UNDERSTANDING ALZHEIMER'S DISEASE

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ALOIS ALZHEIMER

- The disease was brought to modern attention by Dr Alois Alzheimer, with his description of his patient, Auguste Dieter.

- She had the symptoms now associated with Alzheimer's disease:
- Profound loss of memory (everyone)
- Impaired sleep wake cycle (common)
- Accusations of infidelity (less common)

BRAIN PATHOLOGY

- Alzheimer also examined Auguste's brain and published his findings in 1906.
- He identified plaques and tangles in the brain. The plaques are extracellular and the tangles intracellular. We now know that the plaques contain a protein called amyloid. The tangles are caused by another protein, tau.
- It was Kraepelin, who believed that mental illness had a biological basis, who coined the term "Alzheimer's disease".

EARLY AND LATE ONSET AD

- There are two forms of the disease, early onset and late onset. The underlying genetics are very different but the brain pathology is the same.
- Early onset AD before ~age 60, about 5% of all cases.
- Late onset AD, after age 65, these are the majority of the cases. Here age is a risk factor.
- Common figures are that 10% of those over 65 and 20-40% of those over 80 have AD.

AN ANCIENT DISEASE

- Not a new condition.
- Worse still than all decay of limbs is memory's decay, which recalls neither his slaves' names nor the friend's features, with whom he supped but yesternight, nor those whom he begot and bred. Juvenalis 60-140 AD

- In Shakespeare's King Lear, Lear did not recognize his daughter Cordelia.

GOOD NEWS

- The good news is that the *rates* of AD are going down. This was first observed last year in men in England and is now true for both sexes in the US.
- Presumably due to changes in behavior that have been going on for some time.
- EXERCISE, EXERCISE, EXERCISE!

PRESENTATION

- Types of memory.
- Structure of the brain.
- Brain regions and memory.
- Spread of plaques and tangles in AD.
- Consequent memory losses.
- Damage to the Ach system.
- Drugs.
- Reasons for failure (?).
- Helpful life style changes.

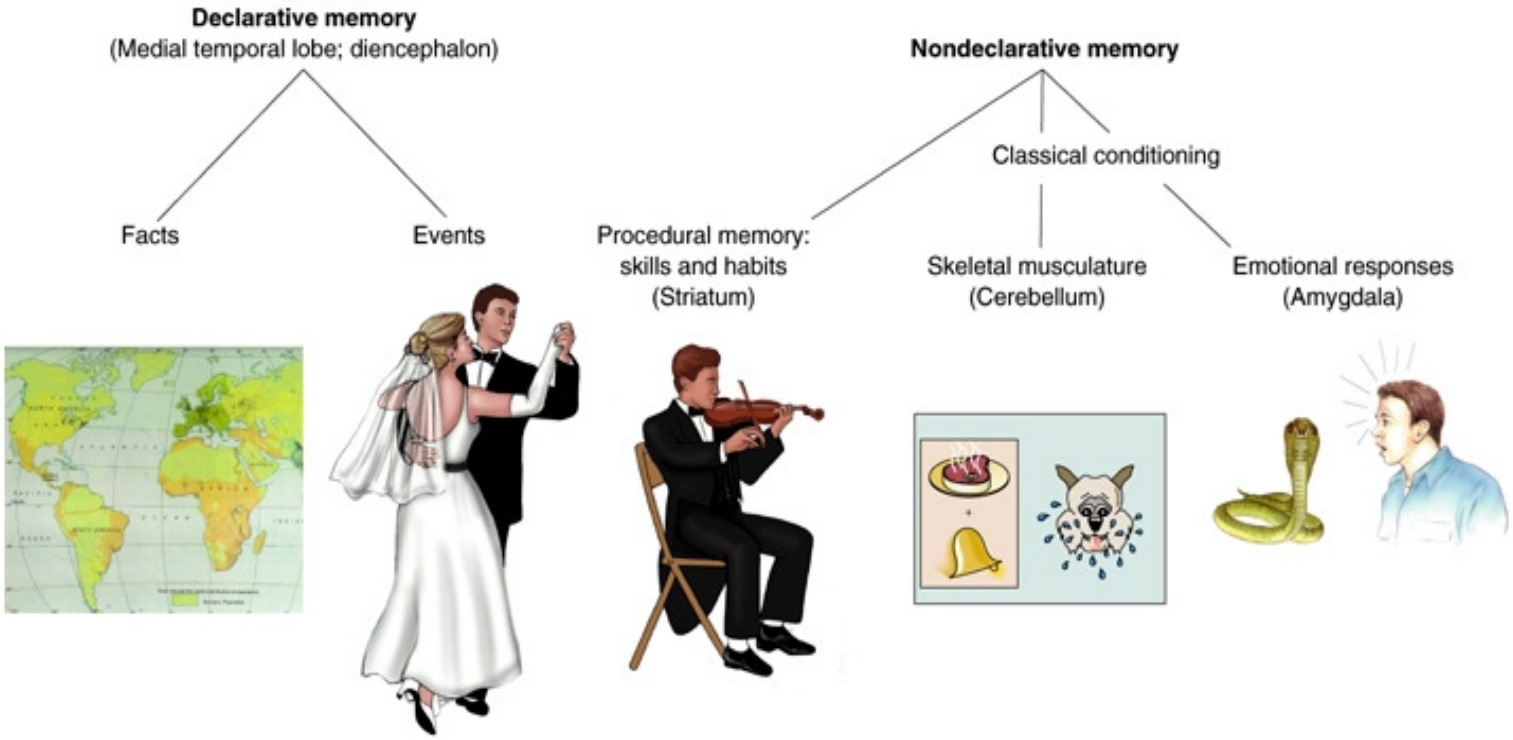
TYPES OF MEMORY

- Episodic memory; memory for events, a wedding, a child's birth, a party, a holiday.
- Nine/ eleven.
- Semantic memory; memory for facts, Paris is the capital of France. The names of things and people.
- You have to store and then retrieve these memories. Sometimes just keep them in mind.

TYPES OF MEMORY, 2

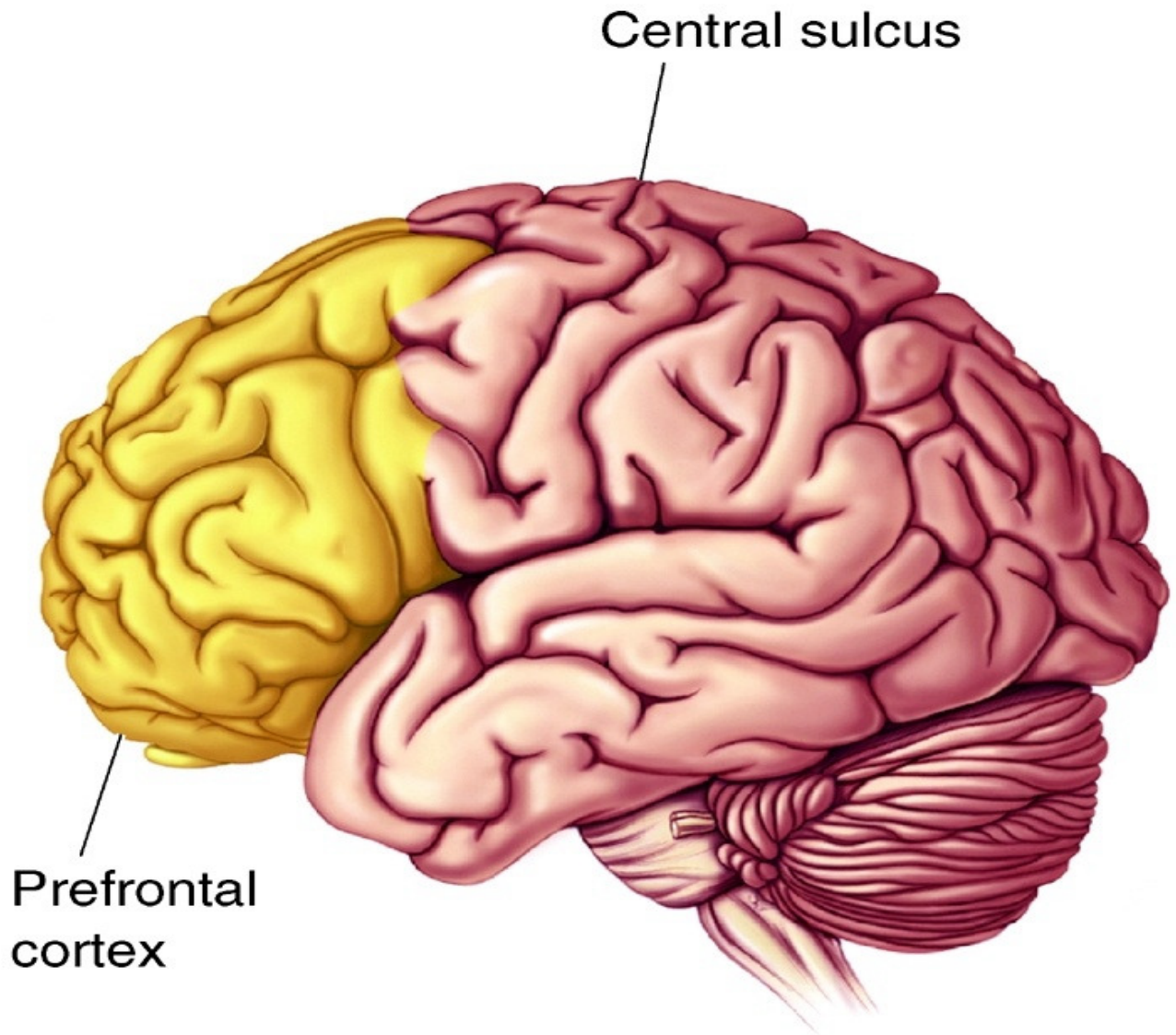
- Habit memory; riding a bicycle, using a computer keyboard.
- Spatial memory; remembering where to go, where things were placed.
- Fear memories, remembering something is dangerous, not smoking in bed.
- The different types of memory depend on different regions of the brain.

