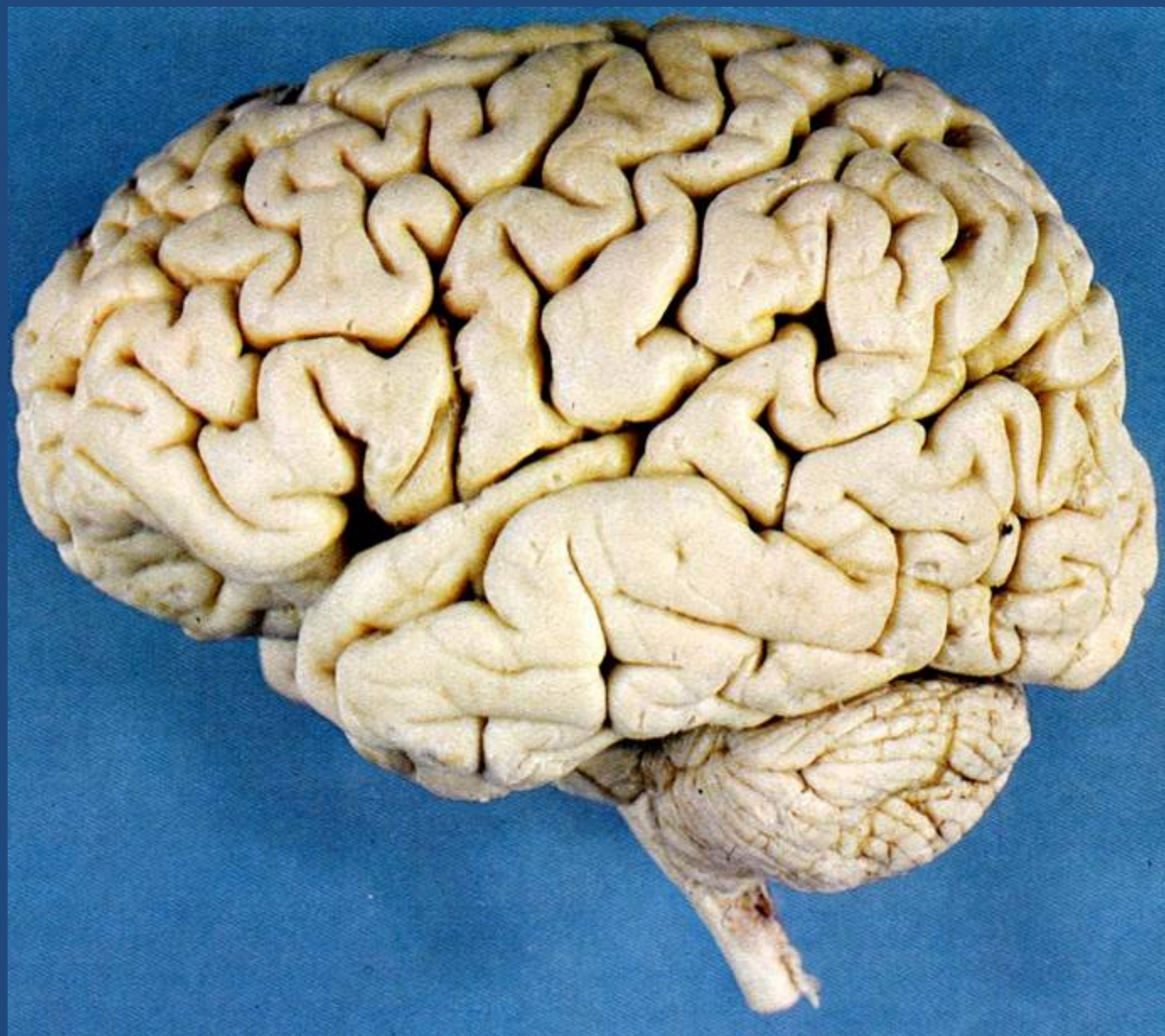
