

DEMENTIA

Sandira V. Segaram M.D.
FACP

A BRIEF OVERVIEW

FINANCIAL INTERESTS

- ◉ I am in the speaker Bureau of Warner Chilcott (US) LLC, for osteoporosis.
- ◉ I have no financial interest in any company which makes medications for dementia.

LEARNING OBJECTIVES

1. What is dementia?
2. What are the types of dementia?
3. Pathophysiology of Alzheimer's dementia
4. Treatment of Dementia
5. New Horizons in the treatment of patients with dementia

DEMENTIA DEFINITION

Dementia is....

- ❖ A chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning

INCIDENCE

- ◉ Dementia may occur at any age but affects primarily the elderly (about 5% of those aged 65 to 74 and 40% of those > 85).
- ◉ It accounts for more than half of nursing home admissions.
- ◉ At least 5 million people in the US have dementia.



CAUSES OF DEMENTIA

- ❖ Most types of dementia are **nonreversible** (degenerative).
- ❖ Alzheimer's disease is the most common type of dementia.
- ❖ Lewy body disease (LBD) is a leading cause of dementia in elderly adults
- ❖ Vascular dementia; dementia caused by multiple small strokes.
- ❖ Parkinson's disease

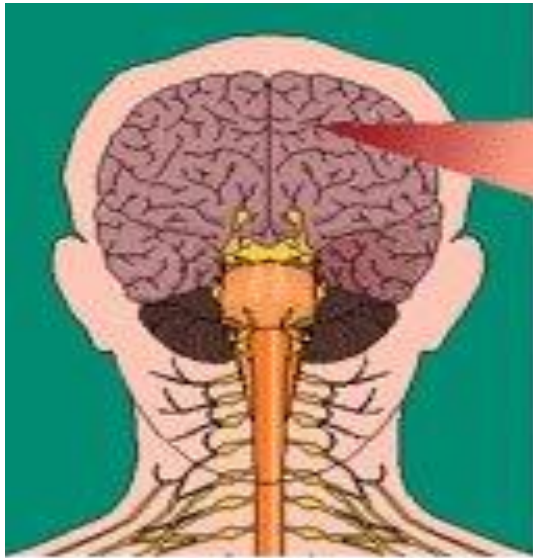
Genetics

- 1st degree relative of a subject with late onset AD has 2x the expected risk of acquiring the disease.
- Concordance rate in twin studies
(Swedish registry) :
 - 59 % for monozygotic twins
 - 35 % for same sex dizygotic twins
 - 24 % for opposite sex dizygotic twins

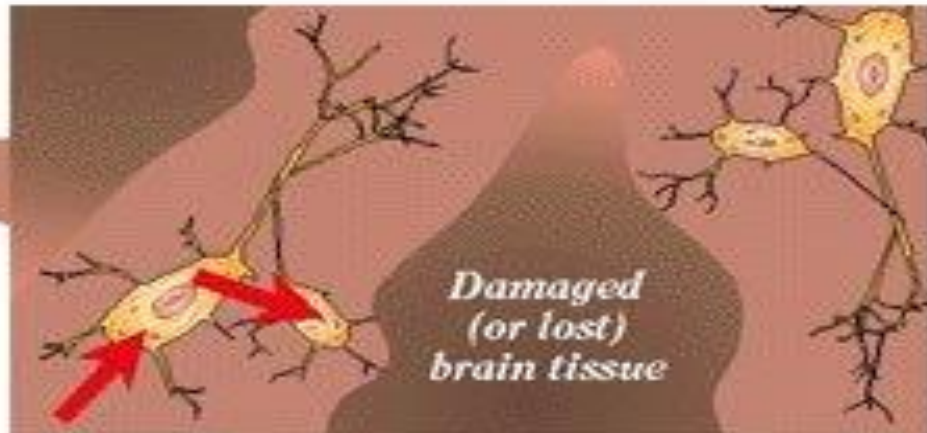
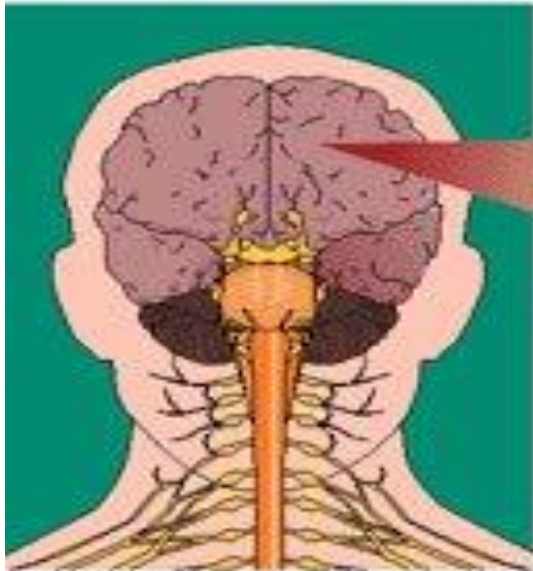
ALZHEIMER'S DISEASE (AD)

- ❖ AD is the **most common** cause of dementia
- ❖ Symptoms of AD begin slowly with memory loss.
- ❖ 3 hallmarks of AD disease process:
 - ⦿ **Amyloid plaques**, - fragments of a protein called beta-amyloid peptide mixed with a collection of additional proteins, remnants of neurons, and bits and pieces of other nerve cells.
 - ⦿ **Neurofibrillary tangles (NFTs)**, found inside neurons, are abnormal collections of a protein called **tau**. Normal tau is required for healthy neurons. However, in AD, tau clumps together causing loss of neuronal function.
 - ⦿ **Loss of connections between neurons responsible for memory and learning**. Neurons can't survive when they lose their connections to other neurons. As neurons die throughout the brain, the affected regions begin to atrophy, or shrink. By the final stage of AD, damage is widespread and brain tissue has shrunk significantly.

ALZHEIMER'S DISEASE

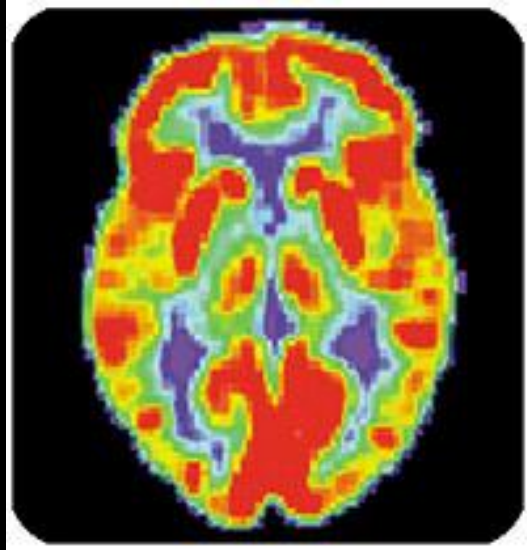


Cells within the brain (*neurons*) transport electrical messages to other parts of the body using chemical transmitters (*neurotransmitters*).



In *Alzheimer's Disease*, areas of the brain tissue are damaged and some messages do not transmit, causing the symptoms of the disease.