THERE ARE TWO MAIN TYPES OF LONG-TERM MEMORY,

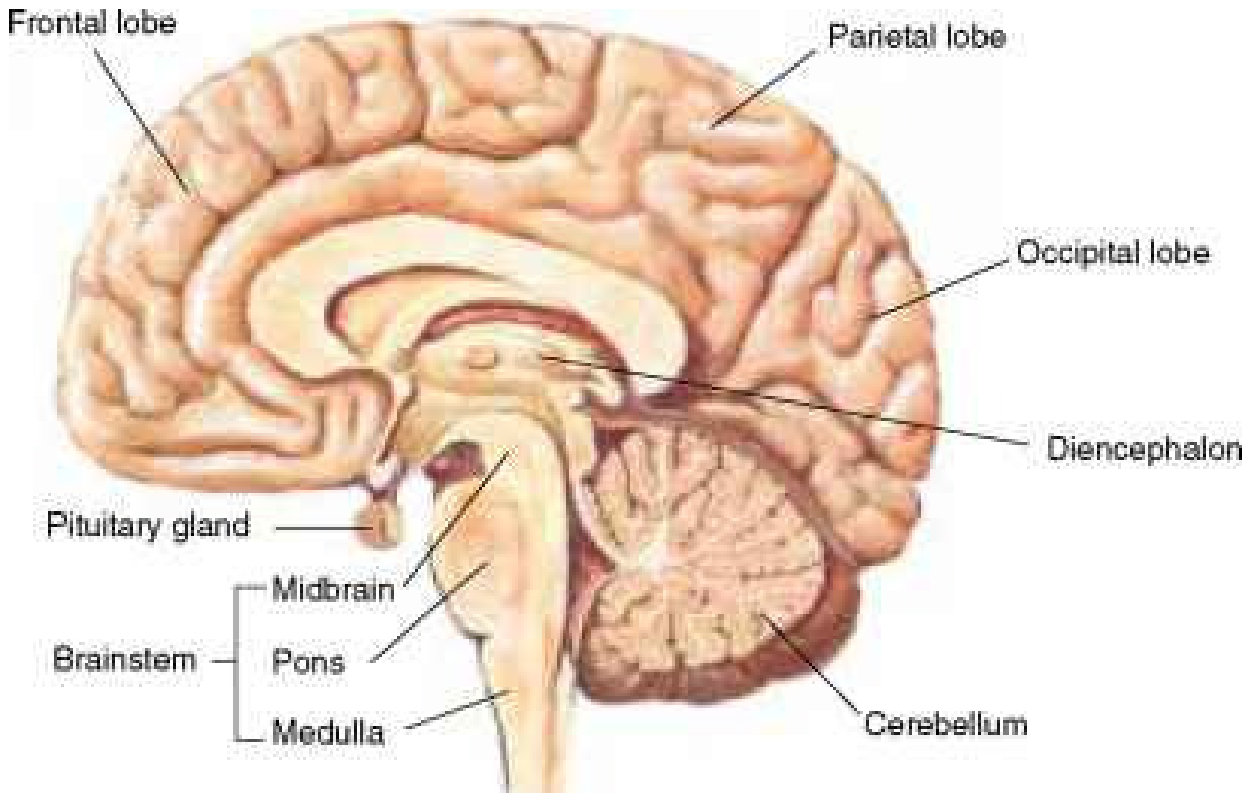


Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins

LATERAL VIEW OF THE CORTEX



MEDIAL, INNER, VIEW OF THE BRAIN



AMYLOID STAGES IN AD

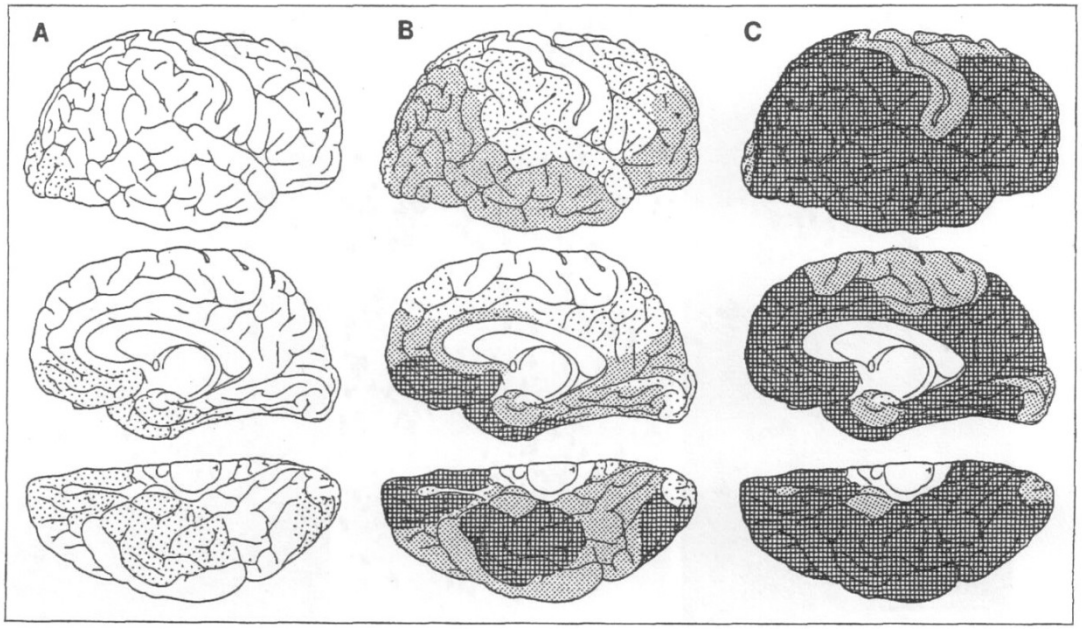
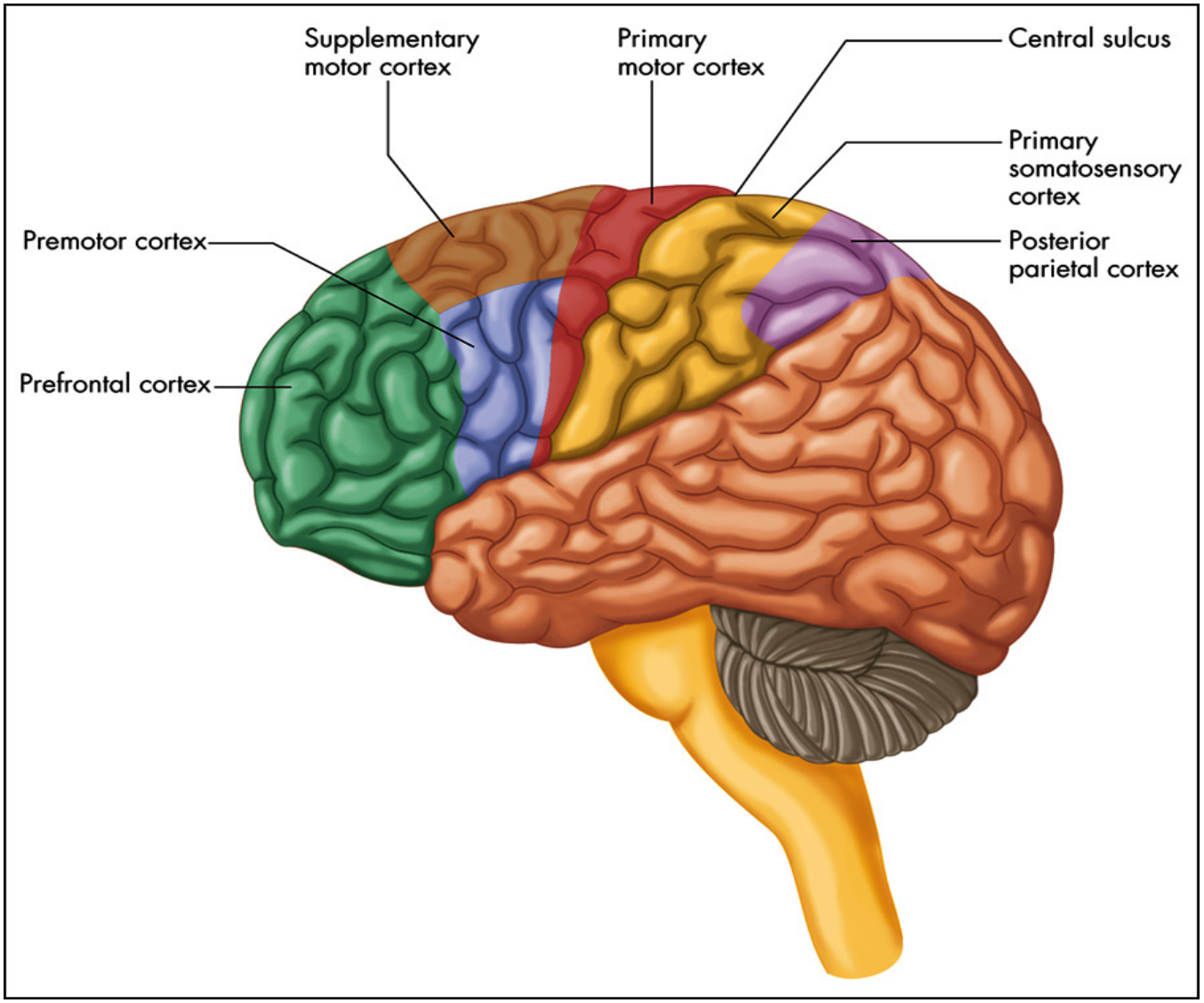


