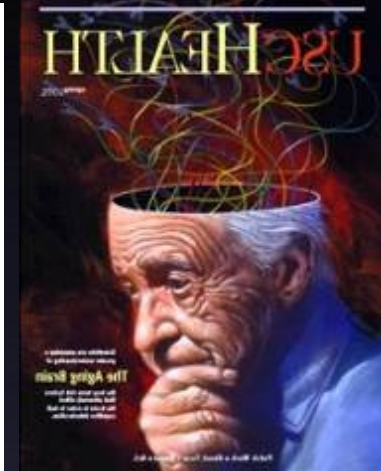
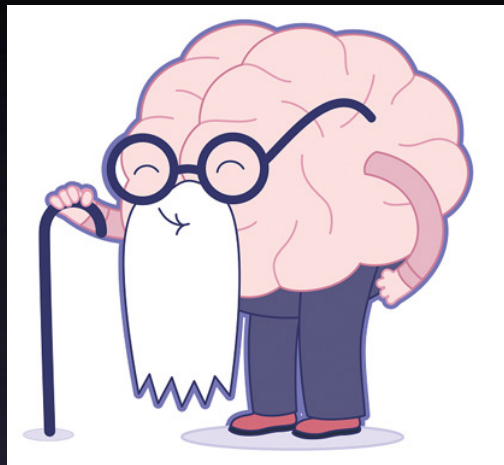


# AGING & CHANGES IN THE BRAIN



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# Objectives

*At the end of this session you should be able to:*

1. Define Aging and its consequences
2. Describe the theories of aging and terms Used
3. Name some Brief Geriatric Assessment Instruments
4. Describe brain changes associated with healthy aging related to structure, chemical, neuropsychological and genetic
5. Describe Important clinical conditions eg; geriatric syndrome, Alzheimer, carotid hypersensitivity

# THE TERM AGEING

- **UNIVERSAL AGEING**: age changes that all people share)
- **PROBABILISTIC AGEING**: age changes that may happen to some (eg type two diabetes).
- **CHRONOLOGICAL AGEING**: referring to how old a person is
- **SOCIAL AGEING**: society's expectations of how people should act as they grow older
- **BIOLOGICAL AGEING**: an organism's physical state as it ages

## Some Theories of Aging

Hypothesis	How It May Work
Genetic	Aging is a genetic program activated in post-reproductive life when an individual's evolutionary mission is accomplished
Oxidative stress	Accumulation of oxidative damage to DNA, proteins, and lipids interferes with normal function and produces a decrease in stress responses
Mitochondrial dysfunction	A common deletion in mitochondrial DNA with age compromises function and alters cell metabolic processes and adaptability to environmental change

## Some Theories of Aging

Hypothesis	How It May Work
Hormonal changes	The decline and loss of circadian rhythm in secretion of some hormones produces a functional hormone deficiency state
Telomere shortening	Aging is related to a decline in the ability of cells to replicate
Defective host defenses	The failure of the immune system to respond to infectious agents and the overactivity of natural immunity create vulnerability to Inf..
Accumulation of senescent cells	Renewing tissues become dysfunctional through loss of ability to renew

**OXYGEN - free radicals ( $O_2^-$ ,  $H_2O_2$ ,  $HO^*$ ) and reactive oxygen species (ROS) are produced in Mitochondria ( $NO + O_2 \rightarrow ONOO^-$ )**