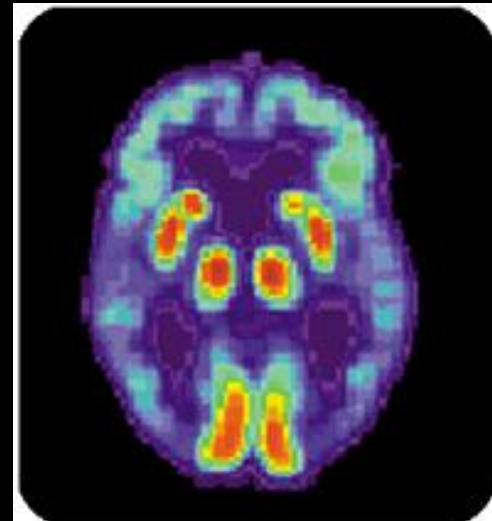
AD and the Brain



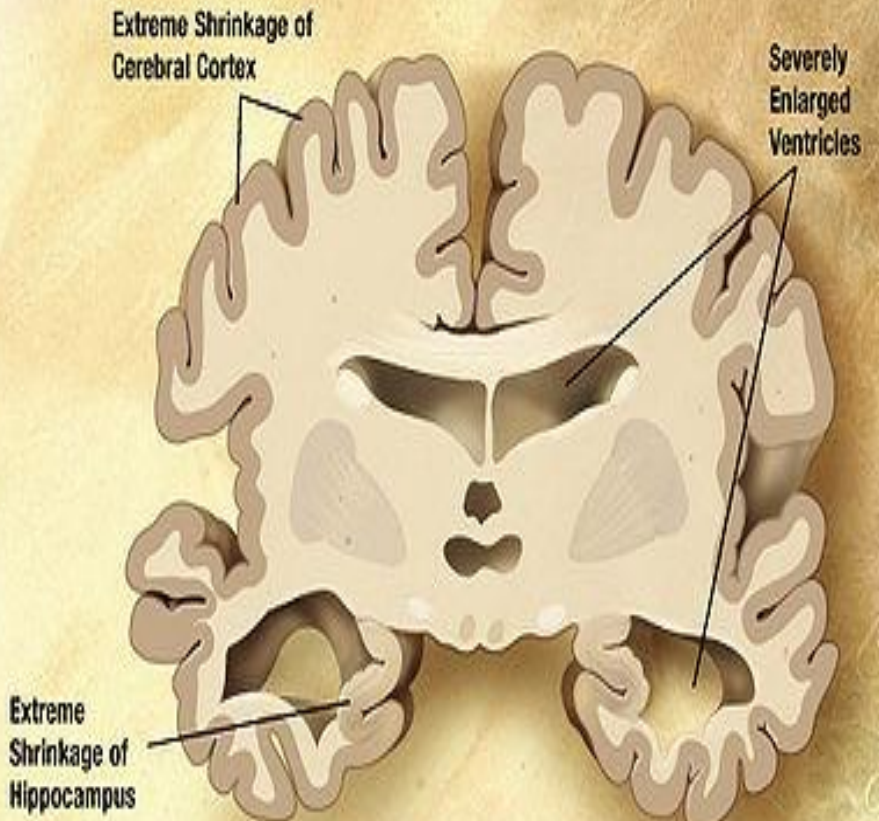
Pet Scan of
Normal Brain

The Changing Brain in Alzheimer's Disease

No one knows what causes AD to begin, but we do know a lot about what happens in the brain once AD takes hold.



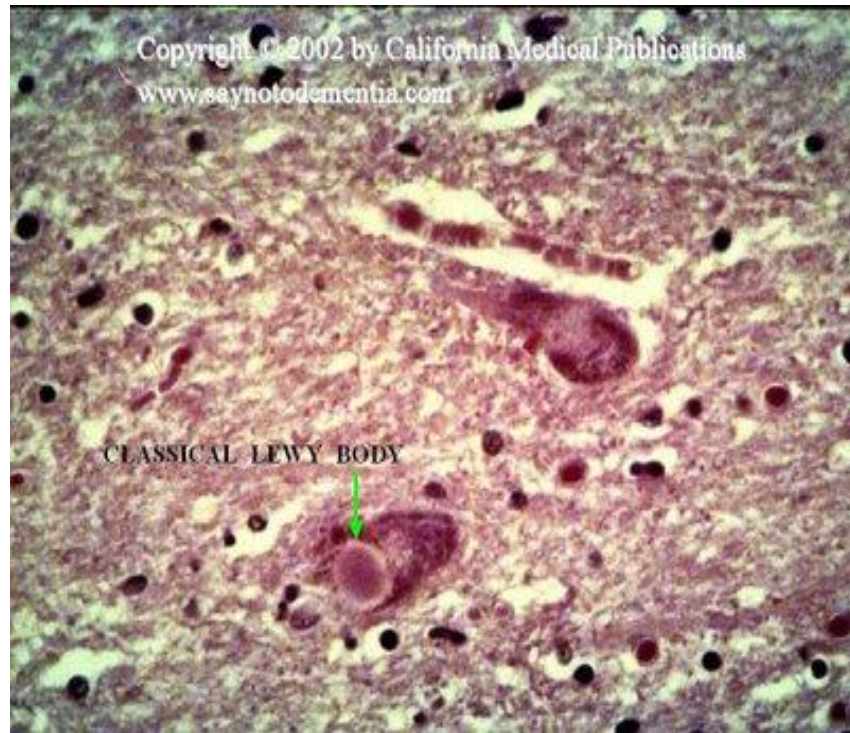
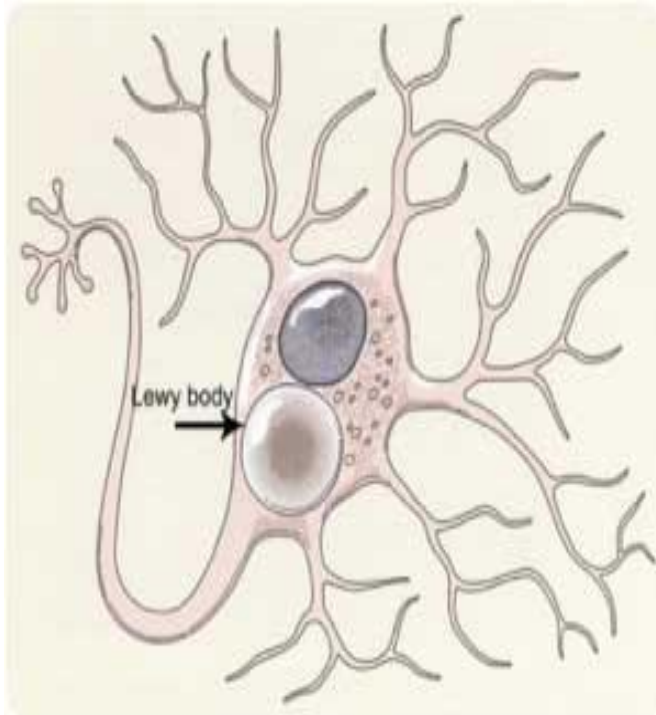
Pet Scan of Alzheimer's
Disease Brain



LEWY BODY DEMENTIA(LBD)

- ❖ Chronic cognitive deterioration characterized by cellular inclusions called Lewy bodies in the cytoplasm of cortical neurons.
- ❖ 3rd most common dementia. Age of onset is typically > 60
- ❖ Visual hallucinations are common and often threatening.
- ❖ Fluctuating cognitive function is a relatively specific feature of Lewy body dementia

