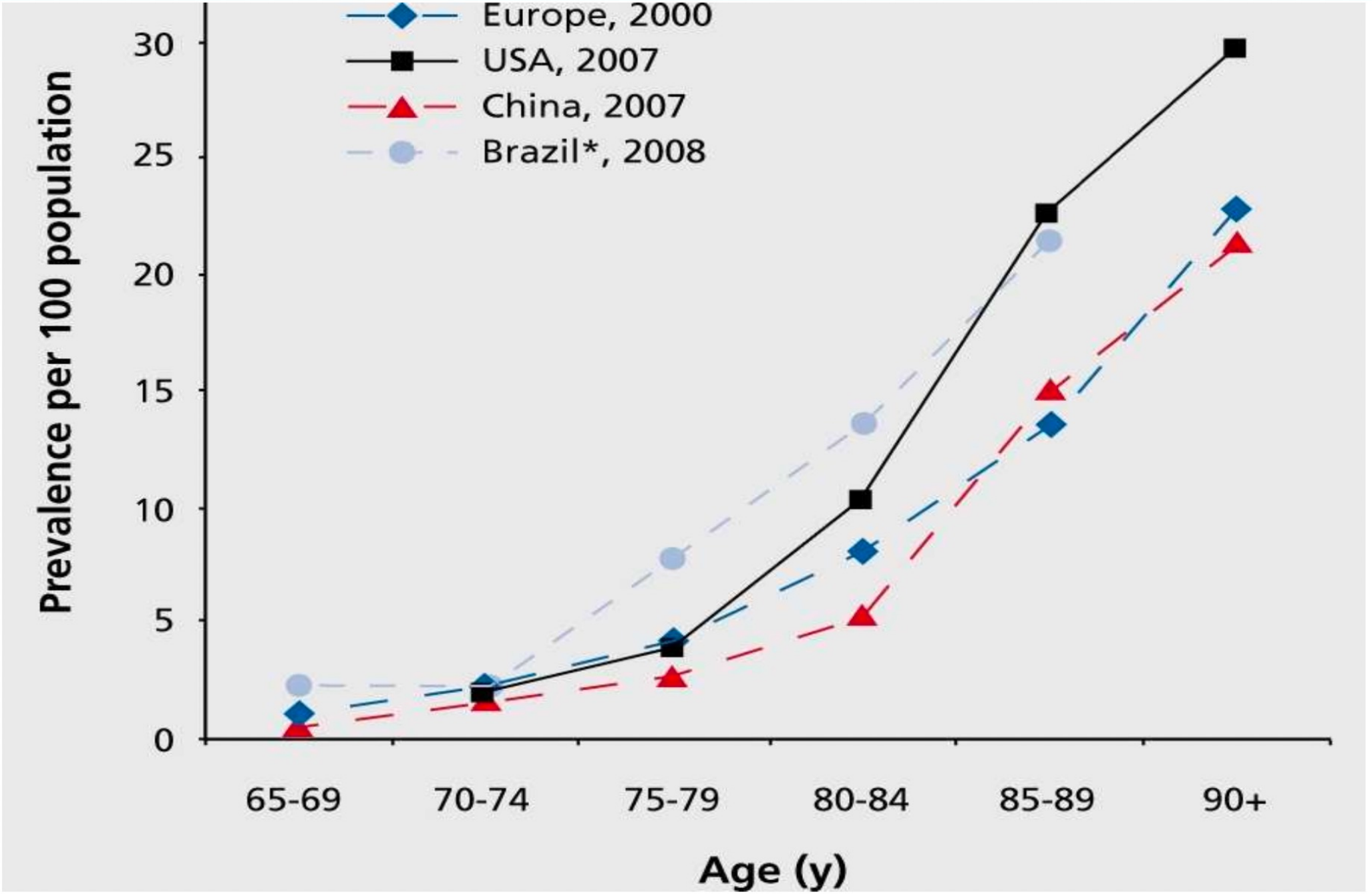
ALZHEIMER'S
is a specific brain disease that accounts for **60-80%** of dementia cases.

DEMENTIA
is a general term for symptoms like decline in **memory, reasoning or other thinking skills.**

Alzheimer's Is A Cause Of Dementia

New Estimate of Dementia Worldwide





Qui et al. (2009). Dialogues in Clinical Neuroscience, 11(2), 111-128.

Risk Factors

- Age
- Family history - strong genetic component
- Females are 2/3 of cases
- More cases in African Americans and Hispanics
- Cardiovascular disease
- Hypertension
- Diabetes
- Not enough aerobic exercise
- Tobacco
- Head injury
- Obesity
- Depression
- Lack of intellectual stimulation/education
- Infrequent social interactions

Protective Factors

- Physical activity
- Increase social interaction
- Antioxidants
- Vitamin C, E, B6 and B12
- Folate
- Omega 3 fatty acid intake
- Speaking > 2 language

Caffeine, Coffee and Alzheimer's

- A 2007 review of observational studies suggested that coffee consumption was associated with a reduced risk of AD by approximately by 30% as compared to non-coffee consumers
- A 2010 review also suggested that daily intake of 3-5 cups of coffee in middle age may lower the risk of the dementia and AD by ab
- A 2017 review concluded that reports indicate that moderate coffee consumption may in fact lower the risk for common neurodegenerative conditions including AD
- A study of 4,615 subjects followed over 5 years found that the use of non-steroidal anti-inflammatory drugs, wine consumption, coffee consumption, and regular physical activity were associated with a reduced risk of AD.
- Interestingly, there was no protection for tea consumers in this study.
- A further study of 1,409 individuals aged 65 to 79 were examined after 21 years' follow-up. Coffee consumption in midlife decreased the risk of AD and dementia in the elderly, with the lowest risk (65% decrease) found in people who drank 3-5 cups/day.
-

AD Pathogenesis

- AD is characterized by generalized cerebral cortical atrophy, neuronal loss, widespread cortical neuritic plaques and neurofibrillary tangles.
- Following mechanisms have been attributed for the development of Alzheimer's dementia
  - Amyloid cascade theory
  - Neuronal loss
  - Cholinergic hypothesis
  - Excitotoxicity
  - Genetic factors

Amyloid Cascade Theory

- Alzheimer’s disease begins with the abnormal build-up of an amyloid protein in the brain from APP (amyloid precursor protein).
- The amyloid cascade hypothesis states that the deposition of the amyloid-β peptide in the brain parenchyma is a crucial step in Alzheimer's disease (AD).
- This concept has influenced and guided much of the academic and pharmaceutical research carried out during the past twenty years.