**CELL METABOLISM**

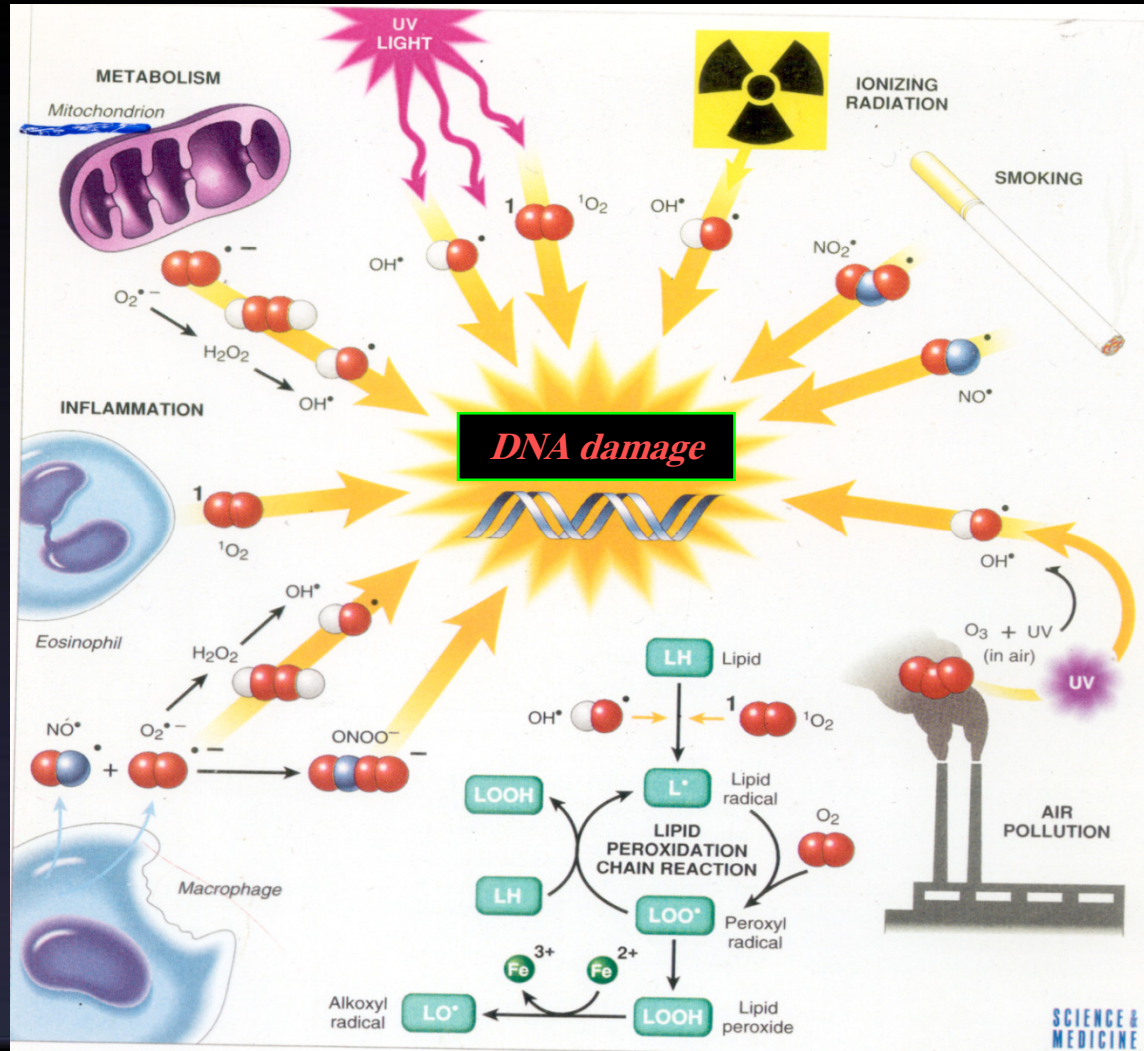
**ENVIRONMENT**

**INFECTION**

**LIFESTYLE**

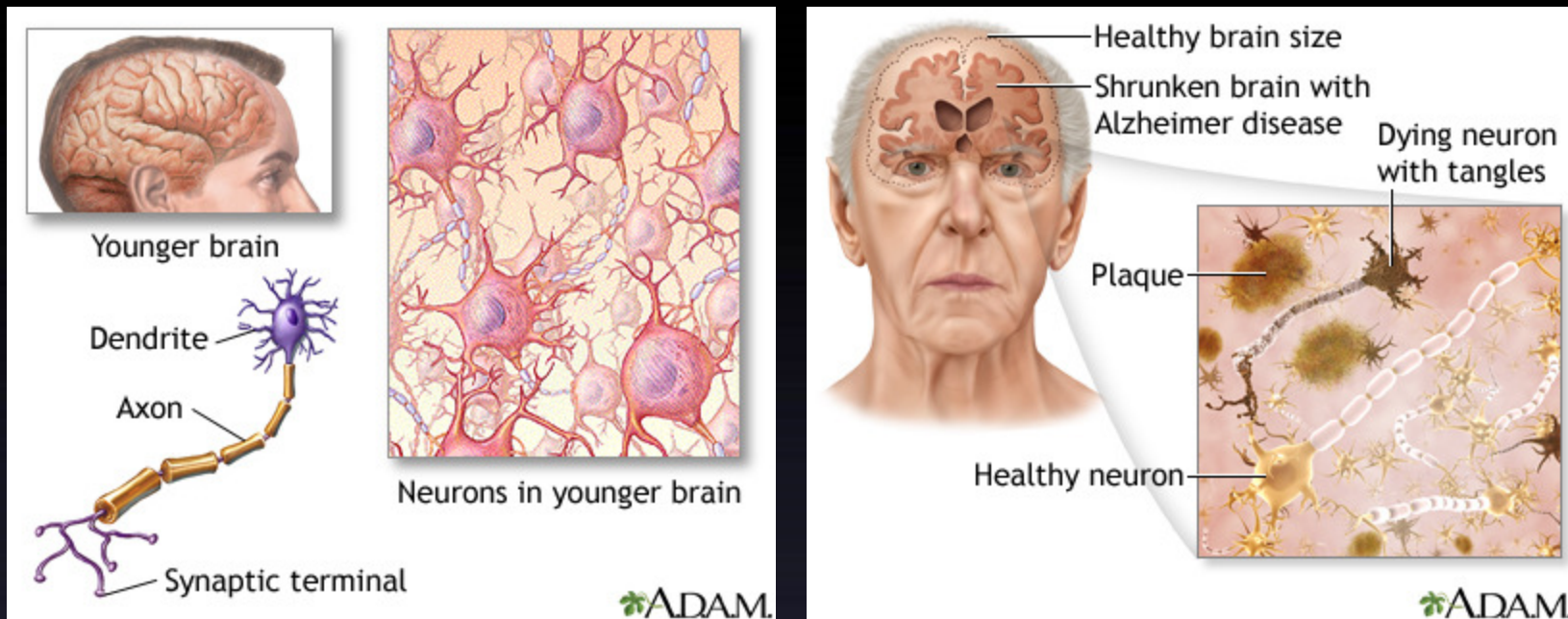
**DIET**

**POLLUTION**





# AGING NERVOUS SYSTEM



**“Use it or lose it!”**

**Individuals who remain mentally active perform better on cognitive tasks than those who engage in mental activity less often**

- **Accelerated rate of brain shrinkage after age 50.**
- **Loss of 100,000 neurons in the cortex per day.**
- **Irreversible process of brain dysfunction.**

# Aging brain

Aging is a major risk factor for most common neurodegenerative diseases, including mild cognitive impairment, dementias including Alzheimer's disease, cerebrovascular disease, Parkinson's disease and Lou Gehrig's disease.

While much research has focused on diseases of aging, there are few informative studies on the molecular biology of the aging brain in the absence of neurodegenerative disease or the neuropsychological profile of healthy older adults.

This Lecture will focus on reviewing the brain changes associated with healthy aging

Structural changes

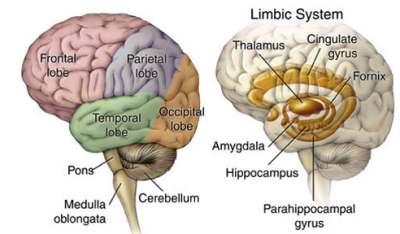
Chemical changes

Neuropsychological

Genetic changes



# Aging nervous system

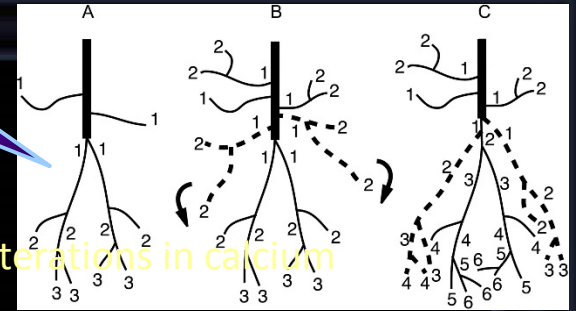


Structure	Regional function
Basal ganglia	Becomes bright in appearance due to iron accumulation (movements affected)
Subarachnoid space	Increase in size due to brain shrinkage
Hippocampus	Reduction in size due to cell loss in the structure. Part of limbic system Involved in learning & long term memory
Ventricles	Increase in size due brain shrinkage.
White Matter	Reduction in size due to neuronal atrophy in the deep brain. Involved in information transmission.

**The cerebellum is the youngest brain region least affected by aging**

## Structural changes

### Dendritic Arborization in new and experienced



### Loss of neural circuits and brain plasticity

- Age-related plasticity deficits in animals is the result of age-induced alterations in calcium regulation