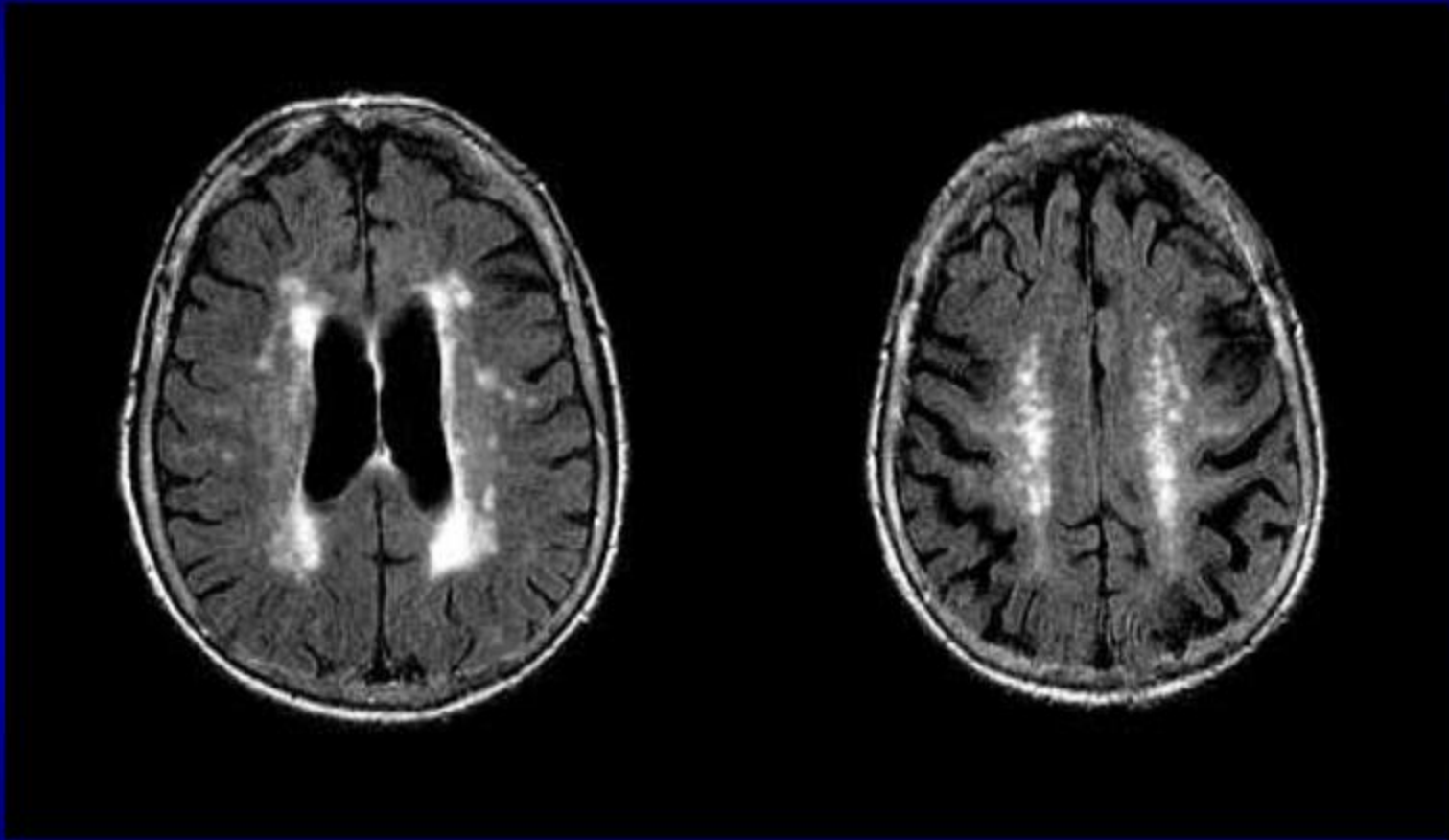
LEWY BODIES (LBS) — ABNORMAL ALPHA SYNUCLEIN FILAMENTS FOUND IN NEURONS



VASCULAR DEMENTIA OR MULTI INFARCT DEMENTIA

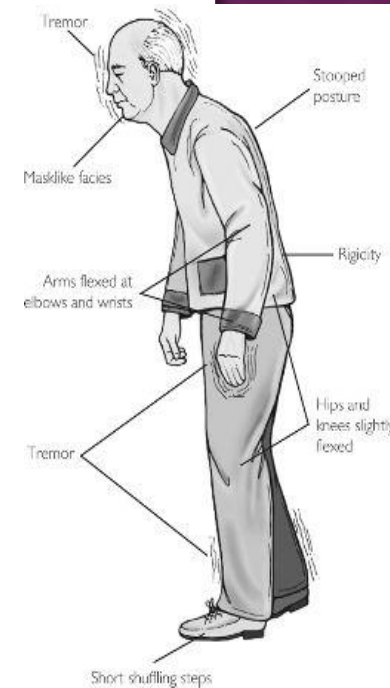
- ❖ Vascular dementia is the second most common form of dementia after Alzheimer disease (AD)
- ❖ Cognitive impairment + acute neurologic event
- ❖ Risk factors (eg, hypertension, diabetes mellitus, hyperlipidemia, smoking, previous strokes)
- ❖ Multiple small cerebral infarcts (or sometimes hemorrhages) cause enough neuronal or axonal loss to impair brain function.

Vascular Dementia



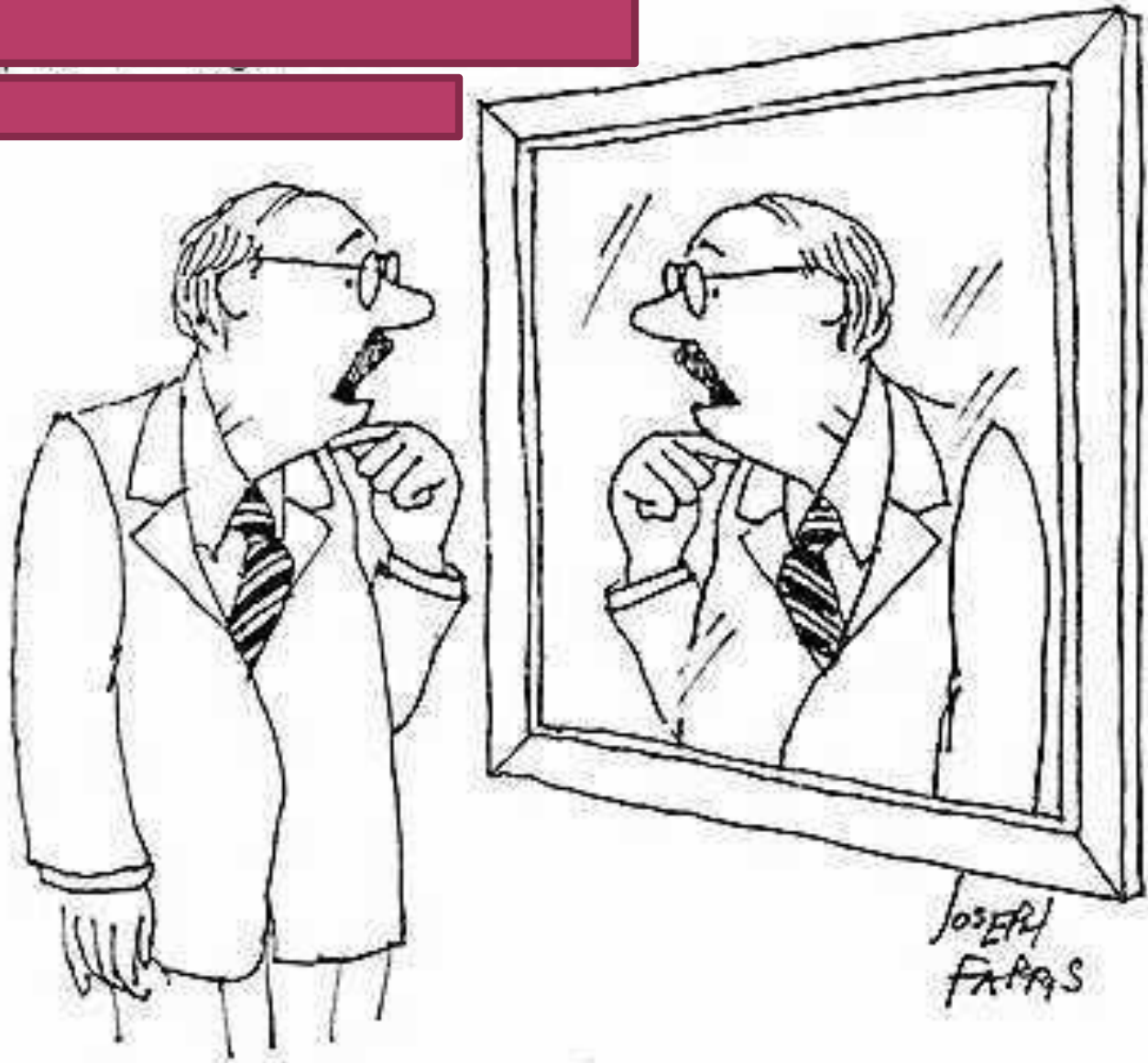
PARKINSON'S DISEASE

- Starting with a slowing of the thought processes it leads to difficulty in concentration and results in total confusion.
- It is associated with stiffness and tremor of limbs, speech impairment and a shuffling gait (body posture)
- Dopamine controls motor function and in PD, neurons producing dopamine are destroyed.



[Redacted]

[Redacted]



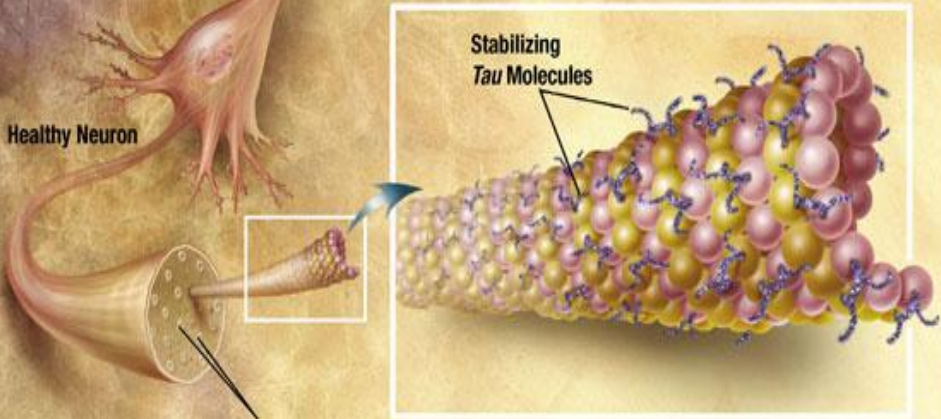
[Redacted]

"I remember the face but I've forgotten your name."