Fig. 1. Distribution pattern of amyloid deposits. **Stage A** Initial deposits can be found in basal portions of the isocortex. **Stage B** The next stage shows amyloid in virtually all isocortical association areas. The hippocampal formation is only mildly involved. **Stage C** In the end-stage deposits can be seen in all areas of the isocortex including sensory and motor core fields. Increasing density of shading indicates increasing numbers of amyloid deposits

TYPES OF CORTEX

- Primary sensory cortex: receives sensory input, visual, auditory and somatosensory.
- Primary motor cortex; sends signals down the spinal chord and thence to the muscles.
- Association cortex; modifications of initial sensory and motor information.

motor cortex regions



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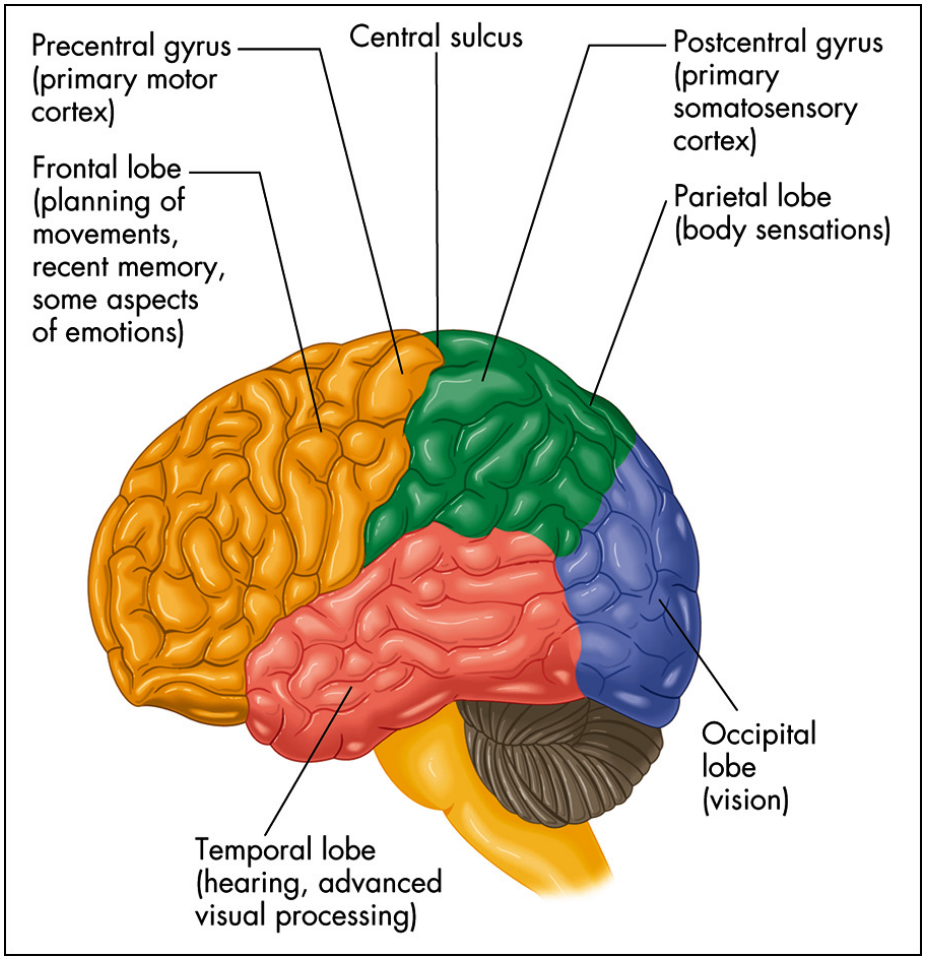
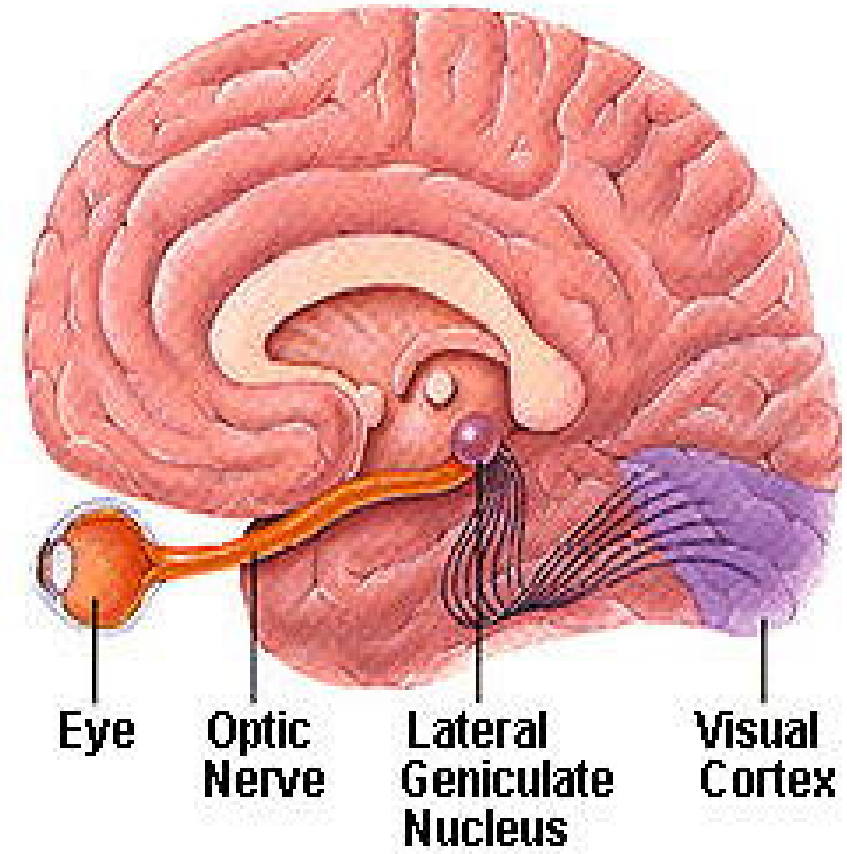
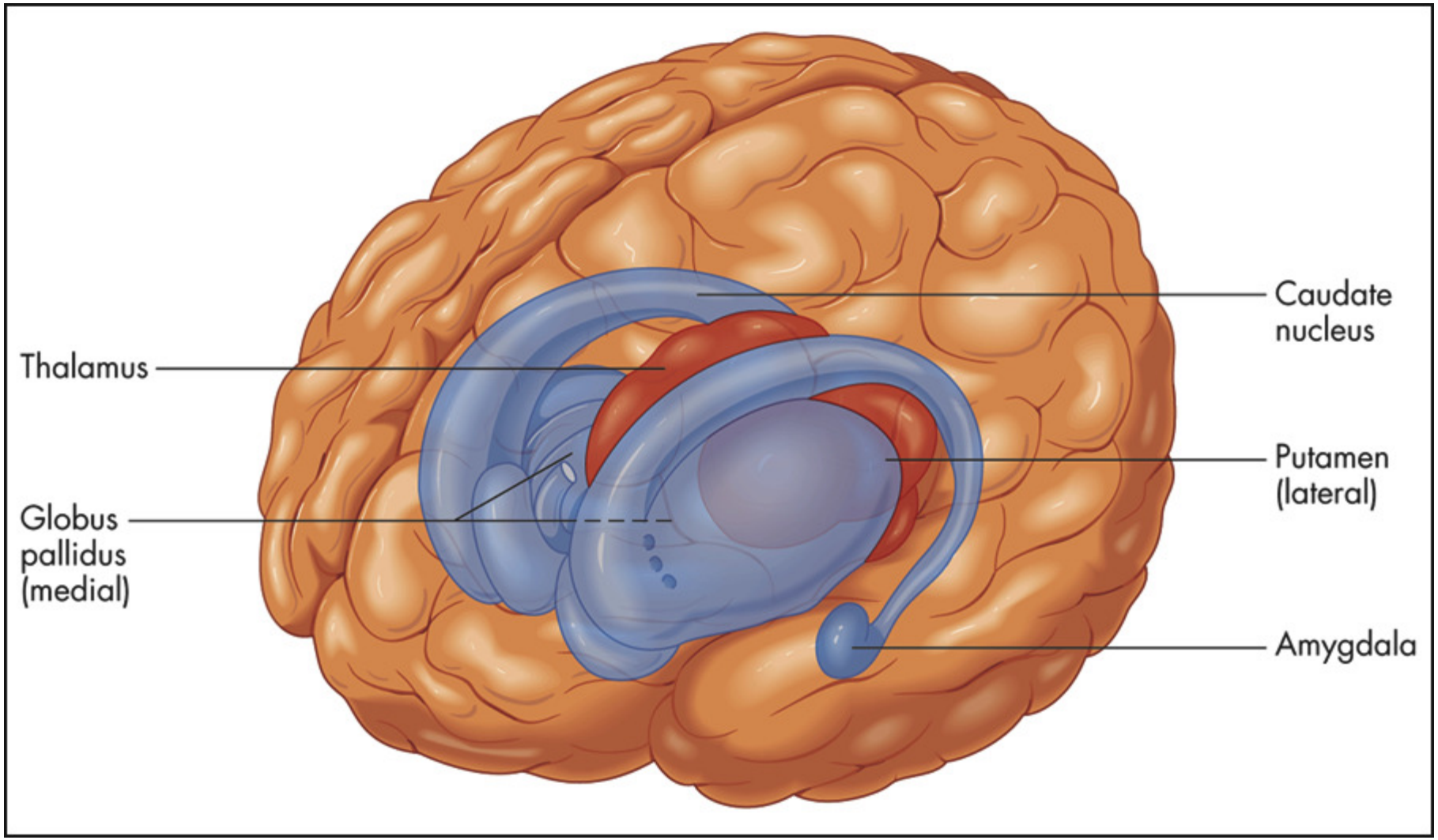
THE CORTEX AND THE LOBES OF THE BRAIN.