Changes in Aβ metabolism
• Increase in total Aβ production
• Increase in the Aβ42/Aβ40 ratio
• Reduced Aβ degradation/clearance
Oligomerization of Aβ42 and initial (diffuse) Aβ42 deposits
Subtle effects of soluble Aβ42 oligomers on synaptic function
Inflammatory responses (microglial and astrocytic activation) and amyloid plaque formation
Progressive synaptic/neuronal injury
Altered neuronal ionic homeostasis & oxidative injury
Aberrant oligomerization and hyperphosphorylation of tau
Widespread neuronal dysfunction and cell death associated with neurotransmitter deficits
Dementia with plaque and tangle pathology

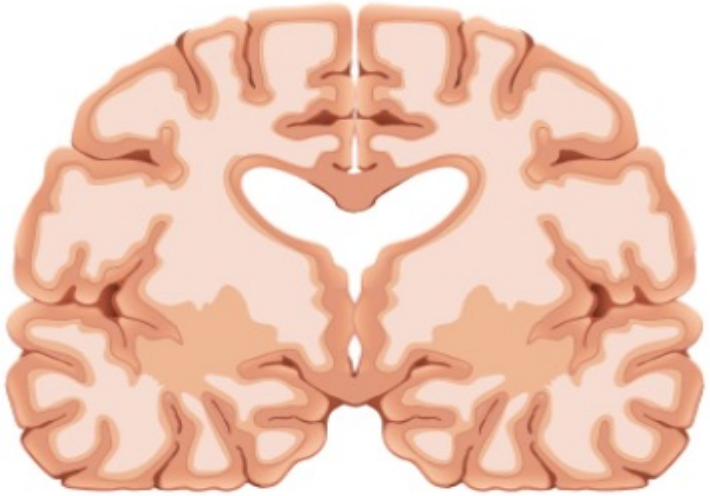
Neuronal Loss

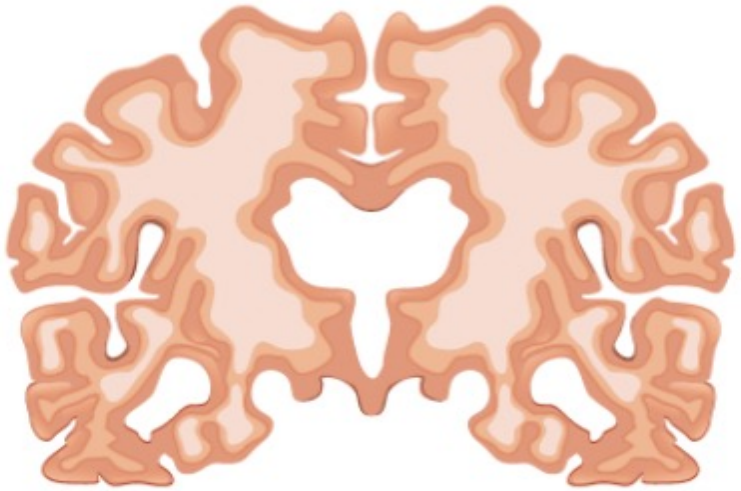
- In Alzheimer's disease, as neurons are injured and die throughout the brain, connections between networks of neurons may break down, and many brain regions begin to shrink.
- By the final stages of Alzheimer's, this process—called brain atrophy—is widespread, causing significant loss of brain volume.