FRONTOTEMPORAL DEMENTIA(FTD)

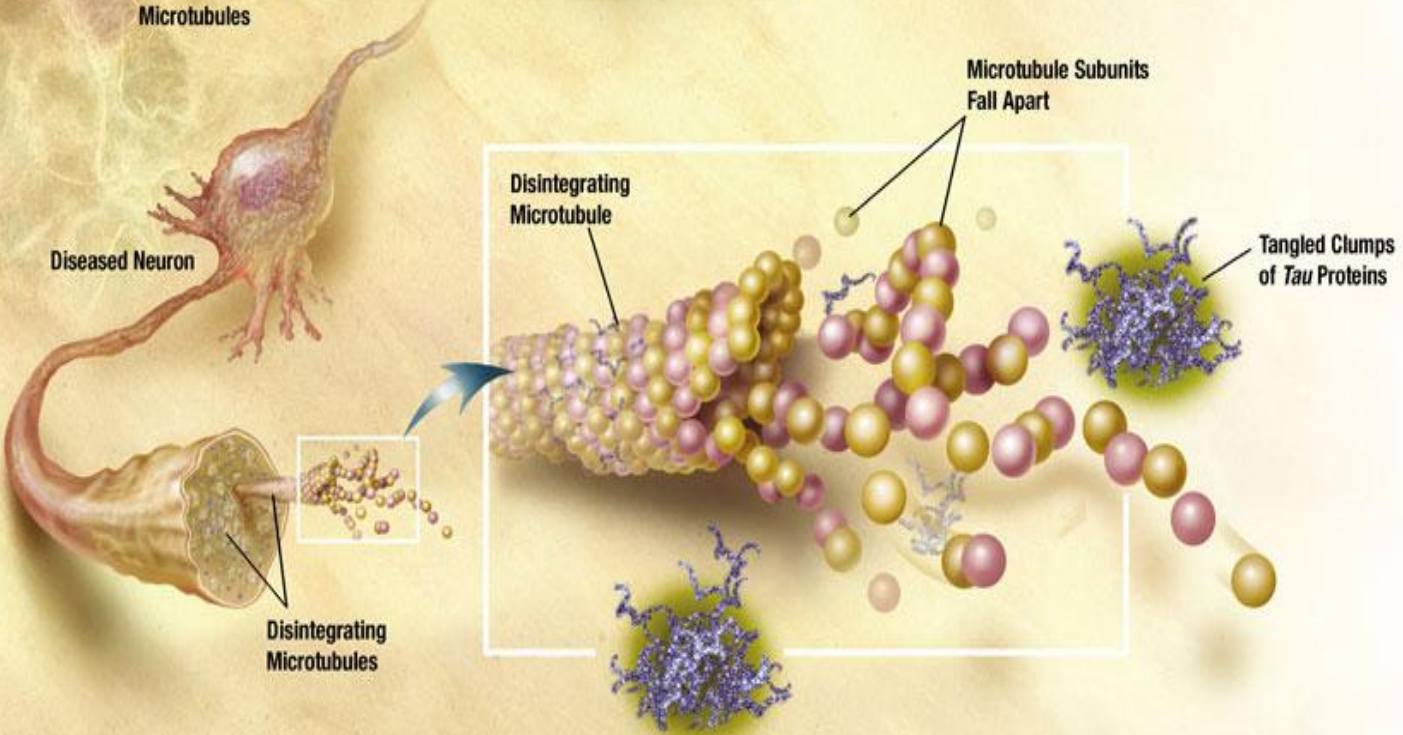
- ◉ A hereditary disorder affecting frontal and temporal lobes (including Pick's disease)
- ◉ FTD accounts for up to 10% of dementias. Age at onset is typically younger (age 55 to 65) than in Alzheimer's disease
- ◉ Tauopathy with mutations on chromosome 17 resulting in abnormalities of the microtubule-binding tau protein.
- ◉ FTD affects personality, behavior, and usually language function more than memory unlike Alzheimer's disease

Healthy Neuron



Microtubules

Diseased Neuron



Disintegrating Microtubules

Disintegrating Microtubule

Microtubule Subunits Fall Apart

Tangled Clumps of Tau Proteins

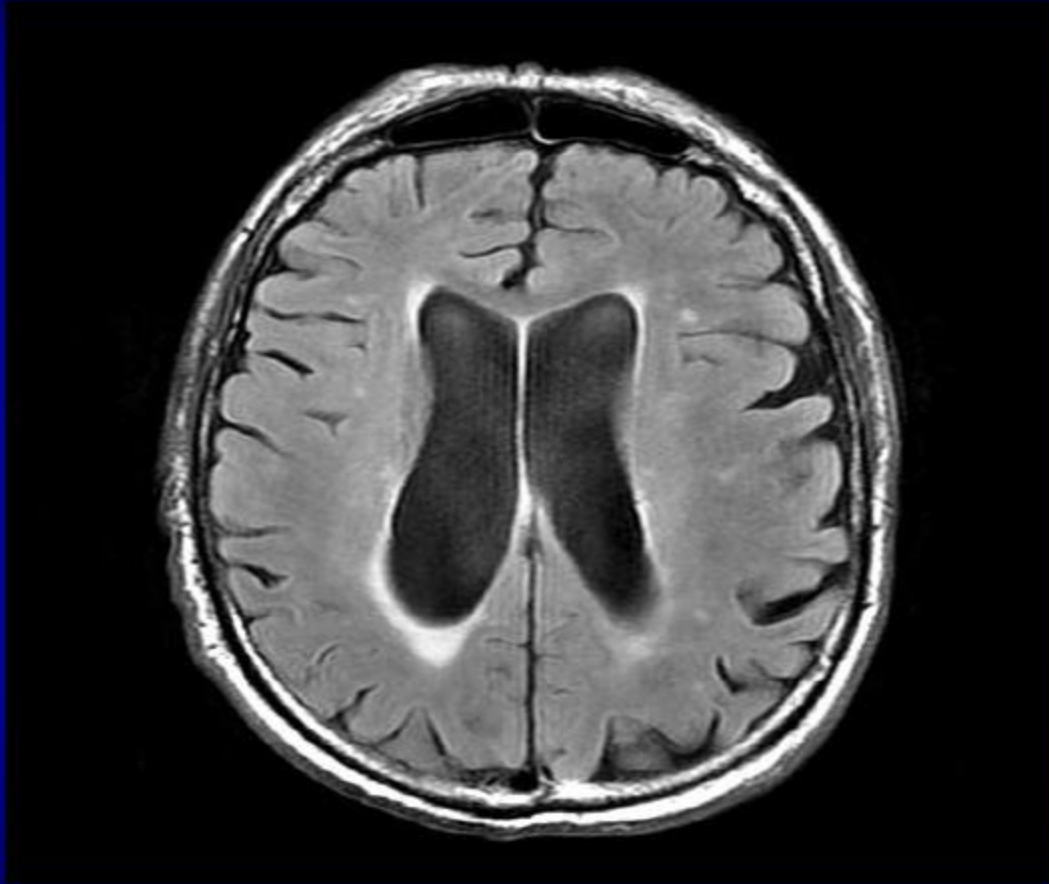
OTHER CAUSES OF DEMENTIA

- ❖ **MULTIPLE SCLEROSIS** (Disseminated patches of demyelination in the brain and spinal cord causing multiple neurologic deficits with remissions and exacerbations)
- ❖ **HUNTINGTON'S DISEASE** (Autosomal dominant disorder characterized by chorea and progressive cognitive deterioration, usually beginning in middle age. Diagnosis is by genetic testing. Treatment is supportive)
- ❖ **PICKS DISEASE** (Variant of FTD, characterized by severe atrophy, neuronal loss, gliosis, and presence of abnormal neurons (Pick cells) containing inclusions (Pick bodies))
- ❖ **PROGRESSIVE SUPRANUCLEAR PALSY** (Rare, degenerative CNS disorder causing loss of voluntary eye movements, bradykinesia, muscular rigidity with progressive axial dystonia, pseudobulbar palsy, and dementia.)
- ❖ **INFECTIONS AFFECTING THE BRAIN SUCH AS HIV/AIDS AND LYME'S DISEASE**

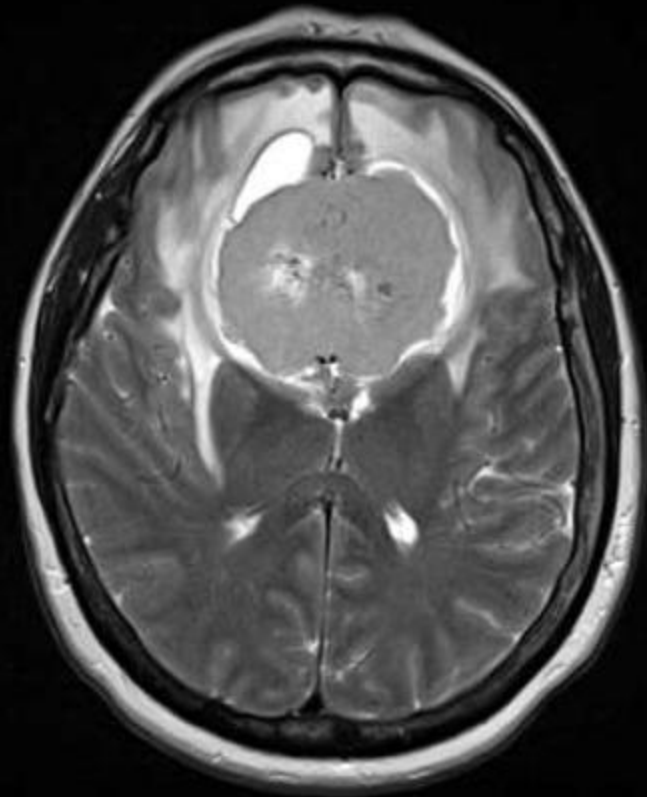
REVERSIBLE CAUSES OF DEMENTIA

- ❖ Brain tumors
- ❖ **Metabolic causes** (changes in serum glucose, calcium and sodium levels)
- ❖ Thyroid disorders
- ❖ Vitamin B12 deficiencies
- ❖ **Normal pressure hydrocephalus** (characterized by **gait disturbance, urinary incontinence, dementia**, enlarged brain ventricles, and normal or slightly elevated CSF pressure, treated by VP shunting)
- ❖ Chronic alcohol abuse