- Some areas would be more vulnerable to aging eg: hippocampus and neocortical circuits
- Age-related cognitive decline is due in part not to neuronal death but to synaptic alterations
- This cognitive deficit is due to functional and biochemical factors such as changes in enzymatic activity, chemical messengers, or gene expression in cortical circuits

### Thinning of the cortex

There is a decrease in **grey matter** volume between adulthood and old age, whereas **white matter** volume was found to increase from age 19-40, and decline after this age

### Age-related neuronal morphology

- Dendritic **arbors** and **dendritic spines** of cortical pyramidal neurons decrease in size and/or number in specific regions and layers of human and non-human primate cortex as a result of age
- A 46% decrease in spine number and spine density has been reported in humans older than 50 compared with younger individuals

### Neurofibrillary tangles

One of the important differences between normal aging and pathological aging is the location of neurofibrillary tangles. In normal, non-demented aging, the number of tangles in each affected cell body is relatively low. However, unlike tangles, plaques have not been found to be a consistent feature of normal aging.

## Chemical changes

### Dopamine

Significant age-related **decline** in dopamine synthesis → notably in the **striatum** and **extrastriatal regions** Significant age-related decreases in all dopamine receptors  $D_1$ ,  $D_2$ , and  $D_3$  → The loss of dopamine with age is thought to be responsible for many neurological symptoms that increase in frequency with age, such as decreased arm swing and increased **rigidity**. Changes in dopamine levels may also cause age-related changes in cognitive flexibility.

### Serotonin

**Decreasing levels** of different serotonin receptors and the serotonin transporter, 5-HTT, have also been shown to occur with age. → in the caudate nucleus, putamen, and frontal cerebral cortex, decline with age.