Visual signals travel to the cortex via the thalamus, the lateral geniculate nucleus is part of the thalamus.



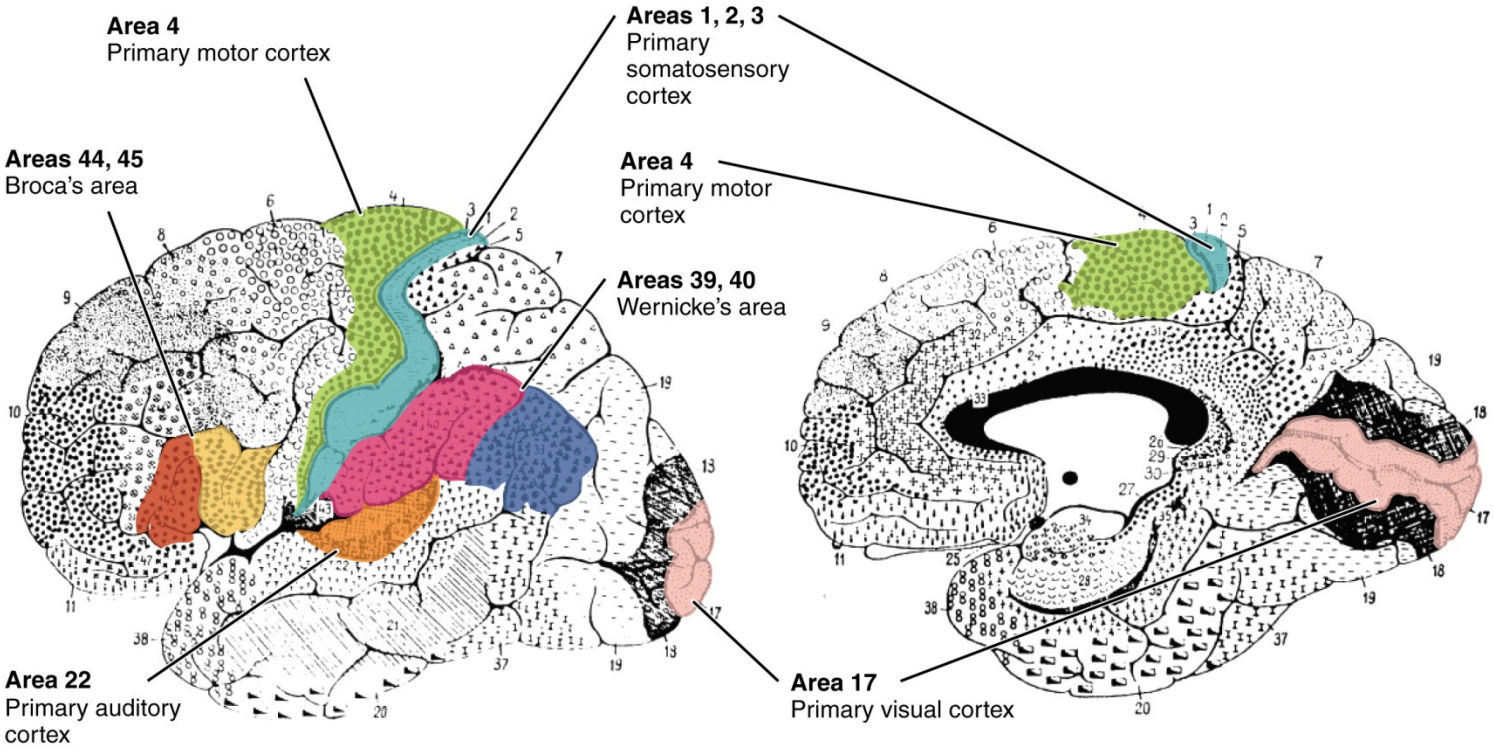
THE THALAMUS AND THE BASAL GANGLIA,



SUBCORTICAL STRUCTURES

- The thalamus receives sensory information and sends it to the apprpriate cortex.
- The basal ganglia are part of the motor system. They connect with the cortex via the thalamus.
- May provide back up for words and facts, maybe involved in memory for music (goes very late).
- The amygdala is involved with emotions. We remember an emotional event better. It helps us learn and remember what is dangerous.

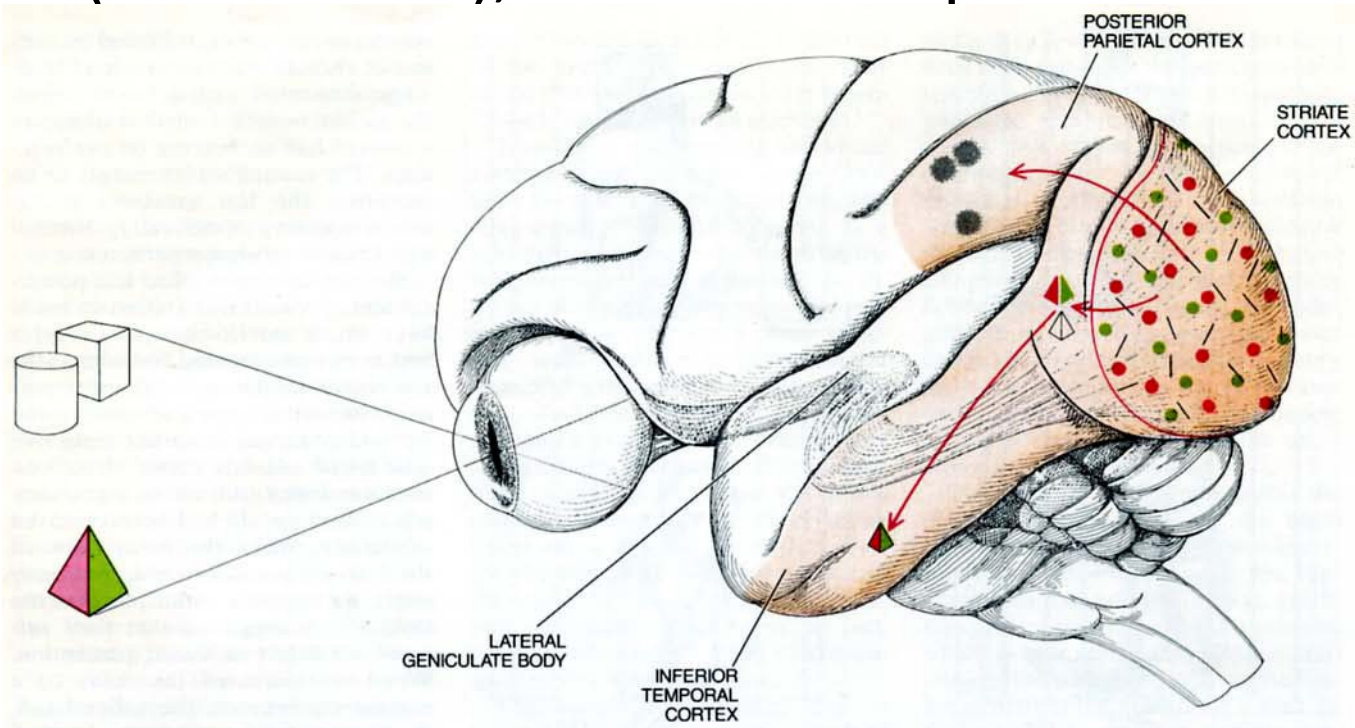
BRODMANN'S AREAS, ANOTHER VIEW OF THE BRAIN, note auditory cortex