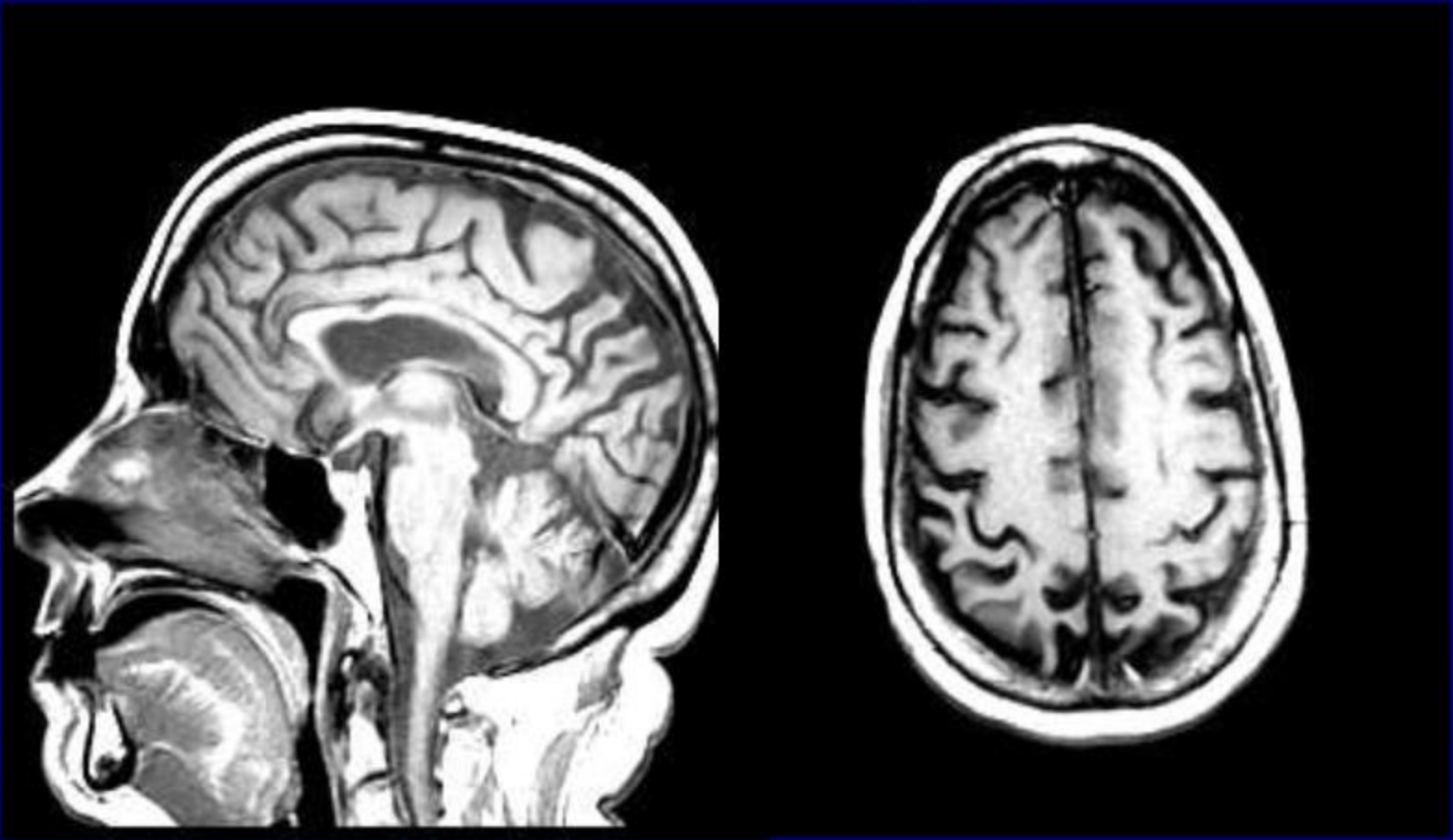
? NPH



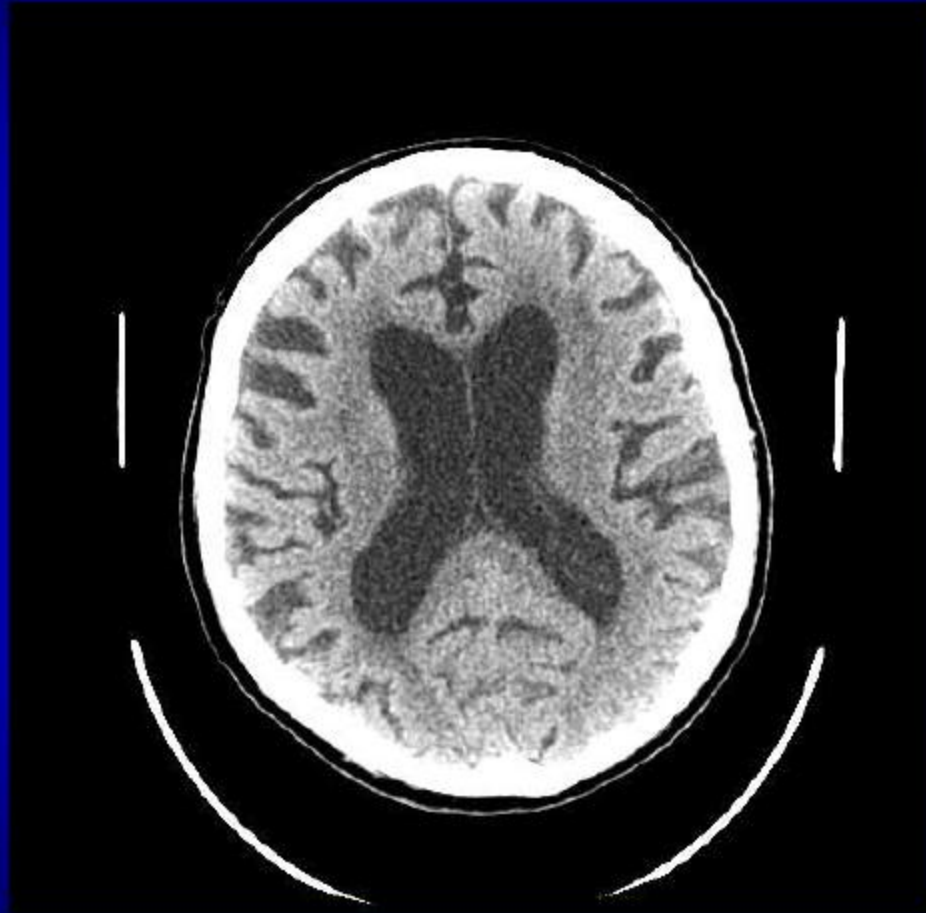
Subfrontal Meningioma



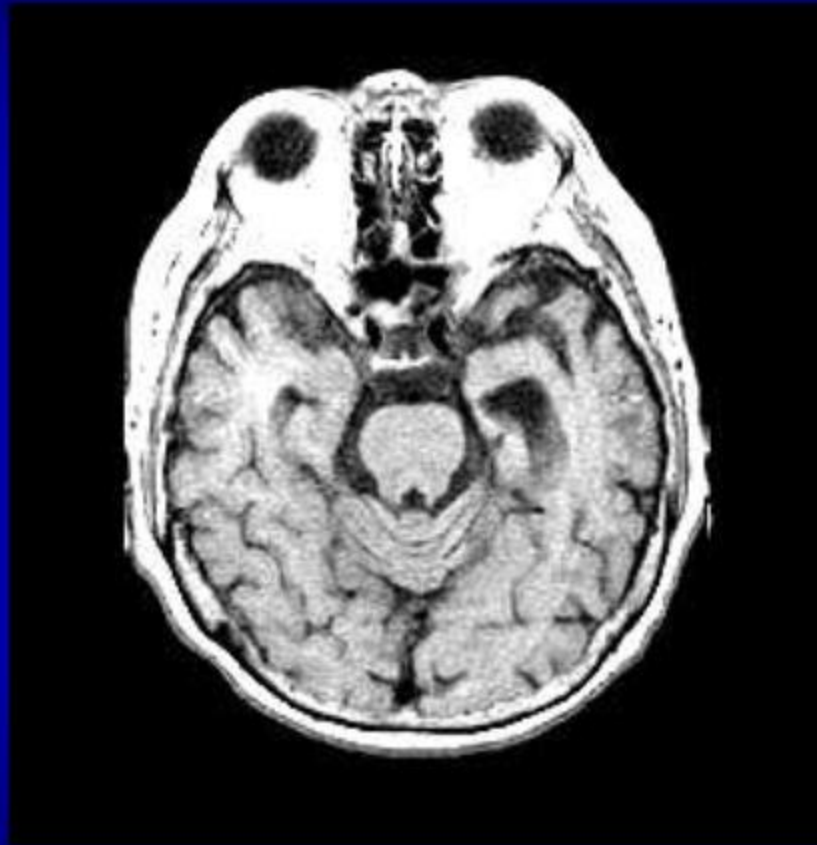
Parietal Atrophy



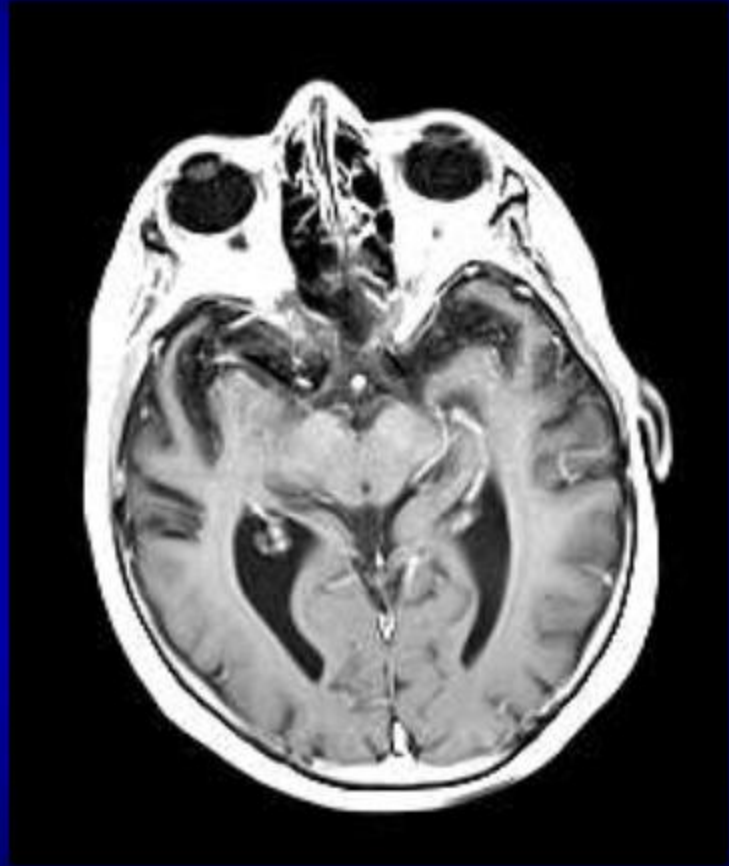
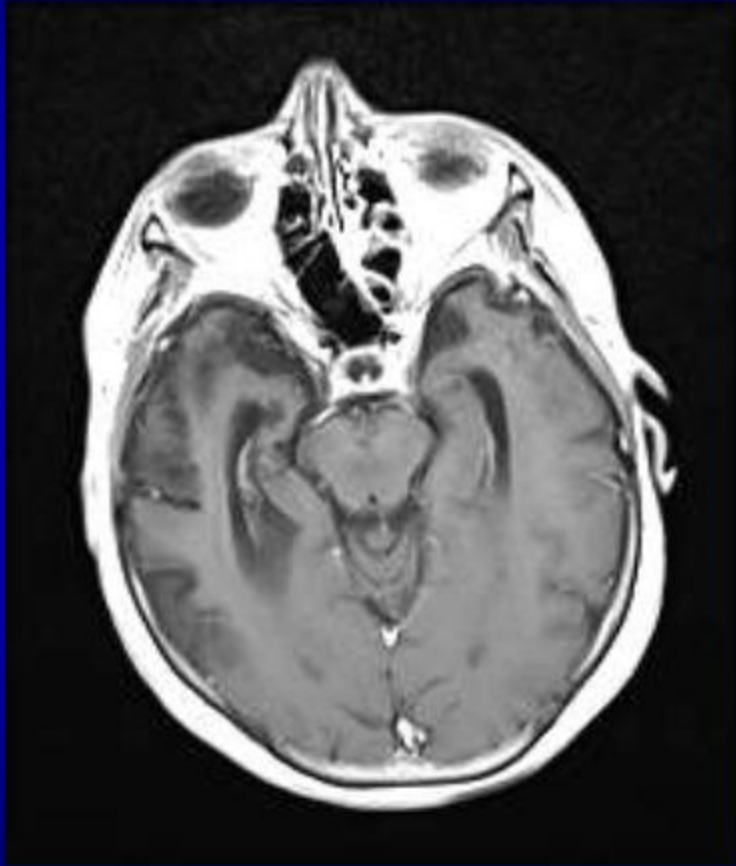
Central and Cortical Atrophy



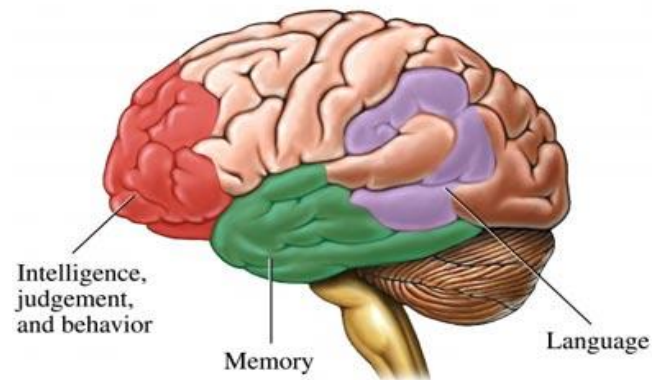
Hippocampal Atrophy



Frontotemporal Dementia



SYMPTOMS



- ❖ Dementia usually first appears as **forgetfulness**.
- ❖ Dementia symptoms include difficulty with many areas of mental function, including:
 - Language
 - Memory
 - Perception
 - Emotional behavior or personality
 - Cognitive skills (judgment, calculation, abstract thinking)

MILD COGNITIVE IMPAIRMENT

- ⦿ MCI is the stage between normal forgetfulness due to aging and the development of dementia
- ⦿ Patients have mild problems with thinking and memory that **do not** interfere with everyday activities and are aware of the forgetfulness
- ⦿ Not all patients with MCI develop full blown dementia but it should alert the physician to the possibility of progression.

MCI...

Symptoms of this include:

- ◉ Forgetting recent events or conversations
- ◉ Difficulty performing more than one task at a time
- ◉ Difficulty solving problems
- ◉ Taking longer to perform more difficult mental activities

EARLY SYMPTOMS OF DEMENTIA

- ◉ Language problems, such as trouble finding the name of familiar objects
- ◉ Misplacing items
- ◉ Getting lost on familiar routes
- ◉ Personality changes and loss of social skills
- ◉ Difficulty performing tasks that take some thought, but that used to come easily, such as balancing a checkbook, playing games (such as bridge), and learning new information or routines

THE SYMPTOMS OF MODERATE DEMENTIA MAY INCLUDE:

- ⦿ Forgetting events in patient's own life history, losing awareness of self
- ⦿ Change in sleep patterns, often waking up at night
- ⦿ Poor judgment and loss of ability to recognize danger
- ⦿ Withdrawing from social contact
- ⦿ Having hallucinations, arguments, striking out, and violent behavior
- ⦿ Difficulty doing basic tasks, such as preparing meals, choosing proper clothing, or driving

SEVERE DEMENTIA

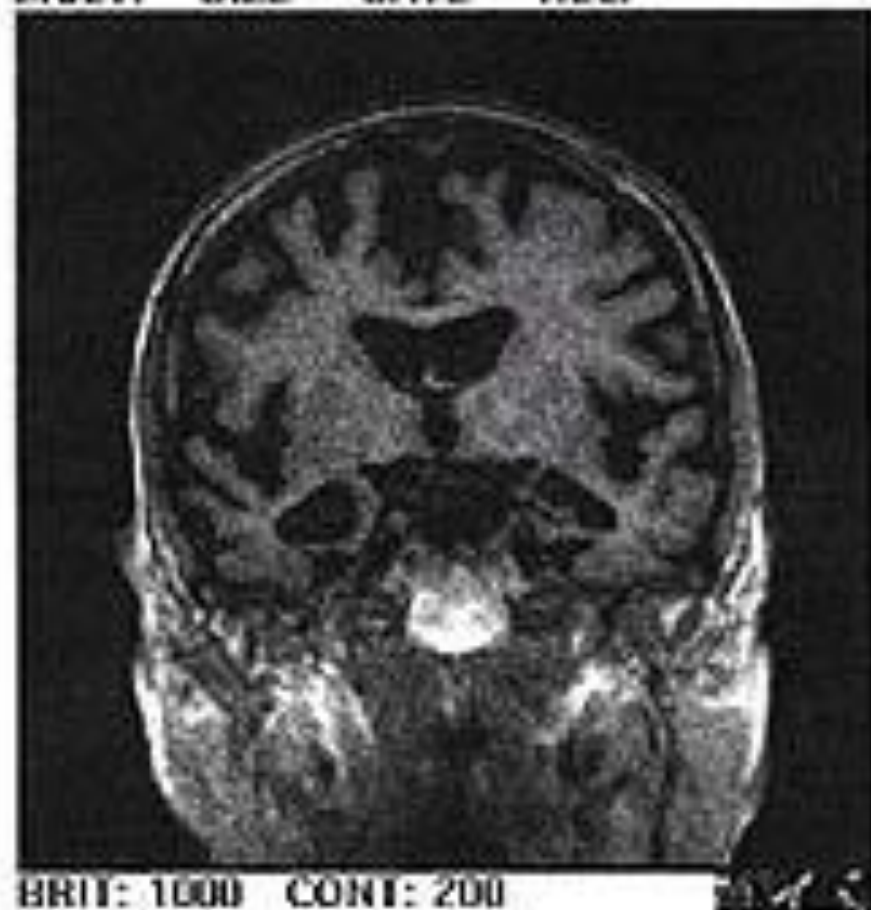
Inability to:

- ⊙ Understand language
- ⊙ Recognize family members
- ⊙ Perform basic activities of daily living, such as eating, dressing, and bathing

Other symptoms that may occur with severe dementia:

- ⊙ Incontinence
- ⊙ Swallowing problems
- ⊙ Mutism

MULTI SIZE SAVE HELP



Brain with A.D

MULTI SIZE SAVE HELP



Normally Aged Brain

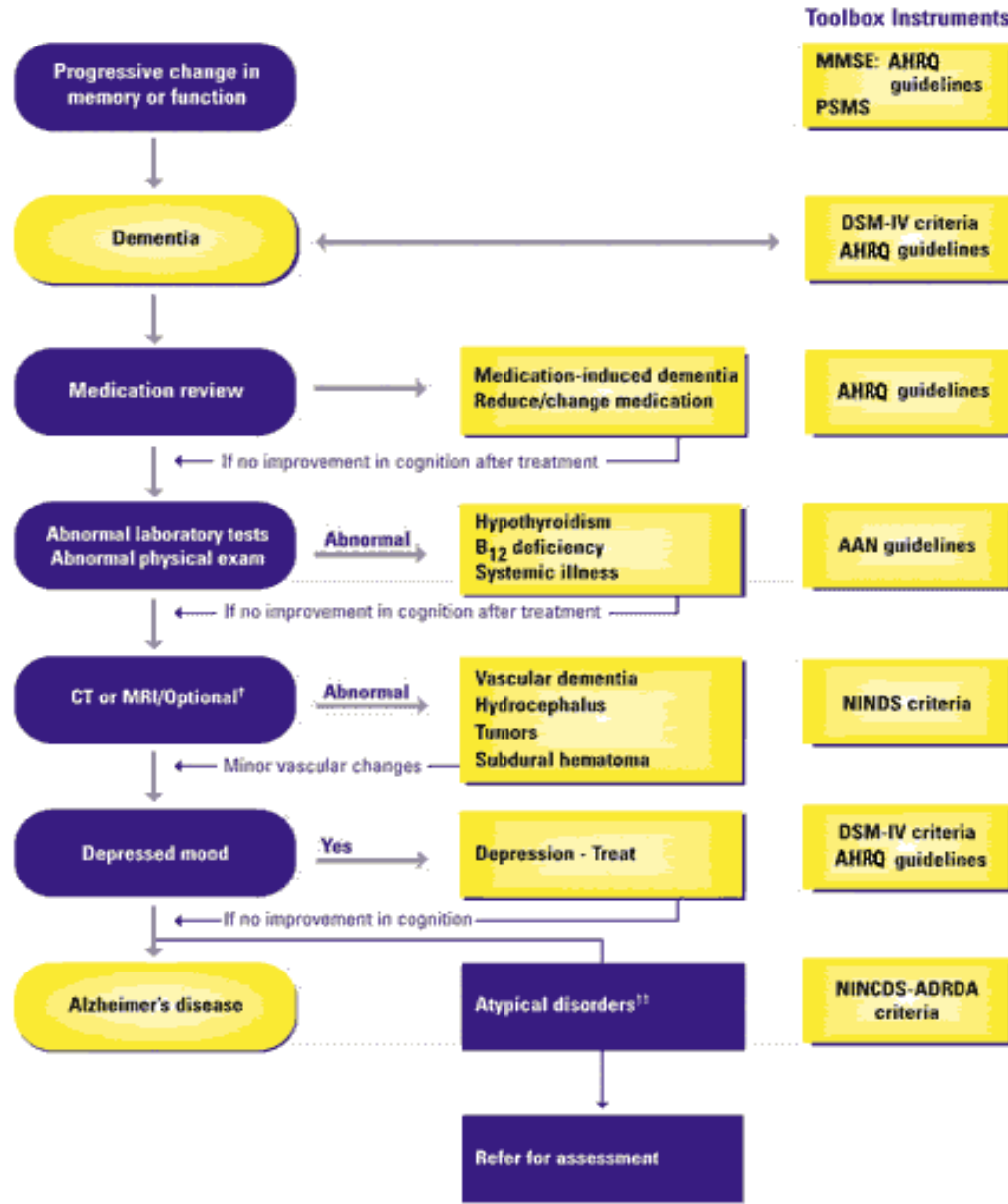
SENIOR CITIZEN BANO:

I STILL HAVEN'T FOUND
WHAT I'M LOOKIN' FOR.

IN FACT...
I CAN'T
REMEMBER
WHAT I CAME
IN HERE FOR
IN THE FIRST
PLACE...

DIAGNOSIS

- ◉ The best screening test for dementia is a short-term memory test; patients with dementia forget simple information within 3 to 5 min.
- ◉ In addition to loss of short-term memory, diagnosis of dementia requires **at least one** of the following cognitive deficits:
 - Aphasia**
 - Apraxia** (inability to carry out learned purposeful movements)
 - Agnosia** (loss of ability to recognize objects, persons, sounds, shapes, or smells)
 - Executive dysfunction** (Impaired ability to plan, organize, sequence, or think abstractly)
- ◉ Each cognitive deficit **must** substantially impair function and represent a significant decline from a previous level of functioning.
- ◉ A formal mental status exam must be done (MMSE)



* Developed and endorsed by the *TriAD* Advisory Board. ©1996 Pfizer Inc and Eisai Inc., with special thanks to J. L. Cummings. Algorithm reprinted from *TriAD*, Three for the Management of Alzheimer's Disease, with permission.

† It is required in patients with focal signs, rapid progression, and headache.

†† This category will contain rare dementias (e.g., frontotemporal degenerations, Jakob-Creutzfeldt disease, Parkinson's disease [and other movement disorders


MINI MENTAL STATUS EXAM

Normal cognitive
function = 27-30

Mild cognitive
impairment = 21-26

Moderate cognitive
impairment = 11-20

Severe cognitive
impairment = 0-10

Maximum score	Score	
5	—	Orientation
5	—	What is the (year) (season) (date) (day) (month)? Where are we: (state) (county) (town or city) (hospital) (floor)?
3	—	Registration Name three common objects (e.g., "apple," "table," "penny"); Take one second to say each. Then ask the patient to repeat all three after you have said them. Give one point for each correct answer. Then repeat them until he or she learns all three. Count trials and record. Trials: —
5	—	Attention and calculation Spell "world" backwards. The score is the number of letters in correct order. (D__L__R__O__W__)
3	—	Recall Ask for the three objects repeated above. Give one point for each correct answer. (Note: recall cannot be tested if all three objects were not remembered during registration.)
2	—	Language Name a "pencil" and "watch." Repeat the following: "No ifs, ands or buts."
1	—	Follow a three-stage command:
3	—	"Take a paper in your right hand, fold it in half and put it on the floor."
1	—	Close your eyes.
1	—	Write a sentence.
1	—	Copy the following design.
	—	
	—	Total score: —

TESTS AND PROCEDURES

Routine laboratory tests for dementia:

- ⊙ B12 level
- ⊙ Liver function tests
- ⊙ Cerebrospinal fluid (CSF) analysis
- ⊙ Drug or alcohol levels (toxicology screen)
- ⊙ Tests for exposure to metals such as lead or arsenic
- ⊙ Serum calcium
- ⊙ Serum electrolytes
- ⊙ Thyroid function tests
- ⊙ TSH level
- ⊙ Urinalysis

Imaging modalities used for diagnosis:

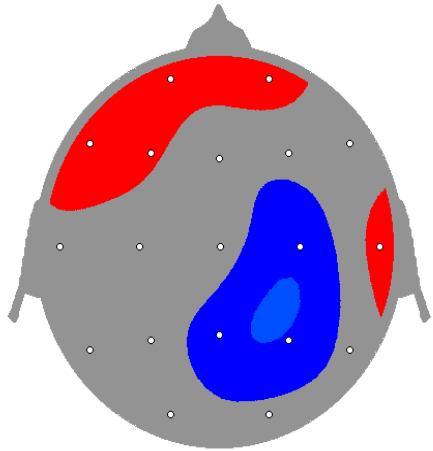
◎ QEEG Brain Topography

- QEEG can differentiate Dementia from normals 85-100%
- Common findings among dementia-increase 2-6 hz
- Decrease in dominant posterior Alpha in AD

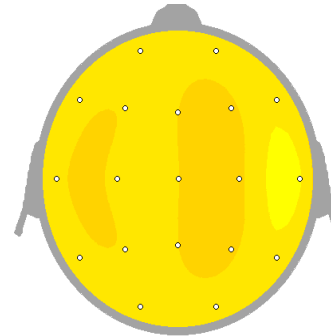
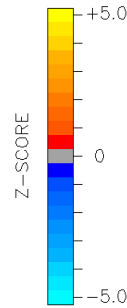
◎ Head CT scan and MRI of head

- ◎ Functional and molecular imaging (eg PET, fMRI, SPECT) are being researched as methods for earlier diagnosis with the possibility of biomarkers being an early indicator of disease.
- PET scans with fluorodeoxyglucose (FDG) have been used to demonstrate reduced use of glucose in areas of the brain important in memory, learning and problem solving

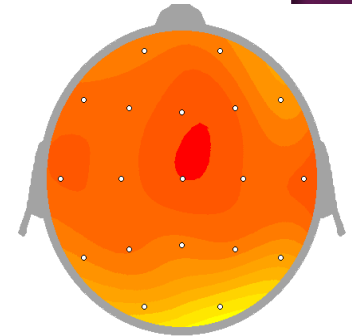
QEEG BRAIN TOPOGRAPHY



ALPHA (7-13 Hz)



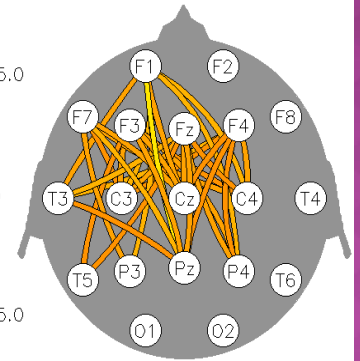
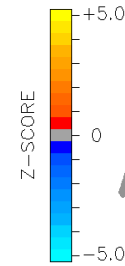
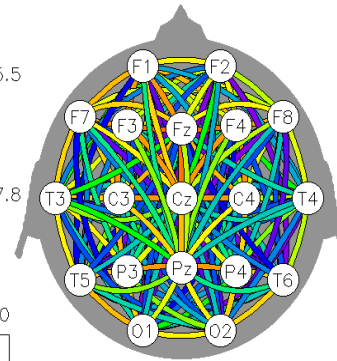
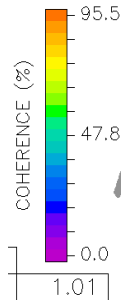
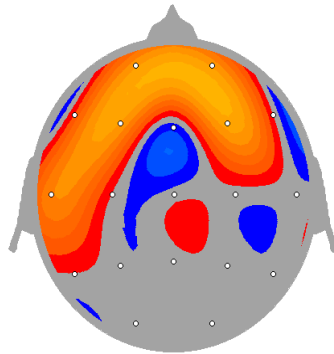
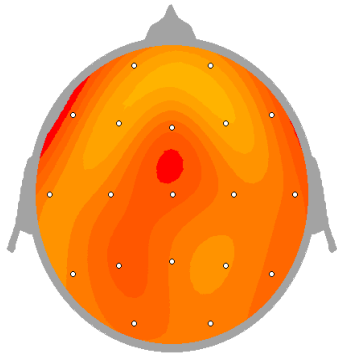
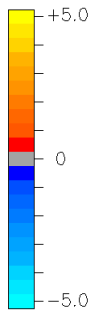
DELTA (0.5-3.5 Hz)

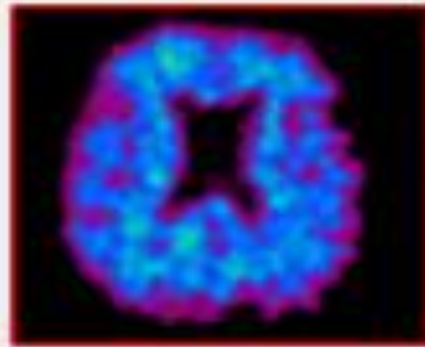
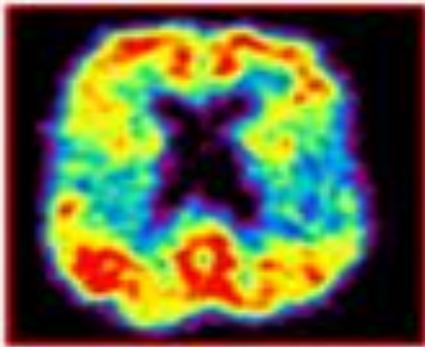


THETA (3.5-7 Hz)

DELTA (0.5-3.5 Hz)

THETA (3.5-7 Hz)





PIB Brain Scan

Red = Amyloid

The PET brain scan on the left is of a person with mild Alzheimer's disease, and the scan on the right is from a healthy adult.

Red areas show the greatest levels of amyloid, and the dark blue indicates no amyloid. The other colors—in order like the colors of a rainbow—show progressively lower levels of amyloid.

*Image credit:
University of Pittsburgh
Medical Center*

PET scan using Pittsburgh compound B (PIB) which is capable of highlighting areas of amyloid deposits

TREATMENT

Treating conditions that can lead to confusion often greatly improve mental functioning. Such conditions include:

- ⦿ Anemia, depression, heart failure, infections, nutritional disorders, thyroid disorders



NEUTRACEUTICALS

- These are substances which are traditionally used to improve symptoms of early dementia or mild cognitive impairment.

- Gingko Biloba
- Curcumin
- Huperzine A
- Acetyl-L-carnitine (ALC)
- Lecithin
- Caffeine (Gurana)
- Medium Chain Triglyceride
- Piracetam
- Vinopocetine
- Phosphatidylserine
- Inositol Nicotinate

MEDICATIONS USED TO TREAT DEMENTIA

- The cholinesterase inhibitors - **Donepezil**, **Rivastigmine**, and **Galantamine** are somewhat effective in improving cognitive function in patients with Alzheimer's disease or Lewy body dementia and may be useful in other forms of dementia.
- These drugs inhibit acetylcholinesterase, increasing the acetylcholine level in the brain.
- **Memantine** an NMDA (*N*-methyl-D-aspartate) antagonist, may help slow progression of moderate to severe dementia and can be used with a cholinesterase inhibitor.

Other drugs (eg, antipsychotics) have been used to control behavior disorders.

- Antipsychotics

(Haloperidol, Risperdal, Olanzapine)

- Mood stabilizers (Fluoxetine, Citalopram)

- Serotonin-affecting drugs (Trazodone, Buspirone)

- Stimulants (Methylphenidate)

*** Anticholinergic medications should be avoided as they can worsen dementia**

MEDICATIONS USED TO SLOW PROGRESSION OF DEMENTIA

❖ DONEPEZIL (Aricept)

- Acetylcholinesterase inhibitor that also includes tacrine (Cognex)



❖ RIVASTIGMINE (EXELON)

- Cholinesterase inhibitor that inhibits both butyrylcholinesterase and acetylcholinesterase.



❖ GALANTAMINE (Razadyne, formerly called Reminyl)

- A competitive and reversible cholinesterase inhibitor. It increases concentration of acetylcholine in the brain.



❖ MEMANTINE (NAMENDA)

- NMDA receptor antagonists. It blocks the action of the neurotransmitter glutamate at these receptors.
- Used in patients who are intolerant to or have contraindications to acetylcholinesterase inhibitors or those with severe Alzheimer's.



CURRENT ALZHEIMER'S RESEARCH:

1. MABT5102A (monoclonal antibody to β -amyloid)

- A randomized, double-blind, parallel-group, placebo controlled study to evaluate the safety and efficacy of MABT5102A in patients with mild to moderate AD by GENENTECH
- Evaluates the inhibition of disease progression in AD based on several assessment scales, biomarkers in CSF, and MRI after 68 weeks of treatment with MABT5102A versus placebo.

FOLLOW UP

- ⦿ Regular follow-up every 4-6 months is recommended to assess the patient's general condition and cognitive and noncognitive symptoms.
- ⦿ Frequent visits may be needed for patients with behavioral problems and patients who are on specific therapies such as neuroprotective agents.
- ⦿ Treatment of risk factors such as hypertension, hypercholesterolemia, and diabetes melitus require special attention.

*THANK YOU
FOR YOUR
ATTENTION*



*QUESTIONS
AND ANSWERS
SESSION*