### Glutamate

Glutamate is another neurotransmitter that tends to **decrease with age**. → lower glutamate concentration in the motor cortex compared to younger subjects → especially in the parietal gray matter, basal ganglia, and to a lesser degree, the frontal white matter, → glutamate may be useful as a marker of brain diseases that are affected by aging

# Neuropsychological

## Changes in orientation

Deficits in orientation are one of the most common symptoms of brain disease, hence tests of orientation are included in almost all medical and neuropsychological evaluations. → small number of studies have examined whether there is a normal decline in orientation among healthy aging adults. Results have been somewhat inconclusive. So although current research suggests that normal aging is not usually associated with significant declines in orientation, mild difficulties may be a part of normal aging and not necessarily a sign of pathology.

## Changes in attention

Many older adults notice a decline in their attentional abilities → a large review of studies on cognition and aging suggest that this hypothesis has not been wholly supported → Results suggest that sustained attention increases in early adulthood and then remains relatively stable, at least through the seventh decade of life. → It is worth noting that there are factors other than true attentional abilities that might relate to difficulty paying attention. **For example, sensory deficits like hearing or vision may make attention it more difficult.**

## Changes in memory

Memory functions, more specifically those associated with the medial temporal lobe are especially vulnerable to age-related decline

## Changes in language

Changes in performance on verbal tasks, vary in predictable patterns with age. For example, behavioral changes associated with age include compromised performance on tasks related to word retrieval, comprehension of sentences with high syntactic and/or working memory demands, and production of such sentences

## Genetic changes

Research focused on discovering the genetic component in developing AD has also contributed greatly to the understanding the genetics behind normal or "non-pathological" aging.

The human brain shows a decline in function and a change in gene expression → This modulation in gene expression may be due to oxidative DNA damage at promoter regions in the genome.

**Genes that are down-regulated over the age of 40 include:**

- GABA A receptor gene
- Genes involved in long-term potentiation (e.g. *CaMKII*)
- Calcium signaling genes
- Synaptic plasticity genes
- Synaptic vesicle release and recycling genes

**Genes that are upregulated include:**

- Genes associated with stress response and DNA repair
- Antioxidant defense

# Aging nervous system

## Changes

- Decreased brain weight
- Cerebral blood flow
- memory
- Alteration in CNS neurotransmitters
- Decreased vibratory sense

## Consequences

- Drug toxicities
- delirium
- Altered mood
- Decreased IQ scores
- “Benign senile forgetfulness”
- Increased postural instability
- Altered gait
- Falls, accidents



# Nervous System

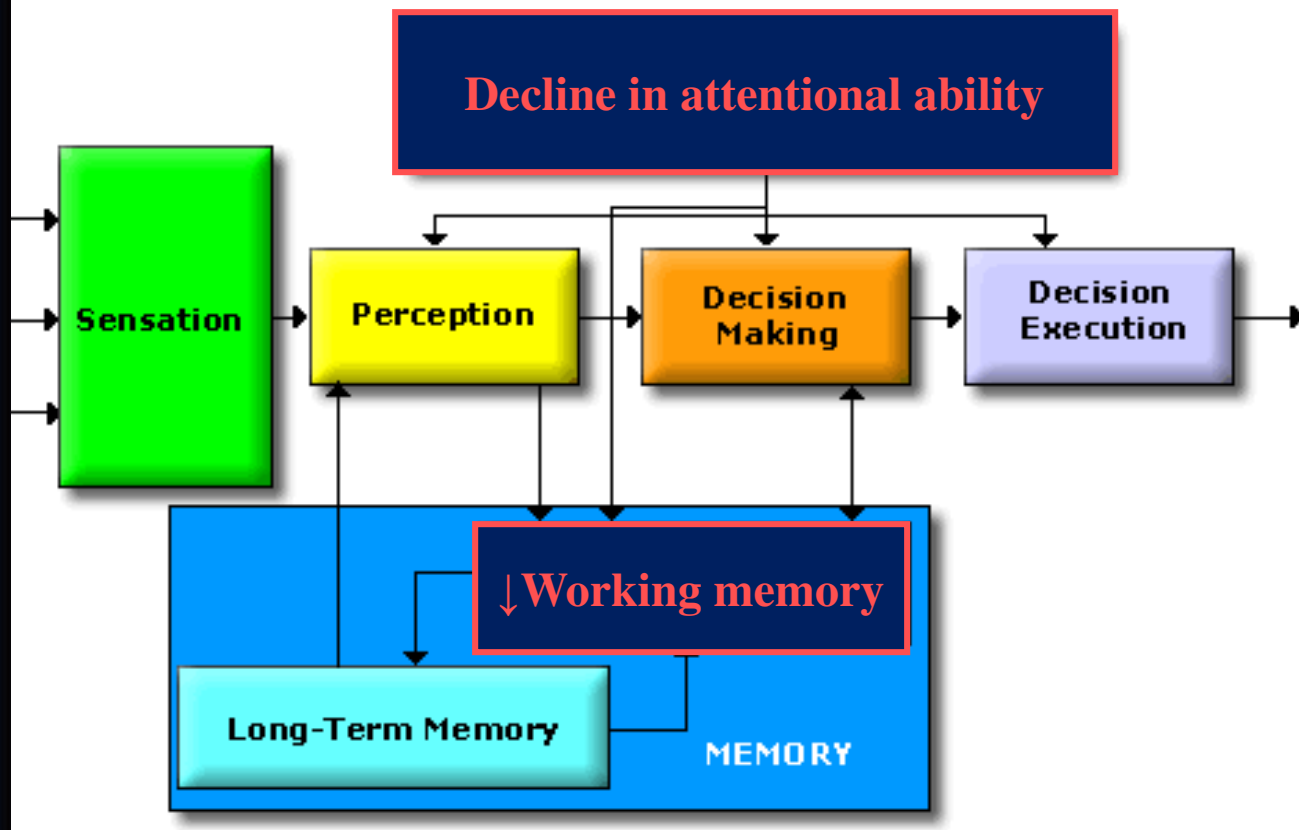
- **Neuronal loss** is normal in the aging brain but the ability to learn remains generally unchanged
- There is loss of **dendritic arborization**
- **Recall memory** is affected more than cognitive function in normal aging
- Lowered **seizure threshold**
- Reduced Sympathetic nervous system activity
- Reduced **Neurotransmitter levels** (Dopamine, Serotonin, Glutamate)
- Changes in sleep patterns
- Increased risk of stroke