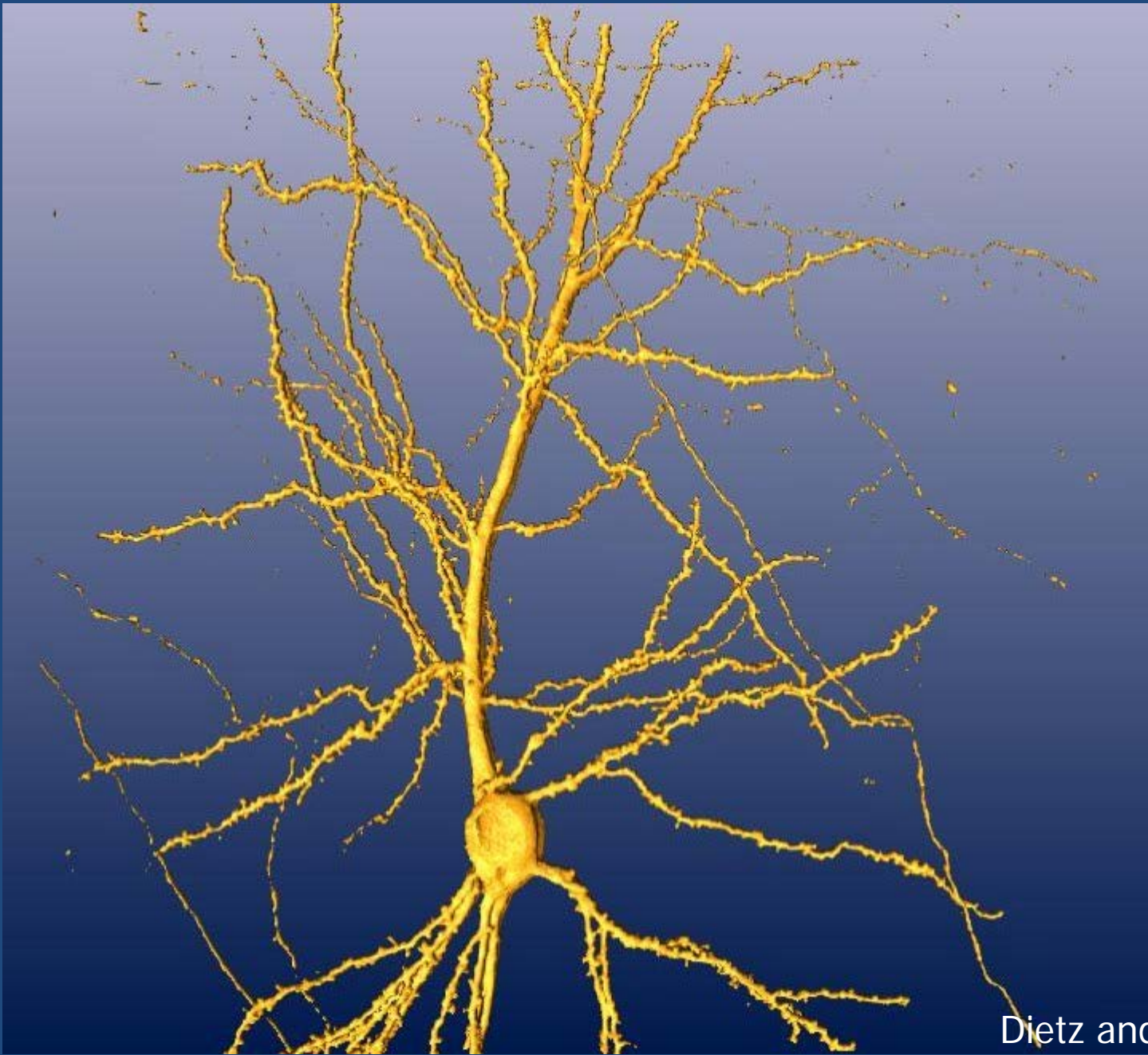