Brodmann's cytotechtonic map (1909):
Lateral surface

Brodmann's cytotechtonic map (1909):
Medial surface

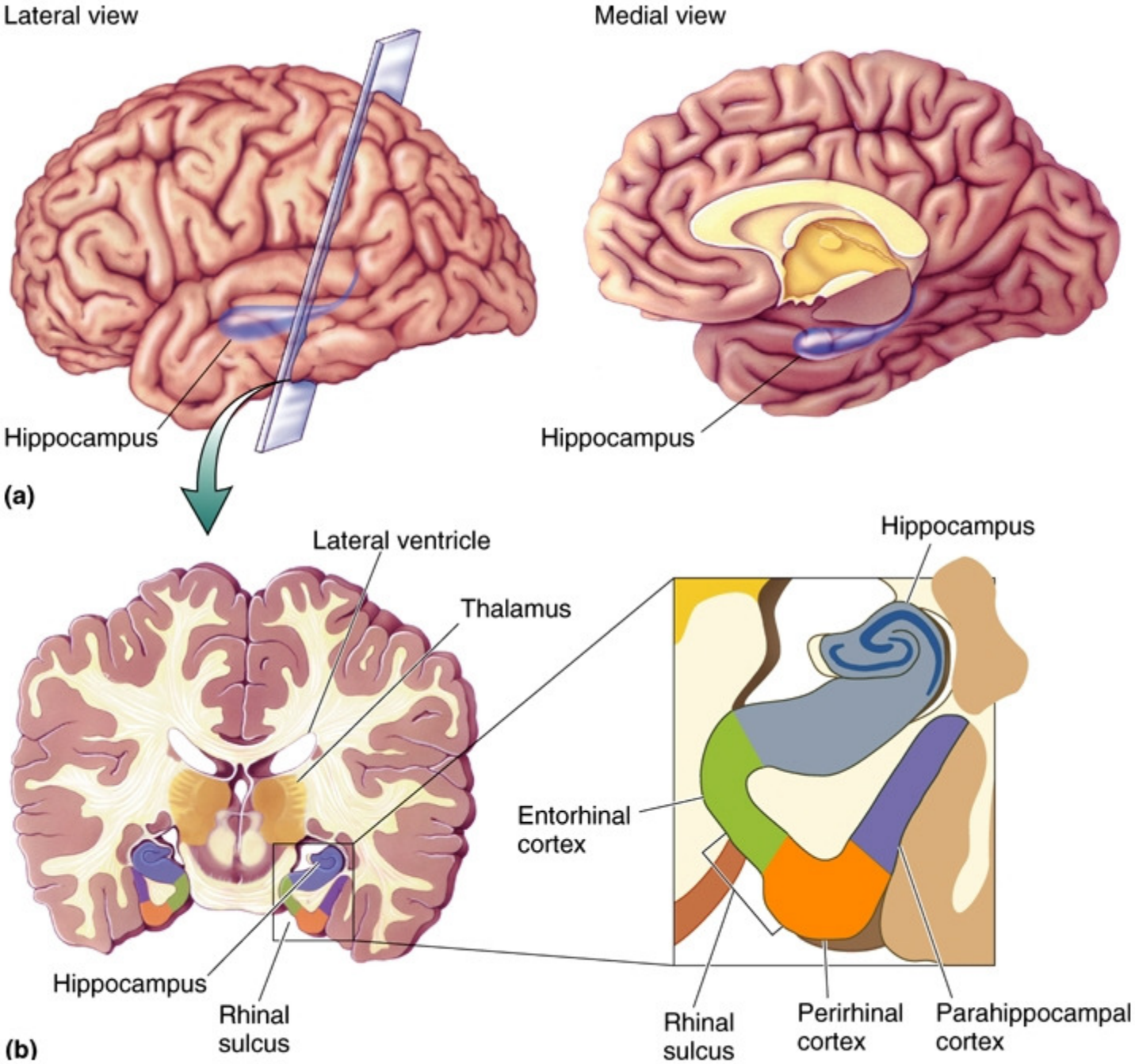
2 VISUAL PATHWAYS, WHAT AND WHERE, (ATTENTION), note the temporal lobe.



VISUAL SYSTEM processes information along two pathways in the cortex, the outer layer of the brain. Initial processing of the information (which arrives from the retina by way of the lateral geniculate body) takes place at the beginning of the pathways, in the striate cortex. Individual neurons there respond to simple, spatially limited elements in the visual field, such as edges and spots of color. Along the lower pathway (which in fact consists of a number of diverging and reconverging channels) neurons analyze broader properties of an object, such as overall shape or color. At the far end of this "object" pathway, in the inferior temporal cortex, individual neurons are sensitive to a variety of properties and a broad expanse of the visual world, which suggests that fully processed information about an object converges there. Along the upper cortical pathway, which has not been studied in the same detail, the spatial relations of a scene are analyzed. A perception of an object's position with respect to other landmarks in the visual field, for example, would take shape in the "spatial" pathway's final station, which is situated in the posterior parietal cortex.

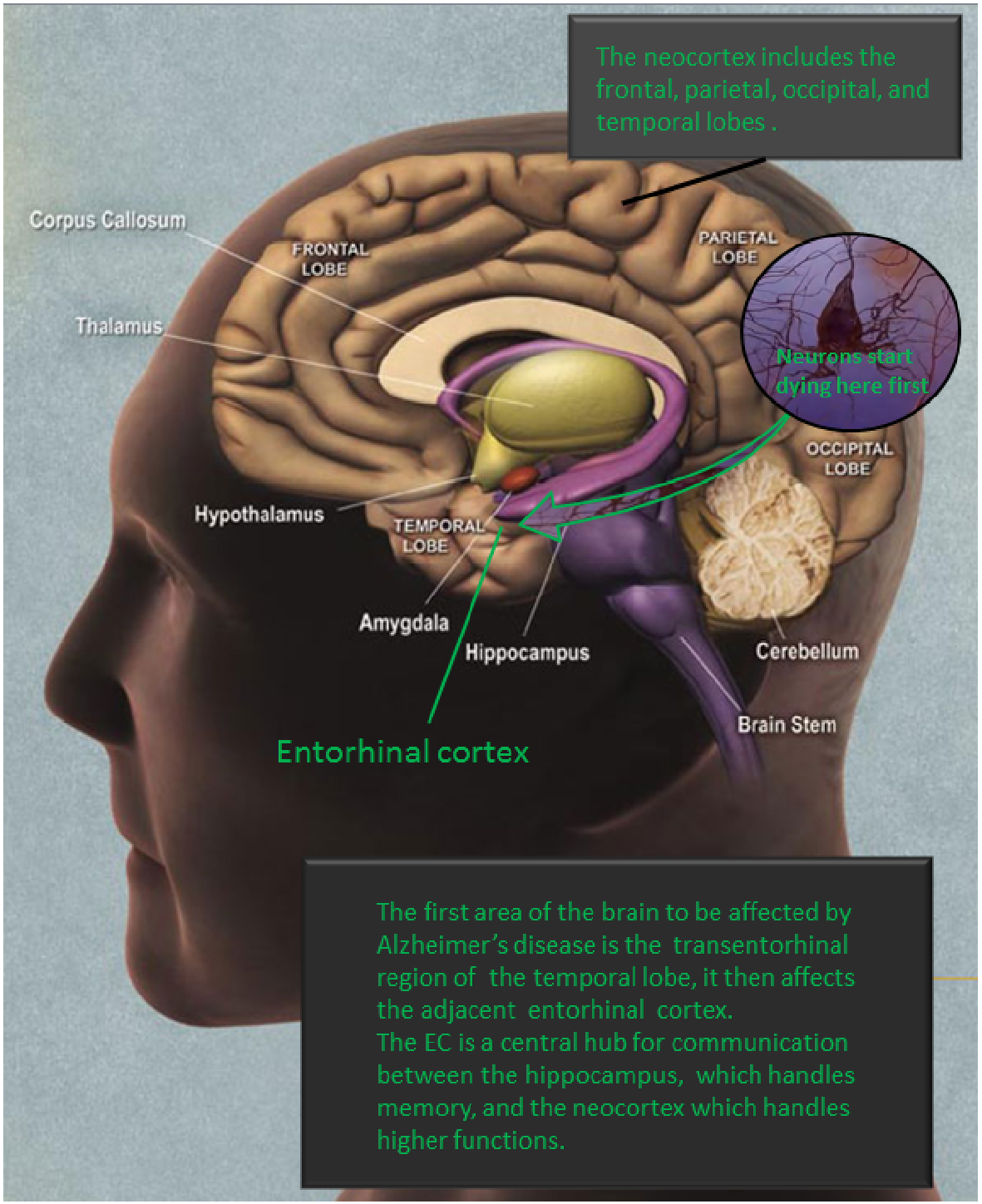
TWO MORE REGIONS

- The entorhinal cortex connects the association cortex to the hippocampus.
- It is also contains “grid cells” which map space, so is important in spatial memory.
- The hippocampus is essential for storing episodic memory, memory for events.
- It contains “place cells” and is essential for spatial memory.