Intellectual functioning defined as “Stored”  
memory increases with age  
Problem solving skills increase with age

# Brief Geriatric Assessment Instruments

Domain	Instrument	Comments
Cognition		
Dementia	MMSE	Widely studied and accepted
	Timed time and change test	Sensitive and quick
Delirium	CAM	Sensitive and easy to apply
Affective disorders	GDS 5-question form	Rapid screen
Visual impairment	Snellen chart	Universally used
Hearing impairment	Whispered voice	No special equipment needed
	Pure tone audiometry	Can be performed by trained office staff
Dental health	DENTAL <sup>c</sup>	
Nutritional status	Weight loss of >4.5 kg (>10 lb) in 6 months or weight <45 kg (<100 lb)	
Gait and balance	"Timed Get Up and Go" test	Requires no special equipment

# COGNITIVE CHANGES IN AGING: MENTAL PROCESSING



## DECLARATIVE MEMORY OR EXPLICIT MEMORY

- EPISODIC MEMORY (Events)
- SEMANTIC MEMORY (Words, language) Late to ↓
- HIPPOCAMPUS AND IS ASSOCIATED WITH CONSCIOUSNESS

## SKILL MEMORY OR IMPLICIT MEMORY

- IT DOES NOT INVOLVE AWARENESS.
- INVOLVES CEREBELLUM, MOTOR CORTEX, SENSORY CORTEX, VISUAL AREAS

There is decline in mental processing via reduction of attentional ability and decline in ability in forming **working memory** (mainly includes short term memory)

There is **decline in explicit memory** that involves hippocampus (surroundings & Skills) and is associated with awareness & attention unlike implicit.

# Hearing

- **Presbycusis:** Part of normal aging (35% people over 60 years of age have bilateral, symmetric & progressive impairment for high pitched sounds sensorineural hearing loss)
- **Cerumen impaction:** is one of the most common reversible cause of conductive hearing loss in elderly

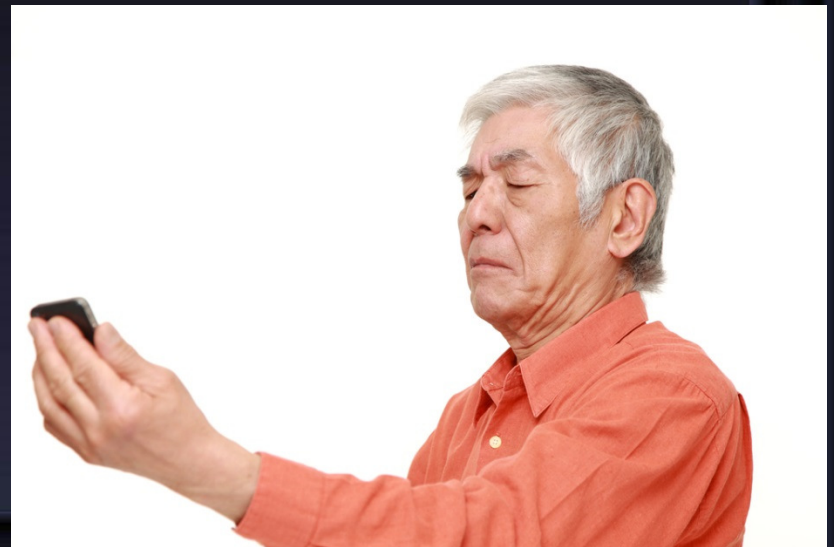


- **Paradoxical hypersensitivity to loud sounds**
- **Exacerbated in the presence of competing background noise**

Slow, persistent decline in hearing with age. The hearing loss begins in the sixth decade and is typically symmetrical, beginning in the high-frequency range.