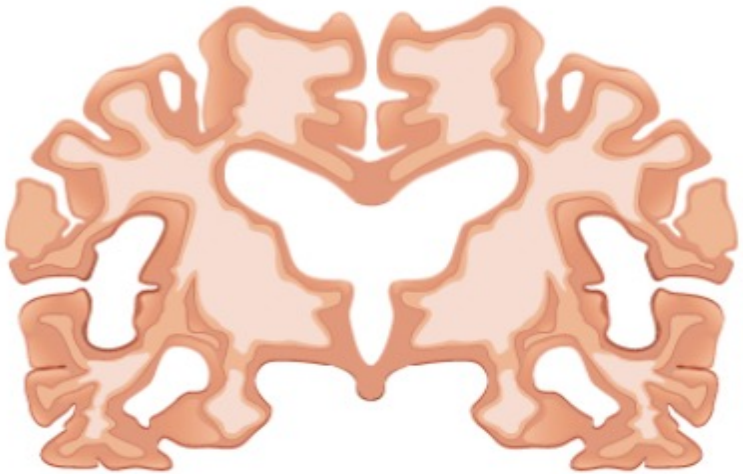
Neuronal Loss

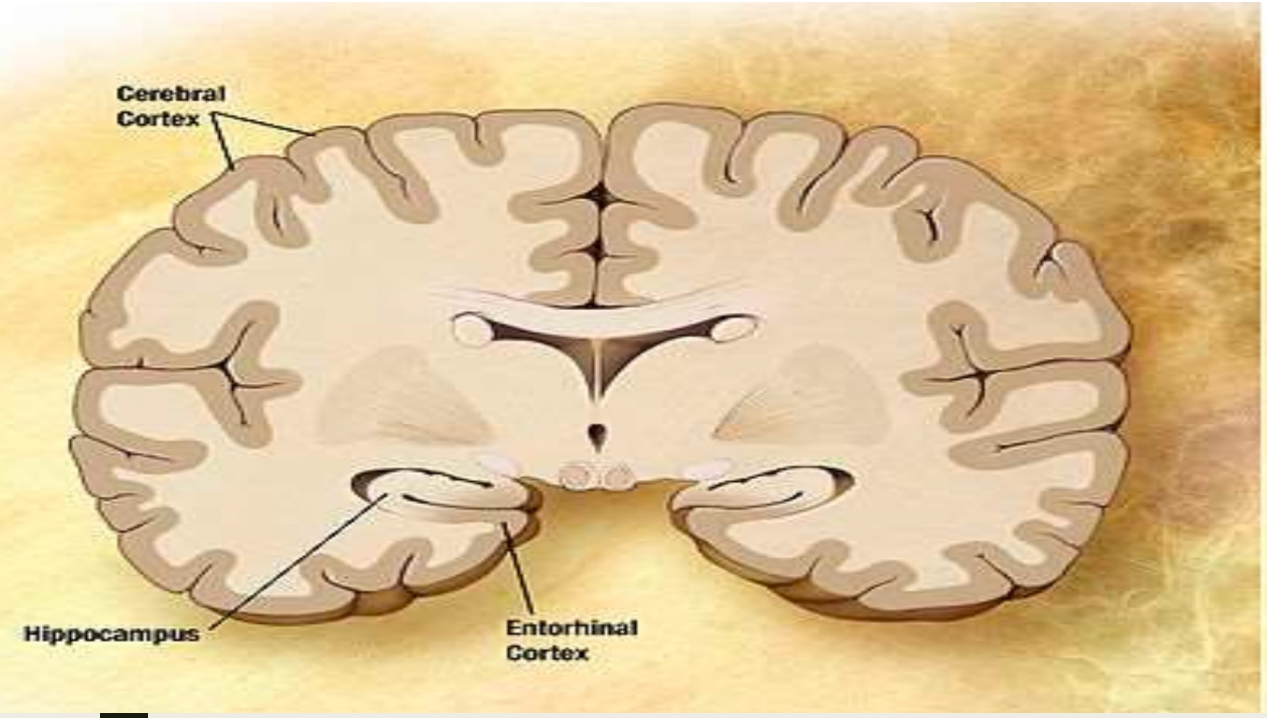
- The classic gross neuro- anatomical observation is
  - Diffuse atrophy with widening cortical sulci
  - Enlarged cerebral ventricles.
  - There is a progressive loss of neurons and their supportive glial cells.
  - The loss is more marked in the entorhinal cortex, hippocampus and basal forebrain.