PREFRONTAL CORTEX

- Very large in humans;
- Retrieves memories for events and for facts.
- Keeps things in mind.
- Inhibits the amygdala. The “brakes of the brain”.


The neocortex includes the frontal, parietal, occipital, and temporal lobes .
Corpus Callosum
FRONTAL LOBE
PARIETAL LOBE
Thalamus
Neurons start dying here first
OCCIPITAL LOBE
Hypothalamus
TEMPORAL LOBE
Amygdala
Hippocampus
Cerebellum
Brain Stem
Entorhinal cortex
The first area of the brain to be affected by Alzheimer's disease is the transentorhinal region of the temporal lobe, it then affects the adjacent entorhinal cortex.
The EC is a central hub for communication between the hippocampus, which handles memory, and the neocortex which handles higher functions.

AMYLOID STAGES

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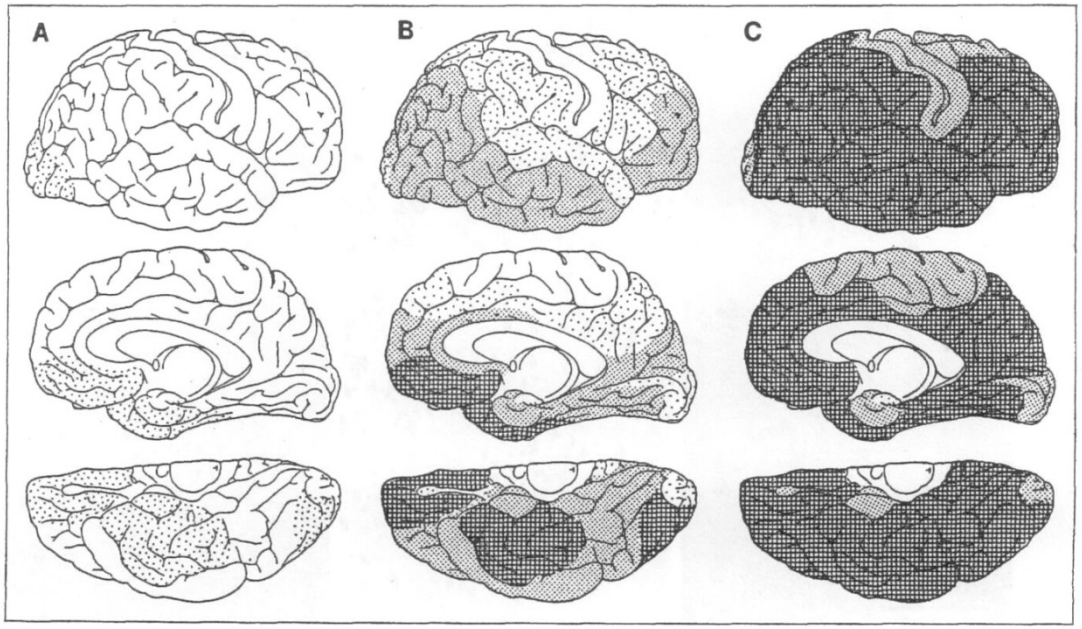


Braak & Braak 1991.

Fig. 1. Distribution pattern of amyloid deposits. **Stage A** Initial deposits can be found in basal portions of the isocortex. **Stage B** The next stage shows amyloid in virtually all isocortical association areas. The hippocampal formation is only mildly involved. **Stage C** In the end-stage deposits can be seen in all areas of the isocortex including sensory and motor core fields. Increasing density of shading indicates increasing numbers of amyloid deposits

NFT CHANGES,(tangles made of tau), Braak and Braak

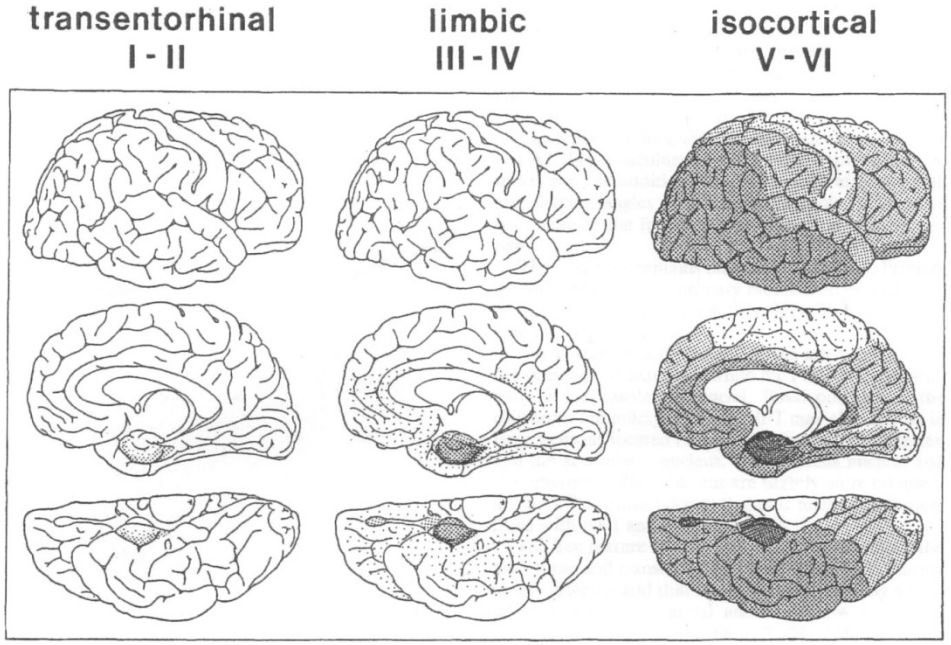


Fig. 4. Distribution pattern of neurofibrillary (NF) changes [neurofibrillary tangles (NFT) and neuropil threads (NT)]. Six stages (I–VI) can be distinguished. Stages I–II show alterations which are virtually confined to a single layer of the transentorhinal region (transentorhinal I–II). The key characteristic of stages III-IV is the severe involvement of the entorhinal and transentorhinal layer Pre-α (limbic III–IV). Stages V–VI are marked by isocortical destruction (isocortical V–VI). Increasing density of shading indicates increasing severity of NF changes

MEMORY OVERVIEW

Sensory information arrives in primary sensory cortex.

It is transferred and processed in association cortex. It passes through the entorhinal cortex to the hippocampus.

It is processed in the hippocampus and returned to the association cortex for storage. It is retrieved by the prefrontal cortex when a memory is called up.

SPREAD OF AMYLOID AND TAU

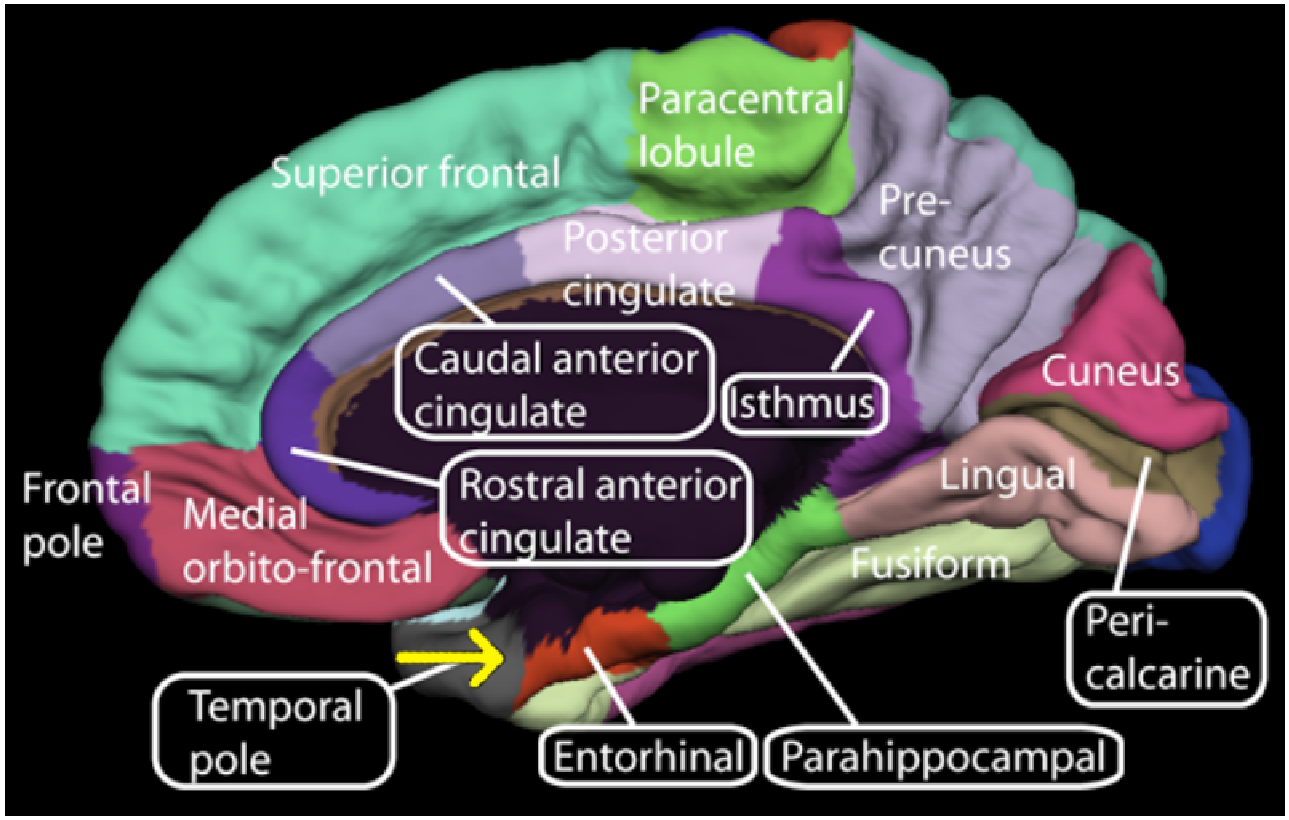
- Damage begins in the medial temporal lobe. The entorhinal and hippocampus are damaged early on. Then the damage spreads to adjacent cortex, including the prefrontal region.
- The primary motor and sensory cortices are damaged last.
- The basal ganglia are damaged later.