# Vision

- Loss of ability to see items that are close up begins in the 40's (**Presbyopia**)
- Size of **pupil** grows smaller with age: focusing becomes less accurate
- Pupil less sensitive to light
- Opacification of lens (**Cataract**)
- Lens of eye yellows making it more difficult to see red and green colors
- **Night vision** not as acute
- **Arcus Senilis**



# Disorders of the Sense of Taste

- Dorsum surface shows loss of filiform papilla
- Foliate papillae more prominent.
- Fissures increase
- Dryness of the mouth
- The ventral surface of the tongue shows the presence of nodular varicose enlargement also known as caviar tongue
- Loss of taste buds with age



Sensory gustatory losses are caused by inflammatory and degenerative diseases in the oral cavity; a vast number of drugs, such as antithyroid and antineoplastic agents; radiation therapy to the oral cavity and pharynx; viral infections; endocrine disorders; neoplasms; and **aging**



# Pain and Sense of Touch

- With age, skin is not as sensitive as in youth
  - Contributing factors include:
    1. Loss of elasticity
    2. Loss of pigment
    3. Reduced fat layer
- Safety Implications:
  1. Lessened ability to recognize dangerous levels of heat
  2. Lessened ability of body to **maintain temperature**
  3. Tendency to develop bruises, skin tears more easily

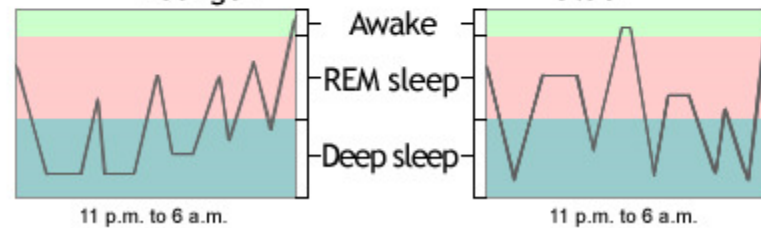
# SLEEP PATTERNS

- It tends to become more fragmented, with more awakenings during the night.
- Total sleep time stays the same or is slightly decreased (6.5 to 7 hours per night).
- The transition between sleep and waking up is often abrupt, which makes older people feel like they are a lighter sleeper than when they were younger.
- **Three or four awakenings** each night
- The **proportion** of slow wave sleep decreases relative to total sleep time, but the proportion of sleep that is REM sleep ↓ or is unchanged

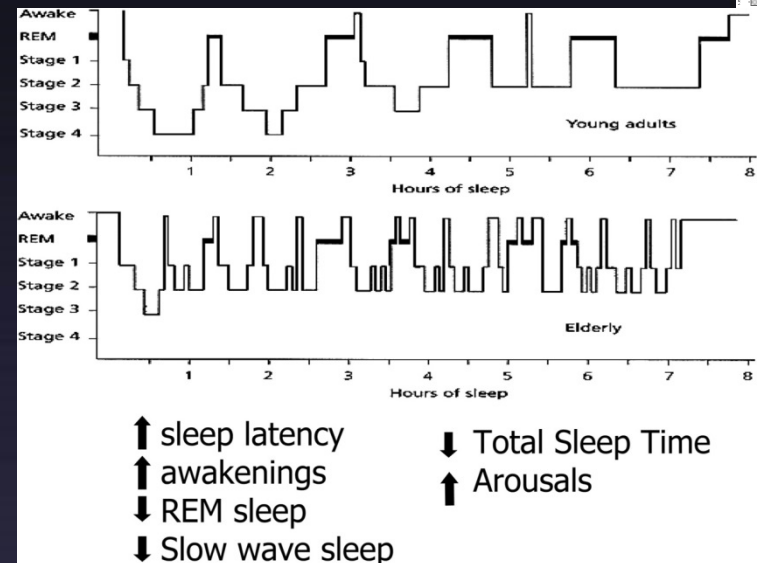


Younger

Older



ADAM.



- ↑ sleep latency
- ↑ awakenings
- ↓ REM sleep
- ↓ Slow wave sleep
- ↓ Total Sleep Time
- ↑ Arousals


= LESS HIGH QUALITY SLEEP

# *Geriatric Syndromes*

- *Dementia and Delirium*
- *Falls*
- *Urinary Incontinence*
- *Pressure Ulcers*
- *Functional Decline*

# Dementia and Delirium

- Dementia is a syndrome of **progressive decline** in which multiple intellectual abilities deteriorate, causing both cognitive and functional impairment.
- Delirium is an **acute state** of confusion
- Delirium may be the only manifestation of a **life-threatening illness** in the older adult.