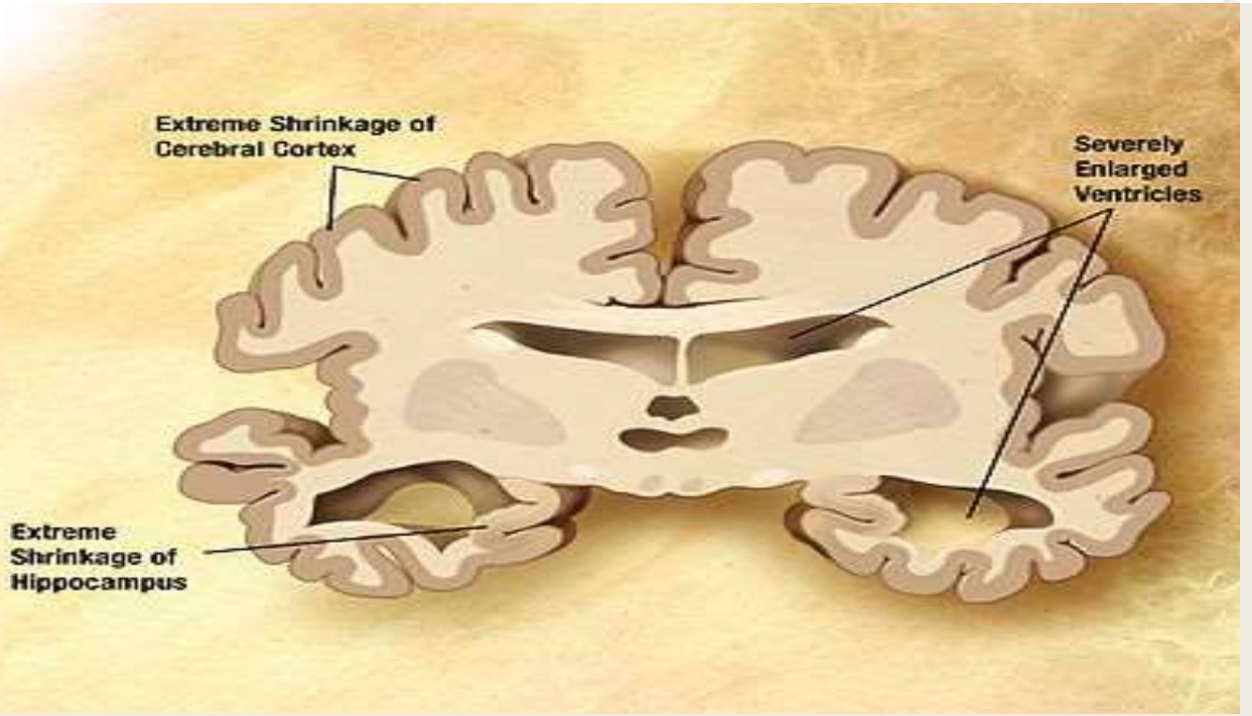
Progression of Alzheimer's Disease

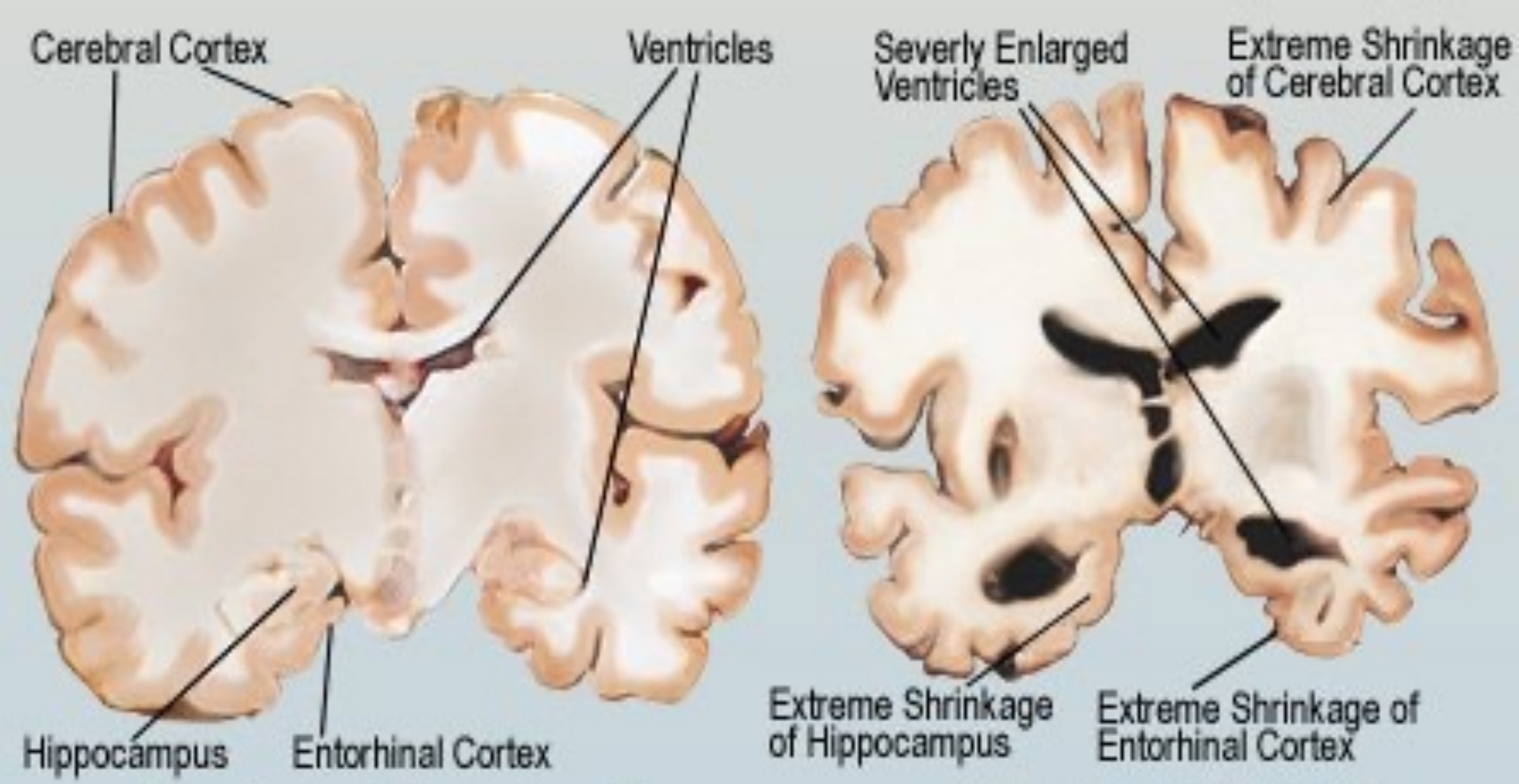


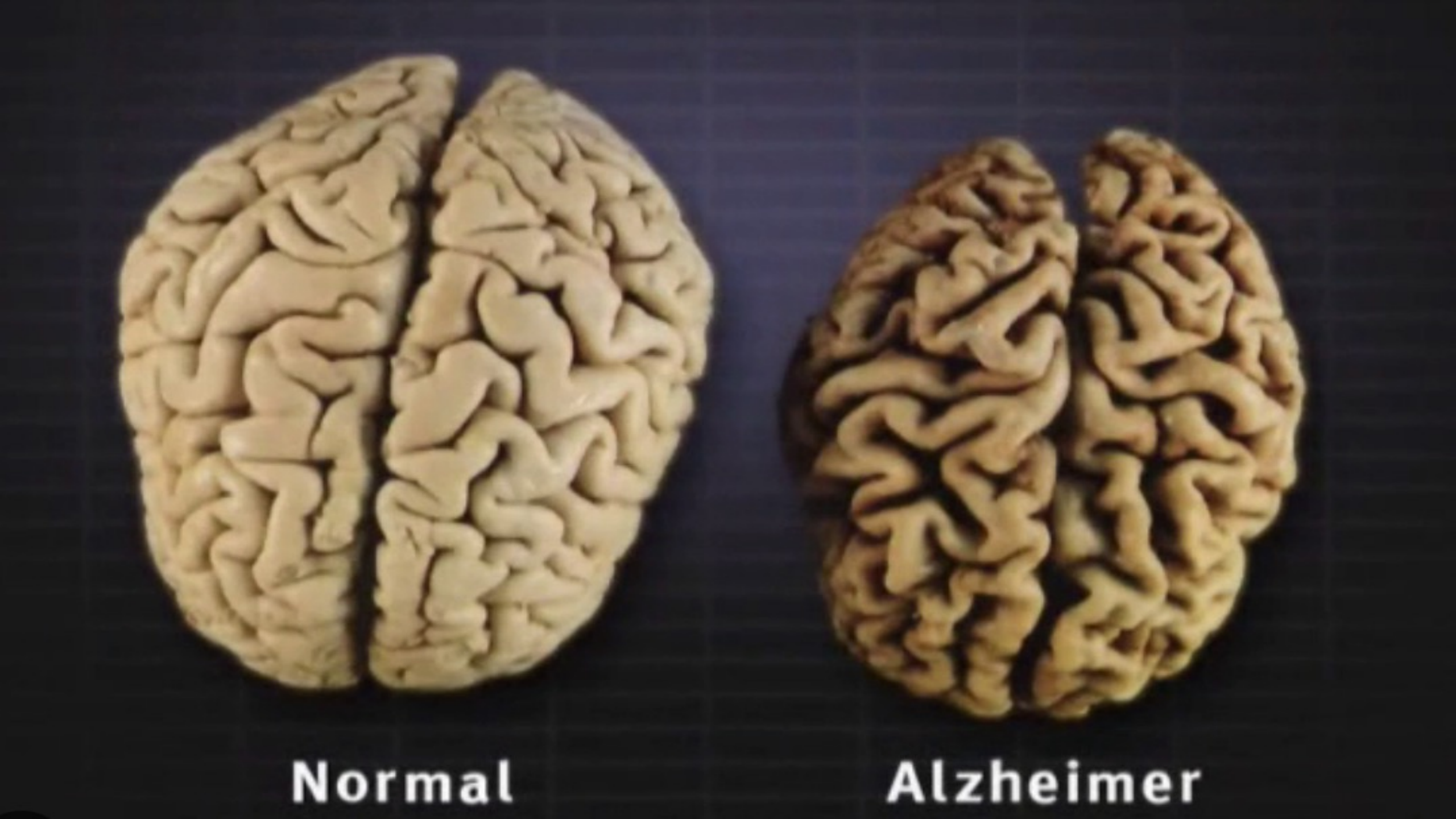


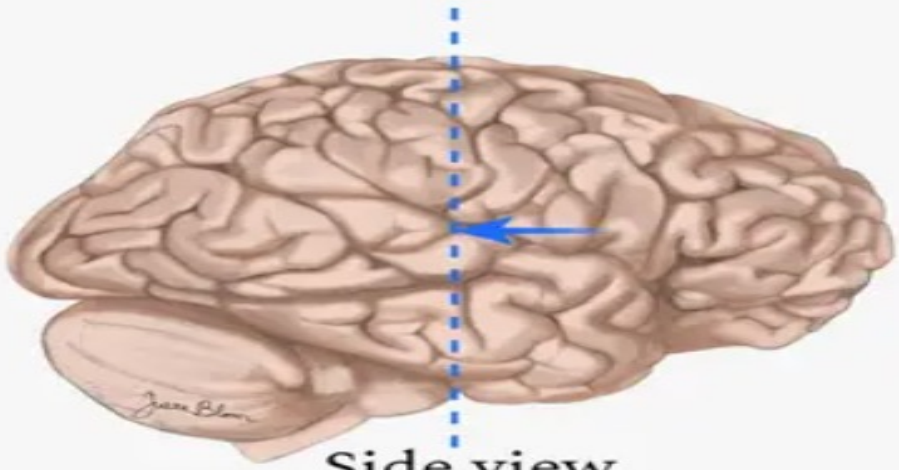




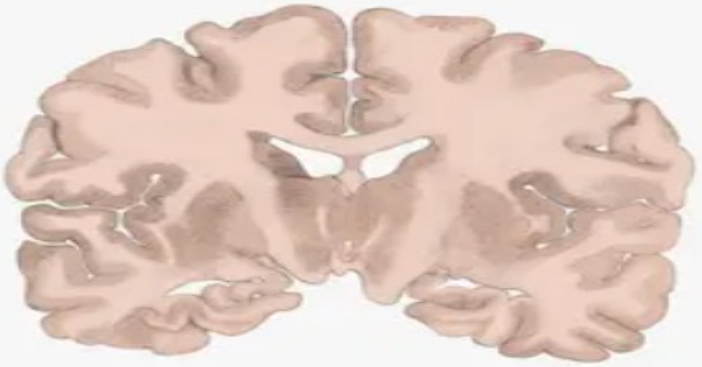



Cerebral Cortex
Ventricles
Hippocampus
Entorhinal Cortex
Preclinical Alzheimer's
Severly Enlarged Ventricles
Extreme Shrinkage of Cerebral Cortex
Extreme Shrinkage of Hippocampus
Extreme Shrinkage of Entorhinal Cortex
Severe Alzheimer's