ROLES OF THE LATERAL TEMPORAL LOBE CORTEX

- Damage here leads to an inability to recognize, or name, familiar objects that are seen.

- Regions of the cortex, e.g. the fusiform gyrus, are needed for facial recognition. Damage in this region of the temporal lobe may lead to prosopagnosia, the inability to recognise faces, including your own.

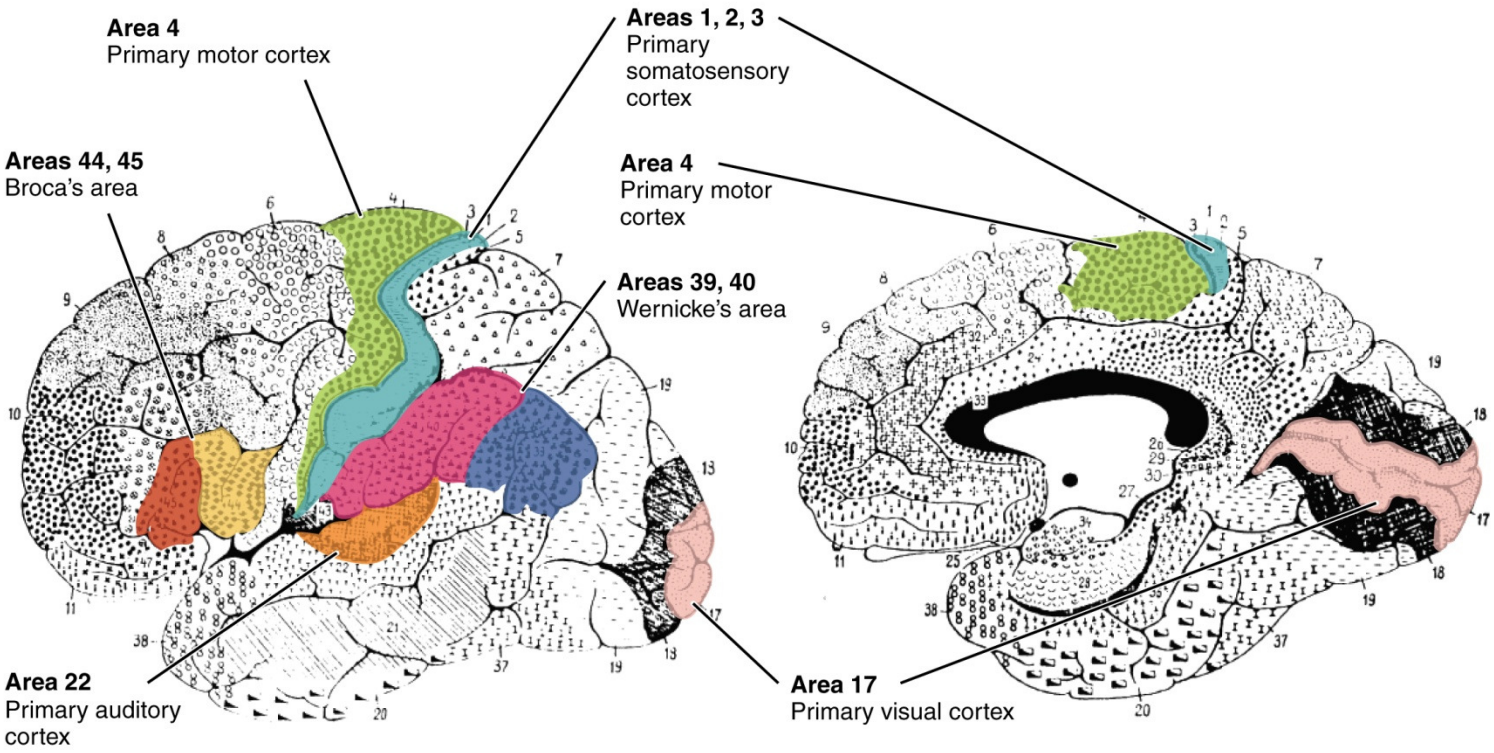
Entorhinal cortex and fusiform gyrus. (wikipedia)



LOSSES IN AD AFTER DAMAGE TO SPECIFIC REGIONS

- EC, damaged early, get lost, begin to be unable to recall words.
- Hippocampus, get lost, forget recent events, e.g. visits by family. Annoying, as patient can recall old memories but cannot form new memories for events. Keeps asking the same question.
- Fusiform gyrus, forget faces e.g. of family.
- Temporal lobe cortex, initially have difficulty recalling a word (pre-frontal retrieval needed). But when the outer/lateral temporal cortex is damaged, the words stored there are gone.

BRODMANN'S AREAS, note Broca's area, involved in speech production



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Lateral surface

Brodmann's cytotechtonic map (1909):
Medial surface

OTHER LOSSES

- Amygdala, become angry, damage to the amygdala, or to the pre frontal cortex which can no longer inhibit the amygdala.
- Do dangerous things, put paper plate on stove.
- Prefrontal cortex, Inability to recall old events or facts.
- Impulsive behavior, paranoia.
- Inability to plan and to see consequences.
- Basal ganglia, inability to type on computer.

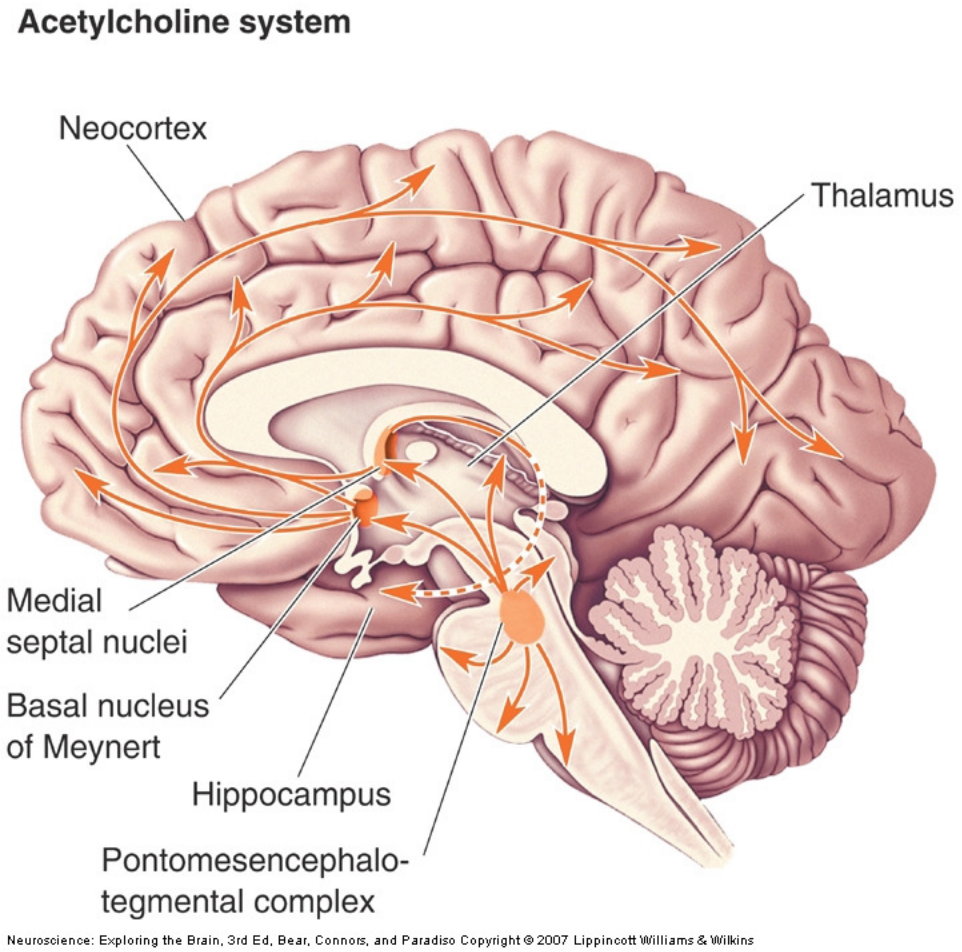
WHAT IS NOT IMPAIRED

- Motor cortex.
- Not necessarily good.
- People try to drive when they should not.
- Parietal lobe damage, do not orient self correctly in space. Pre motor damage, do not plan series of actions.
- Can hit accelerator not brake.
- Spatial losses too.