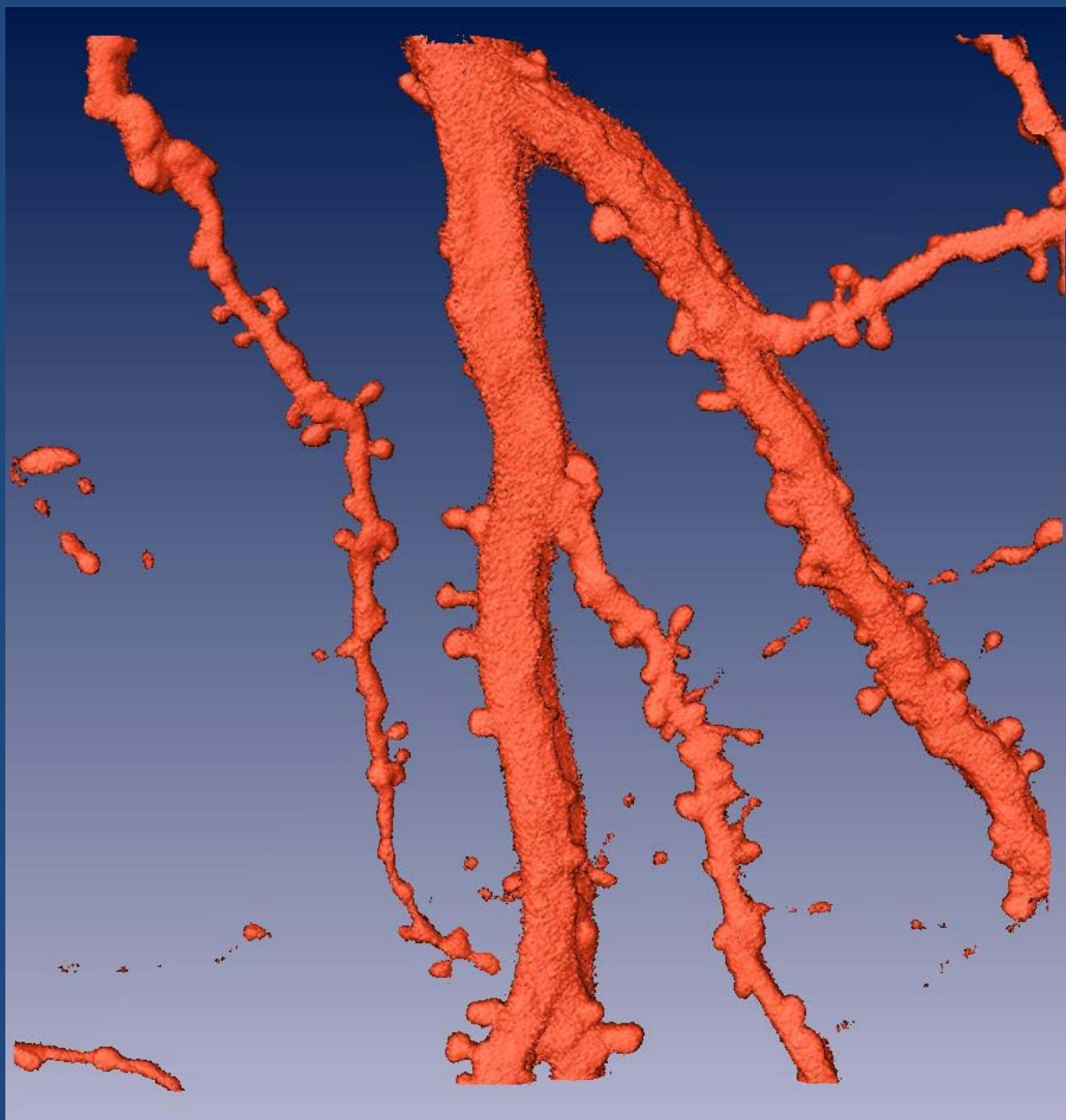