Infection  
Drugs

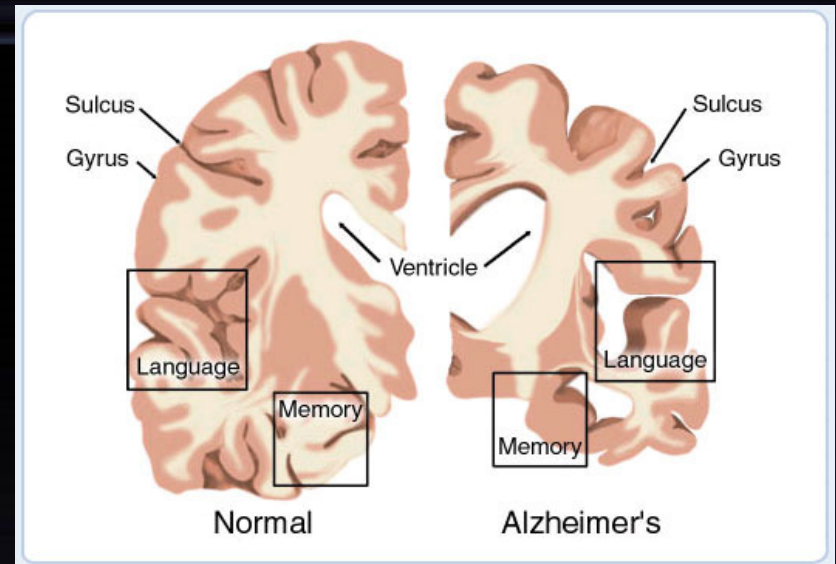
# Alzheimer's Disease

Alzheimer's disease is defined as **premature aging** of the brain, usually beginning in mid-adult life and progressing rapidly to extreme loss of mental powers similar to that seen in very, very old age.

## Features

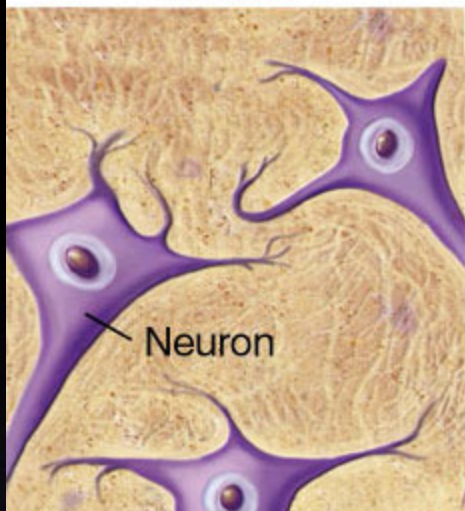
- (1) An amnesic type of memory impairment
- (2) Deterioration of language
- (3) Visuospatial deficits.