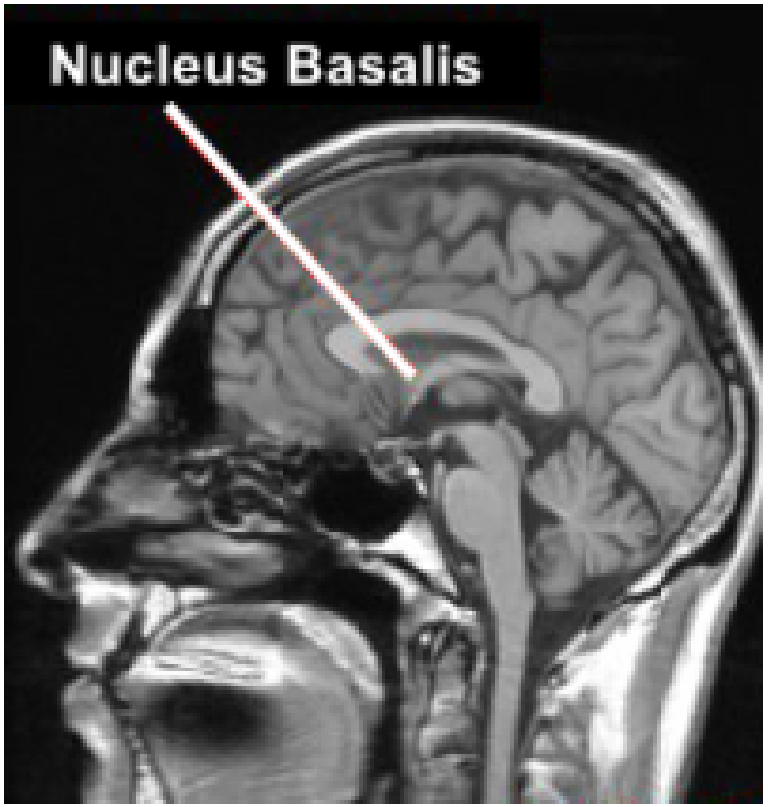
OTHER BRAIN DAMAGE

- The basal nucleus, where the neurotransmitter acetylcholine, ACh is produced, is damaged in AD.
- ACh is used in the hippocampus and is involved in memory.
- Loss of ACh leads to impaired memory. Four of the five approved drugs increase the amount of ACh.
- But there are two ACh systems and the drugs increase the ACh in both systems, causing side effects.

ACETYLCHOLINE SYSTEMS



Nucelus Basalis



DRUGS

- Acetylcholinesterase, AChE, breaks down ACh, therefore the drugs attack AChE. (They may also enhance the response to the ACh there is.)
- They are AChE inhibitors, often called cholinesterase inhibitors.

DRUGS, 2

- But there are side effects.
- ACh is also involved in the motor systems.
- It slows down the heart, this can be dangerous.
- It moves food through the gut. Thus increased levels of ACh here can lead to diarrhea. Also causes increased urination.

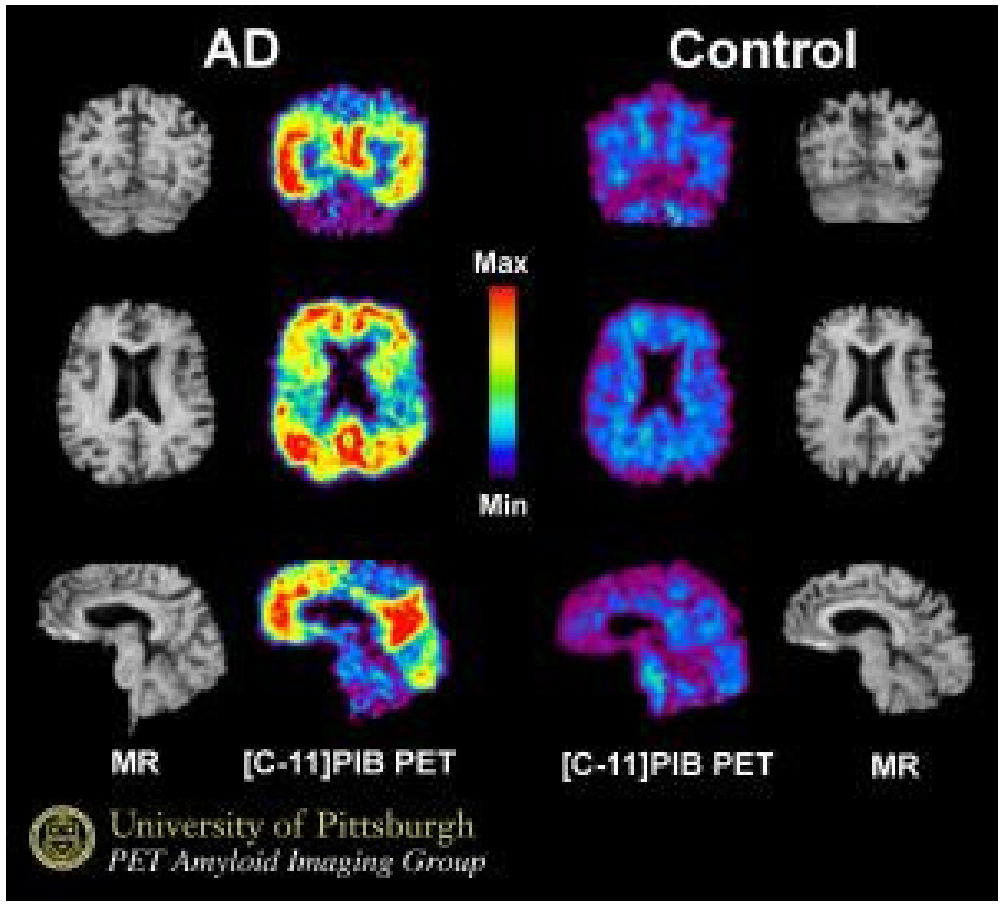
MEMANTINE/NEMANDA

- Memantine, also called Nemanda, the 5th drug approved, operates quite differently.
- It works with the glutamate system. One of the glutamate receptors, the NMDA receptor, is often overactive in AD. Memantine is an NMDA antagonist.
- A combination of an AChE inhibitor and memantine is often given as the disease progresses and can be helpful.

DRUG FAILURES

- Namenda was the last drug to be approved in the US. **In 2006.**
- The last 23 drugs have failed.
- Possibly this is because it is now realised that the brain changes begin many years before behavioral changes are seen.
- We can now see amyloid in the brain of a living person. (Klunk at Pittsburg)

IMAGING AMYLOID IN THE BRAIN, PITTSBURG COMPOUND



BIOMARKERS

- Video “can Alzheimer’s be Stopped?”
- Columbian family has had early onset since the Spanish invasion. Can test descendants for the gene, follow them, scan their brains as they age. See amyloid deposits years before see behavioral changes.
- Researchers are now looking for bio markers that will let them detect AD earlier.

GENETICS OF AD

- Early onset has different genes than late onset. If you have a mutation in a gene called pre senilin1 , you will get AD.
- Late onset has a genetic risk factor. The gene APOE has 3 normal forms, E2, E3, E4.
- Those with a copy of E4 (~20% of the population) are more likely to get AD and here the environmental effects can be stronger.

ENVIRONMENTAL EFFECTS

- Because drug development is lagging, life style changes are attracting more interest.
- Head injury is a risk for dementia.
- Stroke is a risk for dementia, particularly sub-cortical strokes.
- Smoking is a risk, because it is a risk factor for stroke.
- Reduce blood pressure, also a risk for stroke.
- Control diabetes, stroke risk.

STROKE AND AD

- There are those with heavy amyloid and plaques in the brain who do NOT have dementia.
- Study with nuns* showed that Stroke-free brains can compensate for AD lesions.
- Among Sisters with an AD brain, 93% had dementia if they had stroke damage in deep white matter, thalamus or basal ganglia.
- Only 57% were demented if they had an AD brain but no stroke damage. i.e. 43% did not have dementia.

- * “Aging with Grace” Snowdon

POSITIVE ENVIRONMENTAL FACTORS

- Anti-inflammatories are helpful, aspirin OR ibuprofin. (Baby or coated aspirin).
- Statins may be helpful. (Zocor/simvastin)
- Anti-oxidants in the food; blueberries, strawberries, curcumin.
- Nuts (walnuts), leafy green vegetables, red wine,
- Fish.
- Green tea.
- Folic acid, B12, cooked tomatoes.

OTHER FACTORS

- Education beyond HS, then an undergraduate degree, reduces the risk of AD. Theory of Cognitive reserve.
- Education can also delay onset of AD.
- Social support. (also for caregivers.)

MORE POSITIVE BEHAVIORS

- A strong day/night schedule.
- Get enough sleep (helps clear amyloid).
- Mental activity.
- EXERCISE. EXERCISE, EXERCISE.
- (Ballroom dancing.)
- Singing is a way to interact with those with AD.
- Build up strength, balance, so you do not fall.
- All these factors are important in healthy aging too.

SUMMARY

- Understanding how these brain changes affect behavior may be helpful.
- Very prevalent. Ronald Reagan helped publicize.
- Nobody chooses to get Alzheimer's, nobody normally chooses to forget.