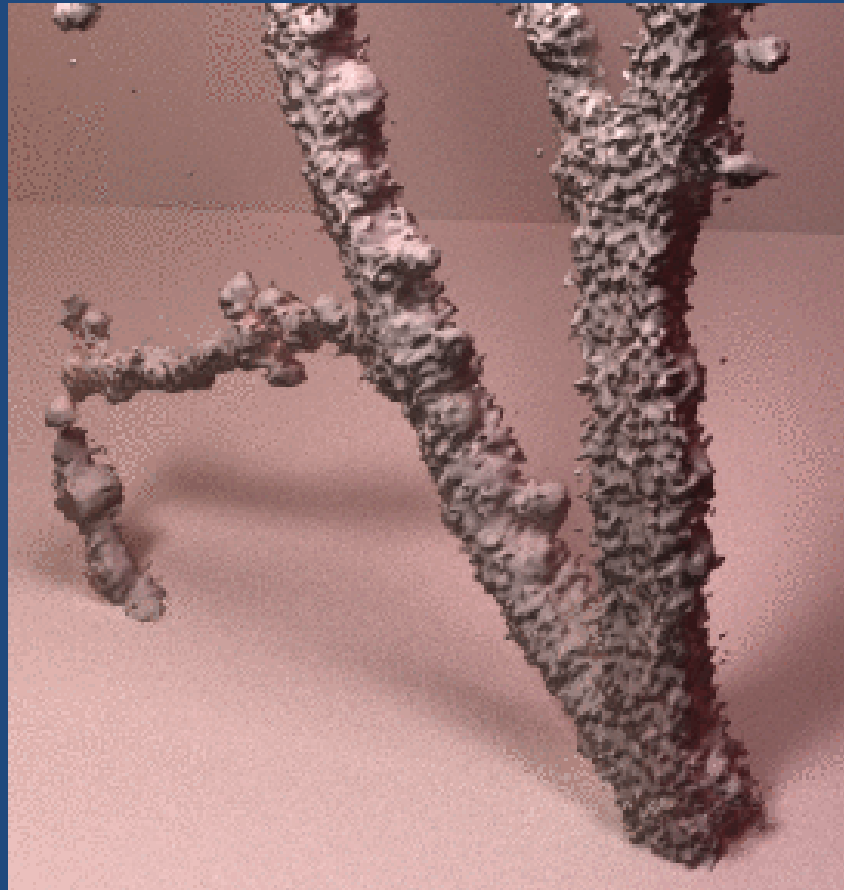
Memory, the emotional brain, and Alzheimer's disease