Normal
Alzheimer

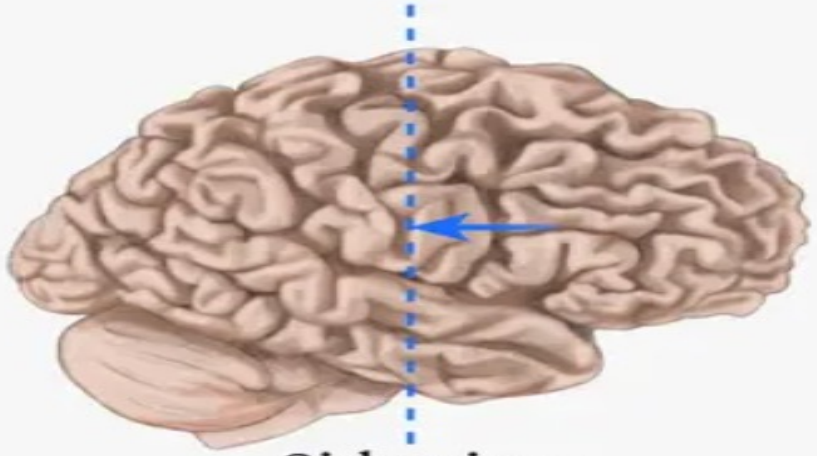


Side view

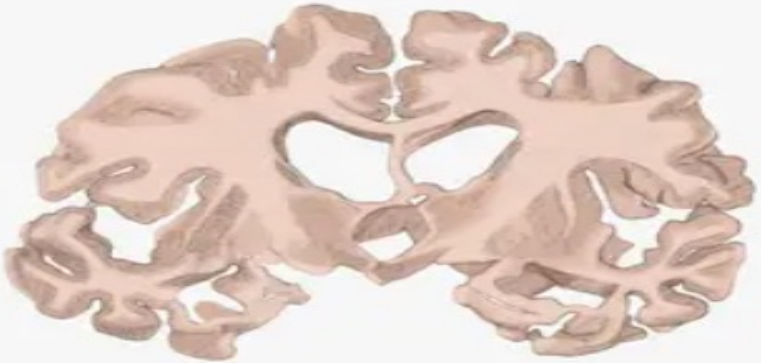


Cross-section

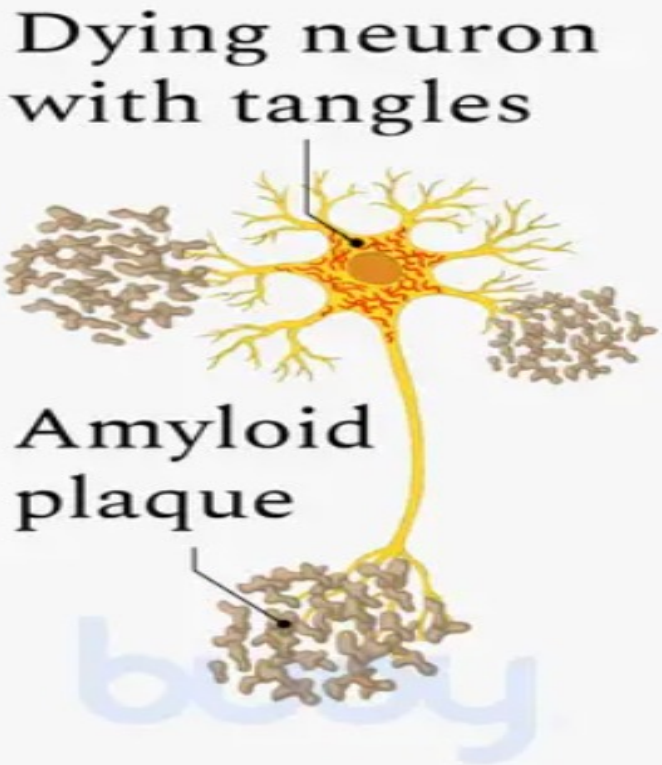
Healthy brain



Side view



Cross-section



Alzheimer's disease

Cholinergic Hypothesis

- The cholinergic hypothesis was initially presented over 20 years ago and suggests that a dysfunction of acetylcholine containing neurons in the brain contributes substantially to the cognitive decline observed in those with AD.
- Levels of acetylcholine, noradrenaline, serotonin, GABA, glutamate, somatostatin, neuropeptide, and substance P have all been documented to be reduced in the brains of AD patients.
- Reductions in acetylcholine and choline acetyltransferase are the most profound.
- Neuronal loss in the basal forebrain, which is the major region from which cholinergic projections originate.

Excitotoxicity

- Excessive release of glutamate into the synapses.
- Excessive influx of calcium into the cells leading to cell death called excitotoxicity.
- Glutamate-mediated neurotoxicity has been implicated in the pathogenesis of Alzheimer's disease (AD).
- Glutamate is the most abundant excitatory neurotransmitter in the mammalian central nervous system (CNS) and is involved in almost all CNS functions.

Genetic Factors and AD

- There are two types of Alzheimer's—early-onset and late-onset.
- Both types have a genetic component.

Early-Onset Alzheimer's Disease

- Early-onset Alzheimer’s disease is rare, representing less than 10 percent of all people with Alzheimer’s.
- It typically occurs between a person’s 30s and mid-60s.
- Some cases are caused by an inherited change in one of three genes

Early-Onset AD

- The three single-gene mutations associated with early-onset Alzheimer's disease are:
  - Amyloid precursor protein (APP) on chromosome 21
  - Presenilin 1 (PSEN1) on chromosome 14
  - Presenilin 2 (PSEN2) on chromosome 1
- Mutations in these genes result in the production of abnormal proteins that are associated with the disease.
- Each of these mutations plays a role in the breakdown of APP, a protein whose precise function is not yet fully understood.
- This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of Alzheimer's disease.

Late-Onset AD

- Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in their mid-60s and later.
- Researchers have found several genes that increase the risk of Alzheimer’s.
- APOE-e4 is the first risk gene identified and remains the gene with strongest impact on risk.
- Researchers estimate that between 40-65% of people diagnosed with Alzheimer's have the APOE-e4 gene.

Genetics and AD

- A child whose biological mother or father carries a genetic mutation for one of these three genes has a 50/50 chance of inheriting that mutation.
- If the mutation is in fact inherited, the child has a very strong probability of developing early-onset Alzheimer's disease.
- An estimated 20-30% of individuals in the United States have one or two copies of APOE-e4
- Approximately 2% of the U.S. population has two copies of APOE-e4.

Signs and Symptoms of AD

Mild AD	Moderate AD	Severe AD
• Forgetfulness	• Disorientation	• Agnosia } More pronounced
• Word finding difficulty	• ↑ memory loss	• Apraxia } More pronounced
• Apathy	• Confusion	• Aggression
• Poor attention	• Insomnia	• Agitation
• Difficulty with complex tasks	• Wandering	• Incontinence
• Depression	• Speech difficulty	• Poor basic ADLs
• Work trouble	• Restlessness	• Gait disturbance
	• Difficulty with IADLs	

Who should be evaluated for AD?

- Age more than 60 years
- People with risk factors – head injury, CV risks
- People with memory or cognitive complaints, with or without change in functioning.
- Memory difficulty noted by friends, relatives or spouse.
- Patient with depression or anxiety without memory complaints

Assessment

- Family History
  - Patient
  - Relatives
- Assessment
  - Comprehensive physical and neurological examination
  - Cognitive evaluation
  - Functioning status
  - Lab work
  - Imaging

History

- Memory impairment – trouble remembering recent conversation, events, appointments, frequently misplaces objects.
- Executive impairment – deterioration of complex task performance, decreased ability to solve problems, impaired driving.
- Drugs
- Focal motor or sensory symptoms
- Behavior personality and mood changes

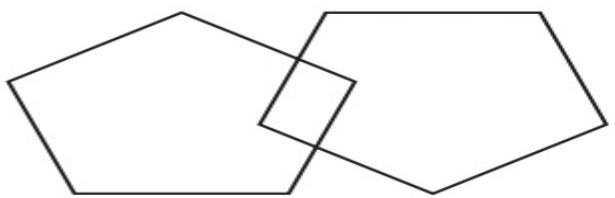
Screening Tools

- Mini Mental State Examination (MMSE) (Folstein et al. 1975)
- St. Louis University Mental State (SLUMS) Exm. (JE Morley, 2000)
- Clock Drawing Test (CDT) (Shulman et al. 1993)
- Bender Gestalt Test (BGT) (Lauretta Bender, 1938)
- Hachinski Ischemic Scale (1975)
- Alzheimer's Disease Assessment Scale (Rosen et al. 1984)
- Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1996)
- Clinical Dementia Rating (Morris, 1993)
- Blessed Dementia Scale (Blessed, 1968)

The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.

Mini-Mental State Exam Scoring

Score	Interpretation
24 - 30	"Normal" range
20 - 23	Mild cognitive impairment or possible early-stage/ mild Alzheimer's disease
10 - 19	Middle-stage/moderate Alzheimer's disease
0 - 9	Late-stage/severe Alzheimer's disease

MMSE Scores & Education Levels

- In higher education levels, the MMSE scores increase and the range of scores narrow.
- Patients with lower education may receive a false positive diagnosis, and conversely, individuals with higher education level may mask any mild cognitive impairment (false negative).