**Motor and sensory abnormalities, gait disturbances, and seizures are uncommon until the late phases of the disease.**

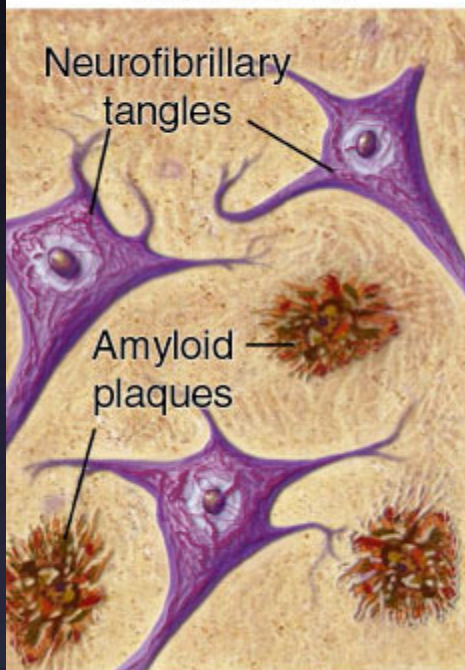




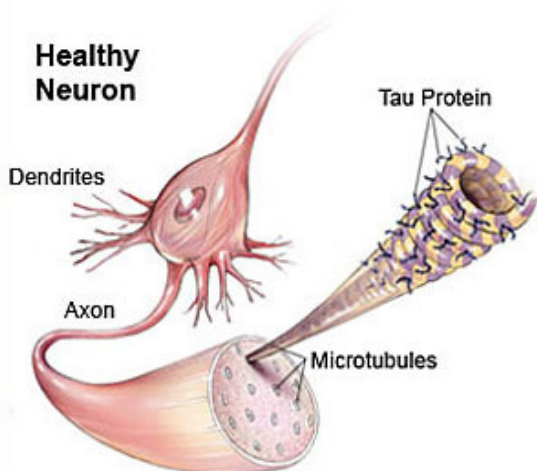
Normal



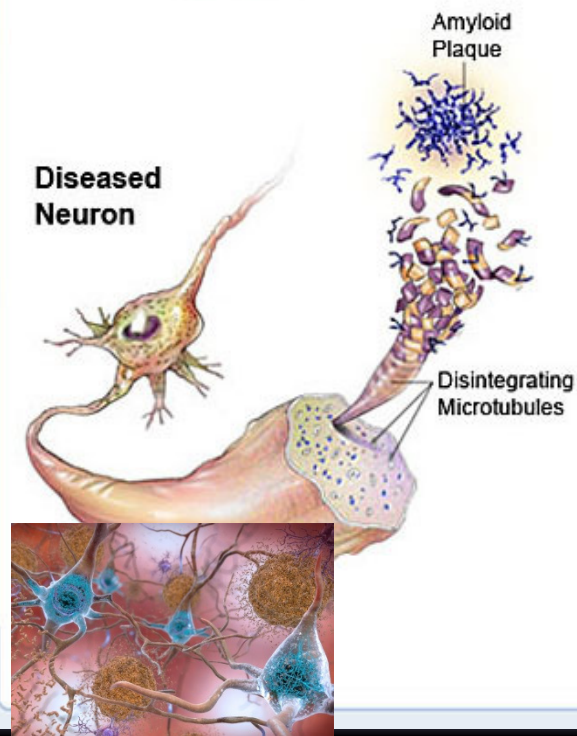
Alzheimer's



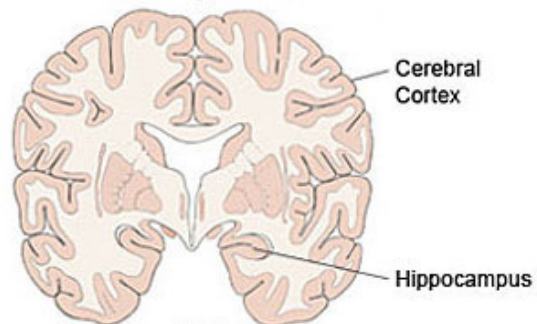
Healthy Neuron



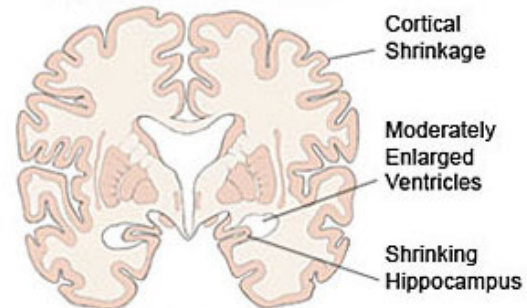
Diseased Neuron



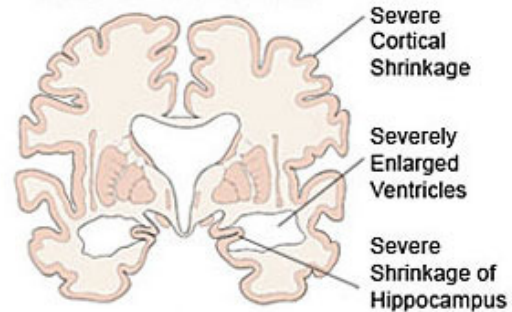
Healthy Brain



Mild Alzheimer's Disease



Severe Alzheimer's Disease





# Neurofibrillary Tangles

- These are insoluble twisted fibers found inside the brain's cells.
- Consist primarily of a protein called **tau**, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another.
- **In normal, non-demented aging, the number of tangles in each affected cell body is relatively low**
- In **Alzheimer's disease**, however, the tau protein is abnormal and the microtubule structures collapse.

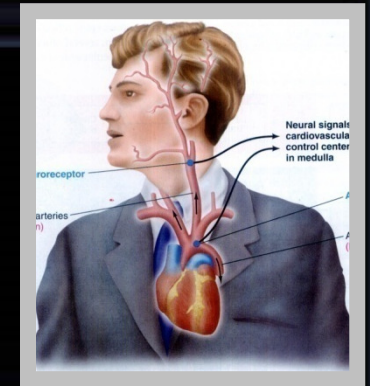
# Amyloid Plaques

- **Plaques have not been found to be a consistent feature of normal aging**
- It is hallmark of Alzheimer's disease
- There is accumulation of **amyloid plaques between nerve cells** (neurons) in the brain.
- Amyloid is a general term for protein fragments that the body produces normally. Beta amyloid is a protein fragment snipped from an amyloid precursor protein (APP).
- In a healthy brain, these protein fragments are broken down and eliminated. In Alzheimer's disease, the **fragments accumulate** to form hard, insoluble plaques.

# Decline in Autonomic Functions

- Aging is associated with **depressed Heart rate variability** which is associated with increased mortality.
- For eg: Changing position from supine to standing may trigger dizziness more frequently with ageing reflect the **diminished cardiovascular sympathetic modulations** and significant decline in overall autonomic functions
- Variation in heart rate response to deep breathing and valsalva manoeuvre is decreased because of impaired vagal control of heart rate with increasing age.

# Carotid sinus hypersensitivity



- Carotid sinus syncope occurs when there is an **exaggerated vagal response to carotid sinus stimulation**
- Provoked by wearing a tight collar, looking upwards or turning the head
- Carotid sinus syndrome occurs in the elderly and mainly results in bradycardia.
- Most common etiologies of atrioventricular block
- **Remember:** Do not massage both carotids simultaneously.