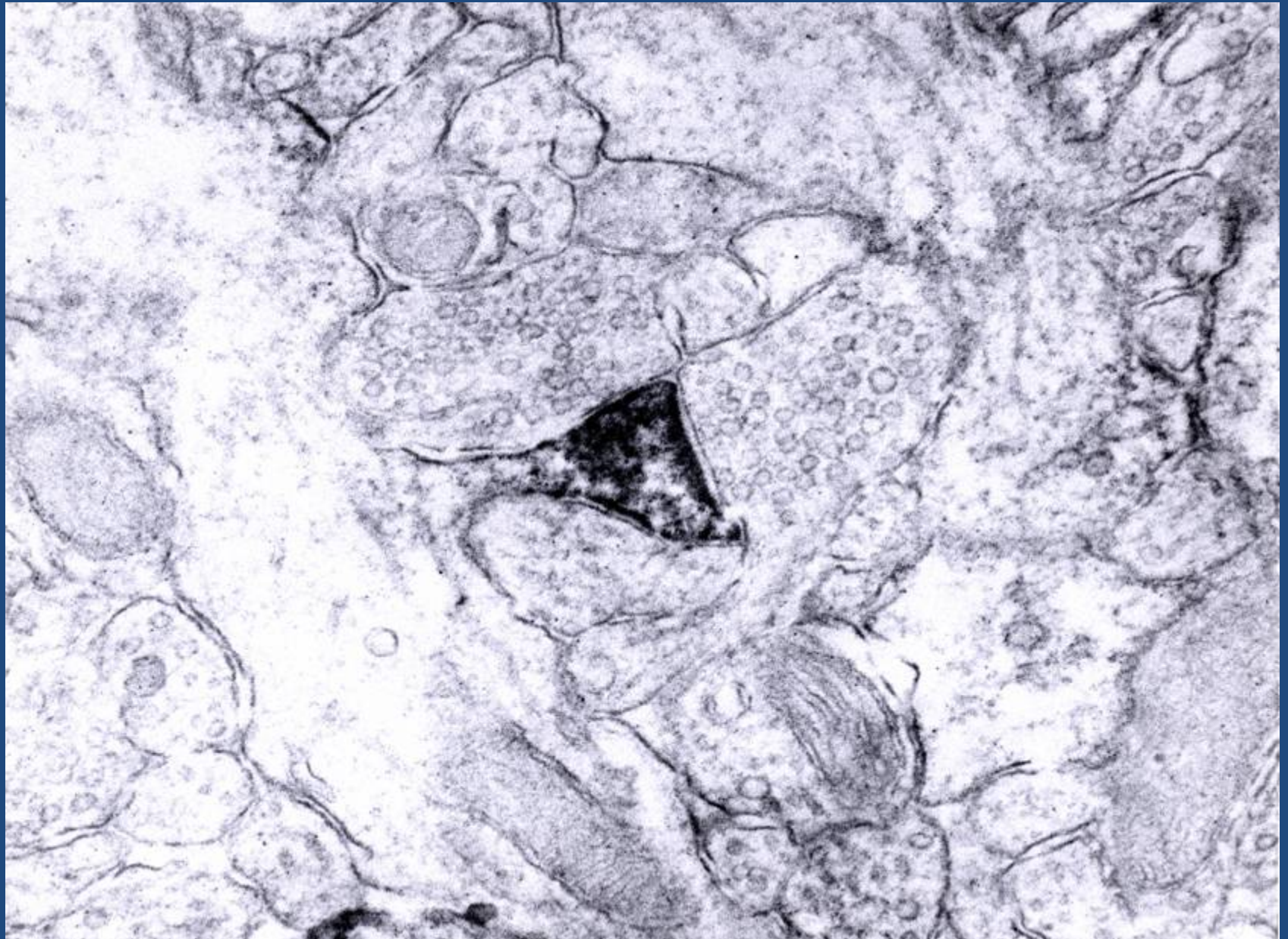




Dietz and Ouimet, 2004.