Hachinski ischemic score

Feature	Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
Hypertension	1
History of stroke	2
Associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

A high score (≥7) suggests vascular dementia, while a low score (≤4) suggests Alzheimer disease.

The Lawton Instrumental Activities of Daily Living Scale

A. Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at all 0

B. Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

C. Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

D. Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

E. Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc. 1
3. All laundry must be done by others 0

F. Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

G. Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

H. Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

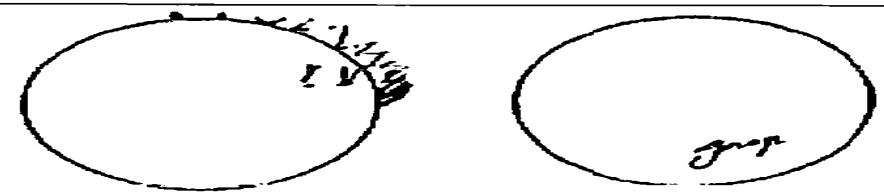
How the Clock-Drawing Test Screens for Dementia

A clinician asks the patient to draw a clock showing a specific time

An abnormally completed clock is cause for further evaluation

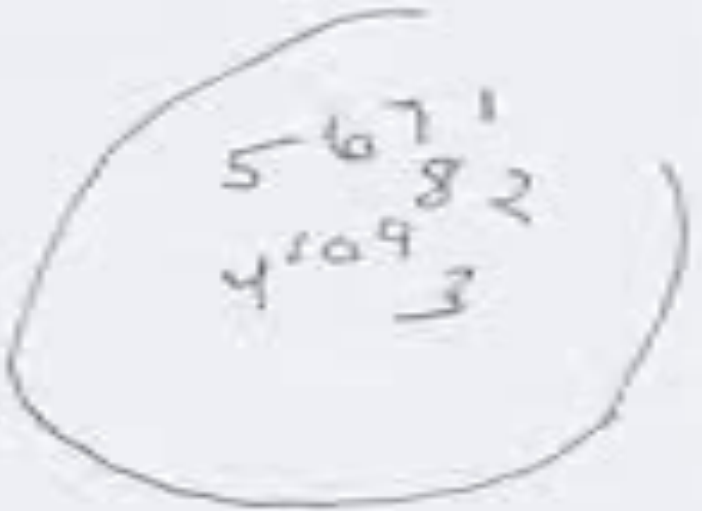
A normal clock indicates the absence of dementia

verywell

1. Perfect	
2. Minor visuospatial errors *Examples* - Mildly impaired spacing of times - Draws times outside circle - Turns page while writing numbers so that some numbers appear upside down - Draws in lines (spokes) to orient spacing	
3. Inaccurate representation of 10 after 11 when visuospatial organization is perfect or shows only minor deviations. *Examples* - Minute hand points to 10 - Writes '10 after 11' - Unable to make any denotation of time	
4. Moderate visuospatial disorganization of times such that accurate denotation of 10 after 11 is impossible. *Example* - Moderately poor spacing - Omits numbers - Perseveration — repeats circle or continues on past 12 to 13, 14, 15 etc. - Right-left reversal — numbers drawn counter clockwise - Dysgraphia — unable to write numbers accurately	
5. Severe level of disorganization as described in 4.	
6. No reasonable representation of a clock Exclude severe depression or other psychotic states. *Examples* - No attempt at all - No semblance of a clock at all - Writes a word or name	

Normal

MCI, early AD



Late AD

Healthy

Alzheimer's

Parkinson's

Patient Name:_____ **Date:**_____
Patient ID #_____

Katz Index of Independence in Activities of Daily Living

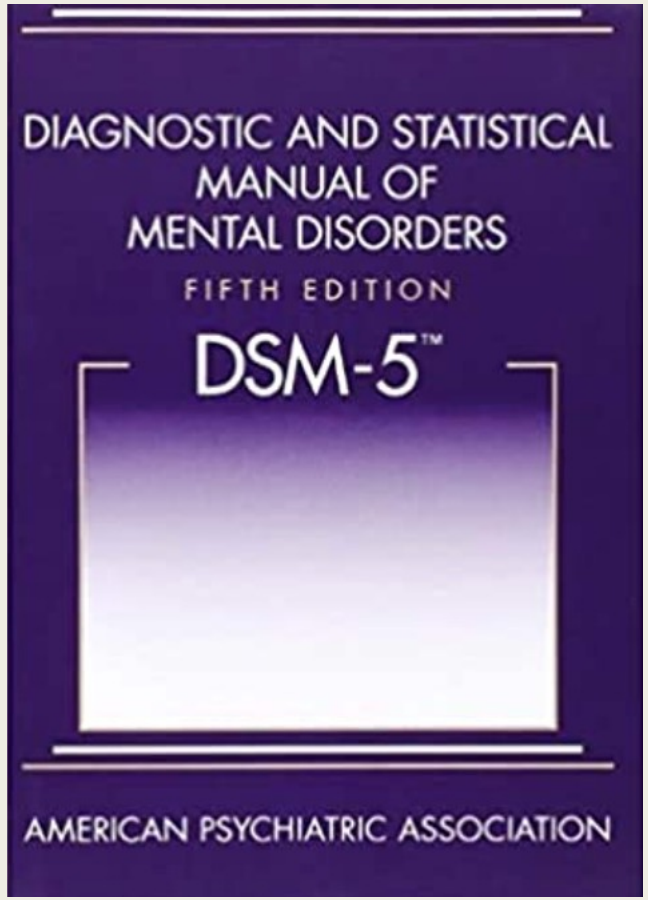
Activities Points (1 or 0)	**Independence** (1 Point) **NO** supervision, direction or personal assistance.	**Dependence** (0 Points) **WITH** supervision, direction, personal assistance or total care.
BATHING Points: _____	**(1 POINT)** Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 POINTS)** Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing
DRESSING Points: _____	**(1 POINT)** Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 POINTS)** Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	**(1 POINT)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 POINTS)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	**(1 POINT)** Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	**(0 POINTS)** Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	**(1 POINT)** Exercises complete self control over urination and defecation.	**(0 POINTS)** Is partially or totally incontinent of bowel or bladder
FEEDING Points: _____	**(1 POINT)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 POINTS)** Needs partial or total help with feeding or requires parenteral feeding.