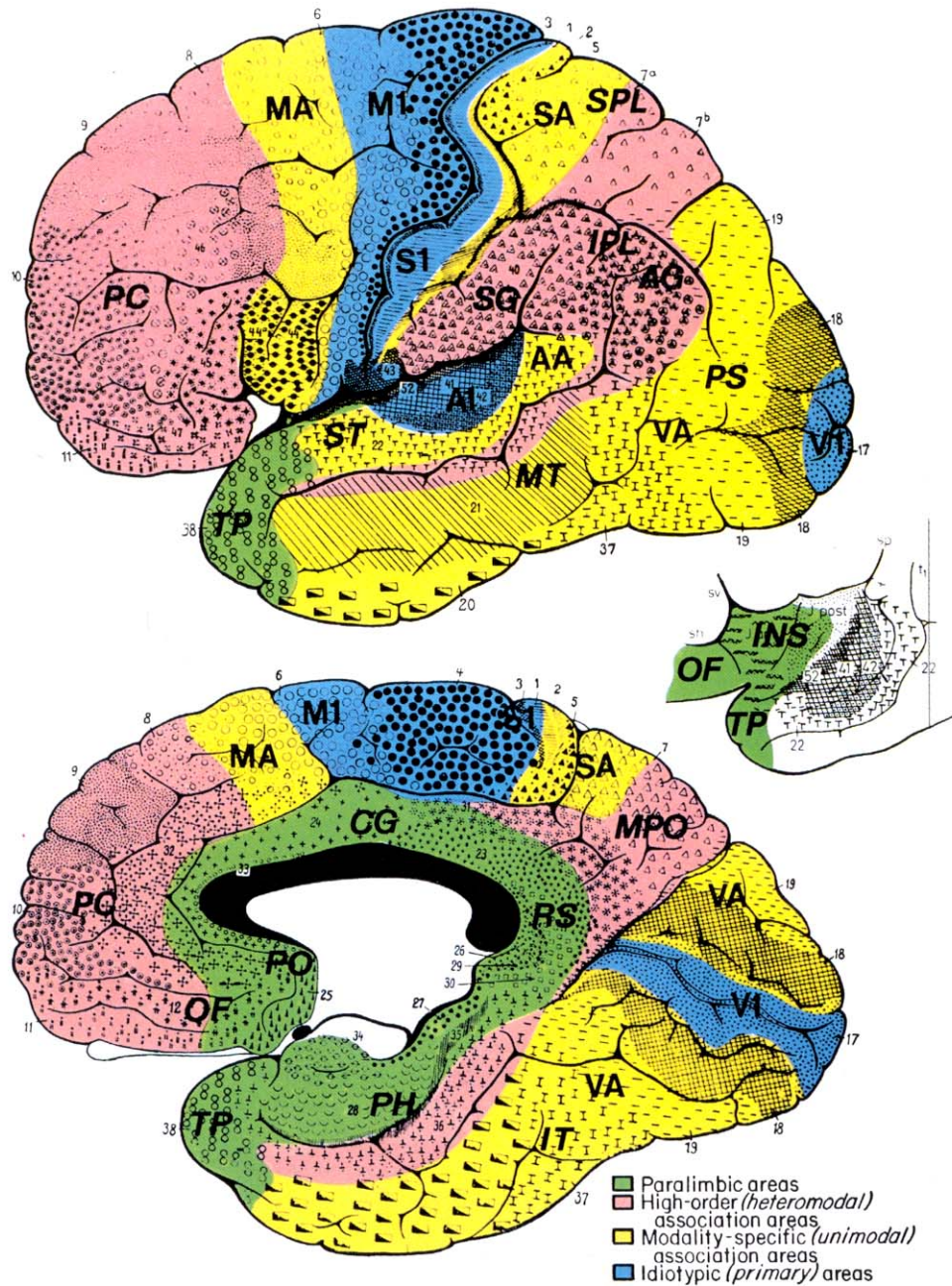






Memory

- Is the strengthening of synaptic contacts
- We remember what is emotionally important to us.
- Interplay between cerebral cortex and the emotional brain is key



Association CORTEX

- Different sensory MODALITIES COME TOGETHER
- ABSTRACT
- FRONTAL AND TEMPOROPARIETAL CORTEX

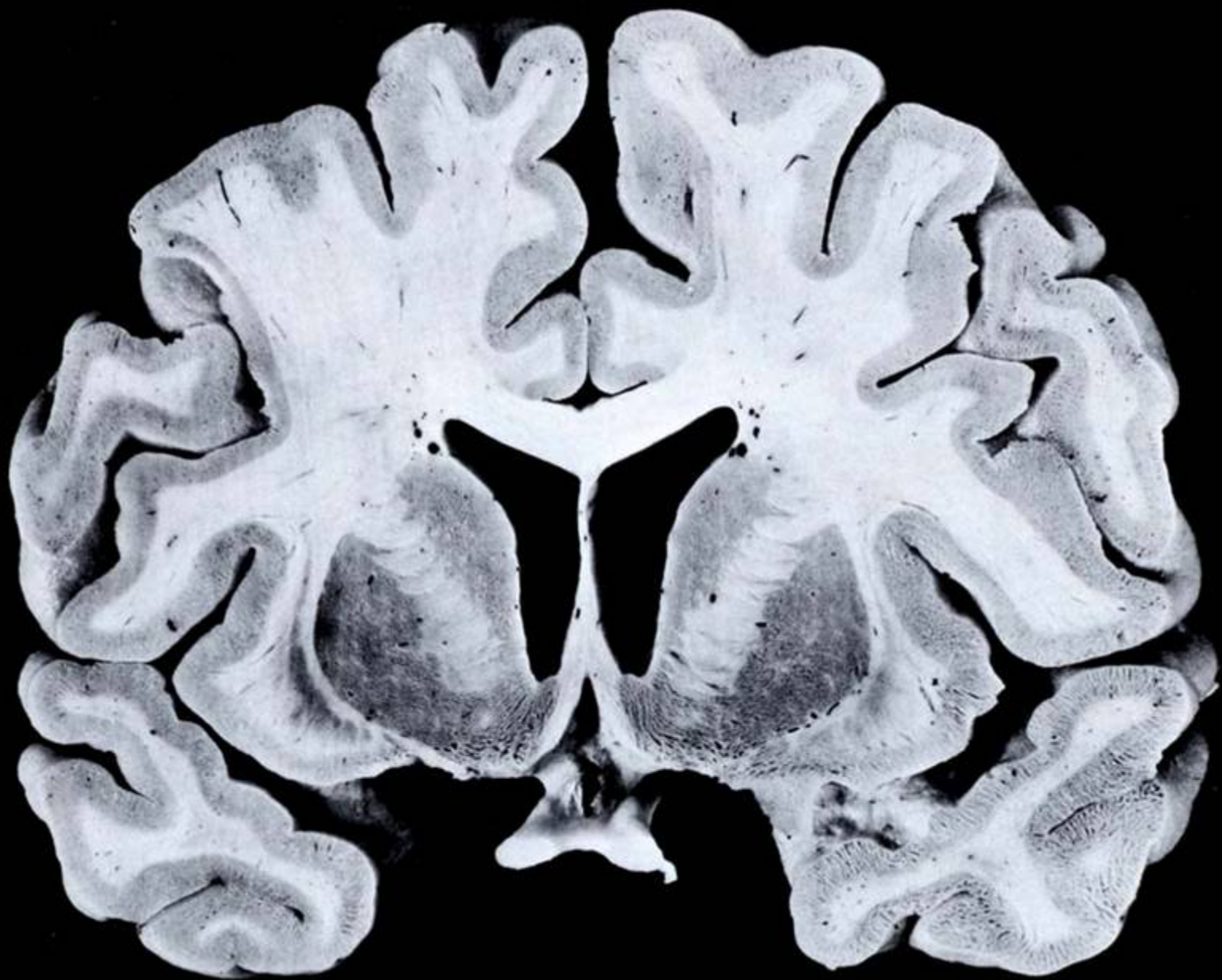
Paralimbic cortex



PARALIMBIC CORTEX FUNCTION

- MEMORY AND LEARNING
- CHANNELING DRIVE AND AFFECT
- HIGHER CONTROL OF AUTONOMIC TONE
- HEAVILY ATTACKED IN ALZHEIMER'S DISEASE

SEPTUM

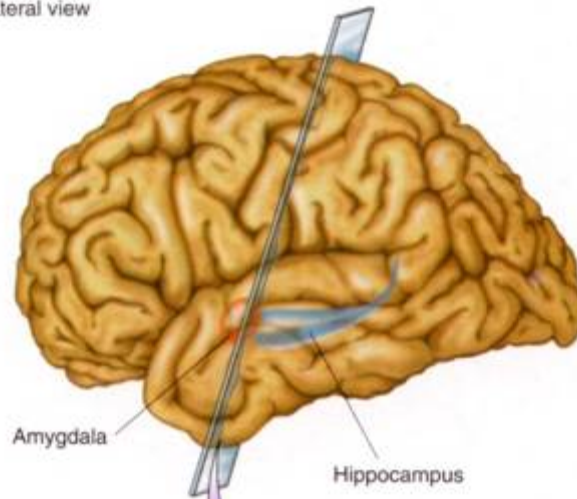


Septum function

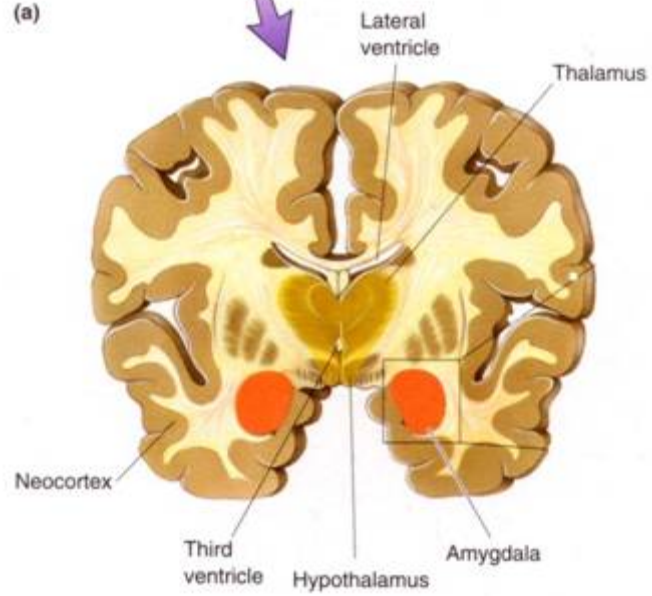
- Damage can cause amnesia
- Can sense pleasure/displeasure
- stimulation via electrodes (Penfield)
- 'desire' neurons
- Major supplier of acetylcholine to other memory areas

AMYGDALA

Lateral view



(a)