TOTAL POINTS: _____ **SCORING:** 6 = High (*patient independent*) 0 = Low (*patient very dependent*

DIAGNOSTIC CRITERIA
DIFFERENTIAL DIAGNOSIS

DSM V Criteria

- NEUROCOGNITIVE DIORDERS
  - DELIRIUM
  - MAJOR NEUROCOGNITIVE DISORDERS
  - MILD NEUROCOGNITIVE DISORDERS



Mild NCD

- Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains based on:
  - Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
  - A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- The cognitive deficits do not interfere with capacity for independence in everyday activities

Mild NCD

- The cognitive deficits do not occur exclusively in the context of delirium.
- The cognitive deficits are not better explained by another mental disorder.
  - Specify: Without behavioral disturbance
  - Specify: With behavioral disturbance
- Specify whether due to
  - Alzheimer’s disease
  - FTD
  - Vascular
  - TBI
  - Substance/medication use .....
  - Unspecified

Major NCD

- Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on:
  1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
  2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- The cognitive deficits interfere with independence in everyday activities.

- The cognitive deficits do not occur exclusively in the context of delirium.
- The cognitive deficits are not better explained by another mental disorder.
  - Specify: Without behavioral disturbance
  - Specify: With behavioral disturbance
- Specify whether due to
  - Alzheimer's disease
  - FTD
  - Vascular
  - TBI
  - Substance/medication use .....
  - Unspecified

Major or Mild NCD Due to Alzheimer's

- The criteria are met for major or mild neurocognitive disorder.
- There is insidious onset and gradual progression of impairment in one or more cognitive domains.
- Criteria are met for either probable or possible Alzheimer's disease as follows:
  - For major neurocognitive disorder
  - For mild neurocognitive disorder

For major neurocognitive disorder

- Probable Alzheimer’s disease is diagnosed if either of the following is present; otherwise, possible Alzheimer ’s disease should be diagnosed.
- Evidence of a causative Alzheimer ’s disease genetic mutation from family history or genetic testing.
- All 3 of the following are present:
  - Clear evidence of decline in memory and learning and at least one other cognitive domain.
  - Steadily progressive, gradual decline in cognition, without extended plateaus.
  - No evidence of mixed etiology

For mild neurocognitive disorder

- Probable Alzheimer’s disease is diagnosed if Evidence of a causative Alzheimer’s disease genetic mutation from family history or genetic testing.
- Possible Alzheimer’s disease is diagnosed if there is no Evidence of a causative Alzheimer ’s disease genetic mutation from family history or genetic testing.

DIAGNOSIS
(ALZHEIMERS ASSOCIATION 2011)
3 Stages of AD

- Preclinical AD requires measurable changes in biomarkers and/or poor performance on challenging cognitive tests.
- MCI - mild changes in memory and other cognitive abilities; these changes can be detected through careful evaluation, but do not interfere with day-to-day activities.
- Dementia - changes in two or more aspects of cognition and behavior that interfere with function in everyday life.

DIFFERENTIAL DIAGNOSIS

- Dementias of other types
- Delirium
- Depression
- Schizophrenia
- Normal aging
- Mental retardation

Pseudodementia	Dementia
Informant aware of memory disturbance and can date the onset accurately	Onset is insidious and informant usually can not date onset.
Patient complains enthusiastically about the memory loss	Unlikely
Questions about cognitive functions lead to DON'T KNOW RESPONSE accompanied by irritation	Try their best but are incorrect
History is usually short and often there is a previous history of depressive episode	History is long and depressive episode may or may not be present
Depressed patients perform better on memory tests.	Don't perform well
Memory complains are accompanied by insomnia, diurnal variation etc.	May or may not be present

Feature	Delirium	Dementia
Onset	Insidious	Sudden
Duration	Months to years	Hours to week
Attention	Preserved	Fluctuates
Memory	Impaired	Impaired recent and immediate
Speech	Word finding difficulty	Incoherent
Sleep & wake cycle	Fragmented sleep	Disrupted sleep, day night reversal
Thoughts	Impoverished	Disorganized
Awareness	Unchanged	Reduced
Alertness	Usually normal	Hypervigilant or reduced vigilance

Characteristics	Alzheimer's Disease	Vascular Dementia
Sex	Women	Men
Age	Generally over age 75 years	Generally over age 60 years
Onset & progression	Gradually progressive	Episodic with stepwise deterioration
History of hypertension	Less common	Common
History of stroke(s) Transient Ischemic Attack(s),or neurological symptoms	Less common	Common
Hypertension	Less common	Common
Focal neurological signs	Uncommon	
Emotional lability (sudden mood changes)	Less common	More Common
Cognitive deficits	Uniform	Patchy

Picks Disease
Frontotemporal Dementia

- Picks Disease - FTD
- Alzheimer's Facts and Figures

Features	Pick’s Disease (FTD)	Alzheimer's
Personality change	Early	Late
Amnesia	Late	Early
Language disturbances	Early	Late
Stereotypes	Early	Mid or Late
Apraxia, agnosia, alexia	Late	Variable
Kluver-Bucy syndrome	Early	Late
Visuospatial disorientation	Rare	Common
Age of risk	Mean 50, up to 80yrs	Risk increases with age
CT Scan	Fronto-Temporal atrophy	Widespread atrophy
Gross Pathology	Anterior hemisphere atrophy	Posterior hemisphere atrophy
Histopathology	Pick’s bodies	Neurofibrillary tangle

Preventive Measures

- Exercise regularly
- Eat a healthy diet rich in fruits and vegetables
- Engage in social and intellectually stimulating activities
- Control type 2 diabetes
- Lower high blood pressure levels
- Lower high blood cholesterol levels
- Maintain a healthy weight
- Stop smoking
- Get treatment for depression

Still Alice - Lost

Still Alice - The Art of Losing