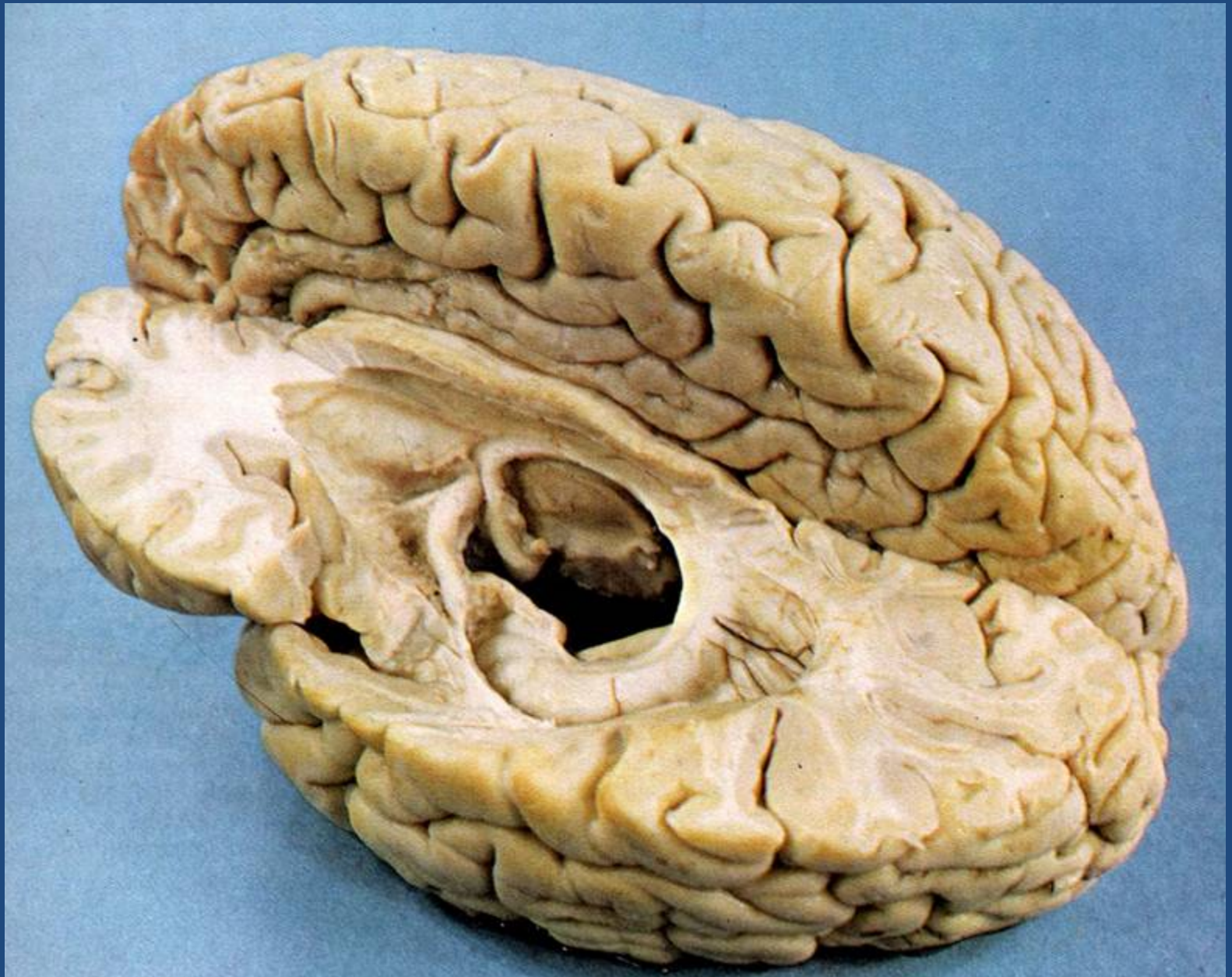


(b)

AMYGDALA FUNCTION

- ASSOCIATES APPROPRIATE EMOTIONAL RESPONSE WITH EXTRAPERSONAL OBJECTS (memory)
- (Hey, this is not my house: It's an identical replica!)
- ASSOCIATES DRIVE WITH APPROPRIATE TARGET
- VERY ACTIVE IN SOCIAL SITUATIONS
- SEX AND VIOLENCE
- PTSD

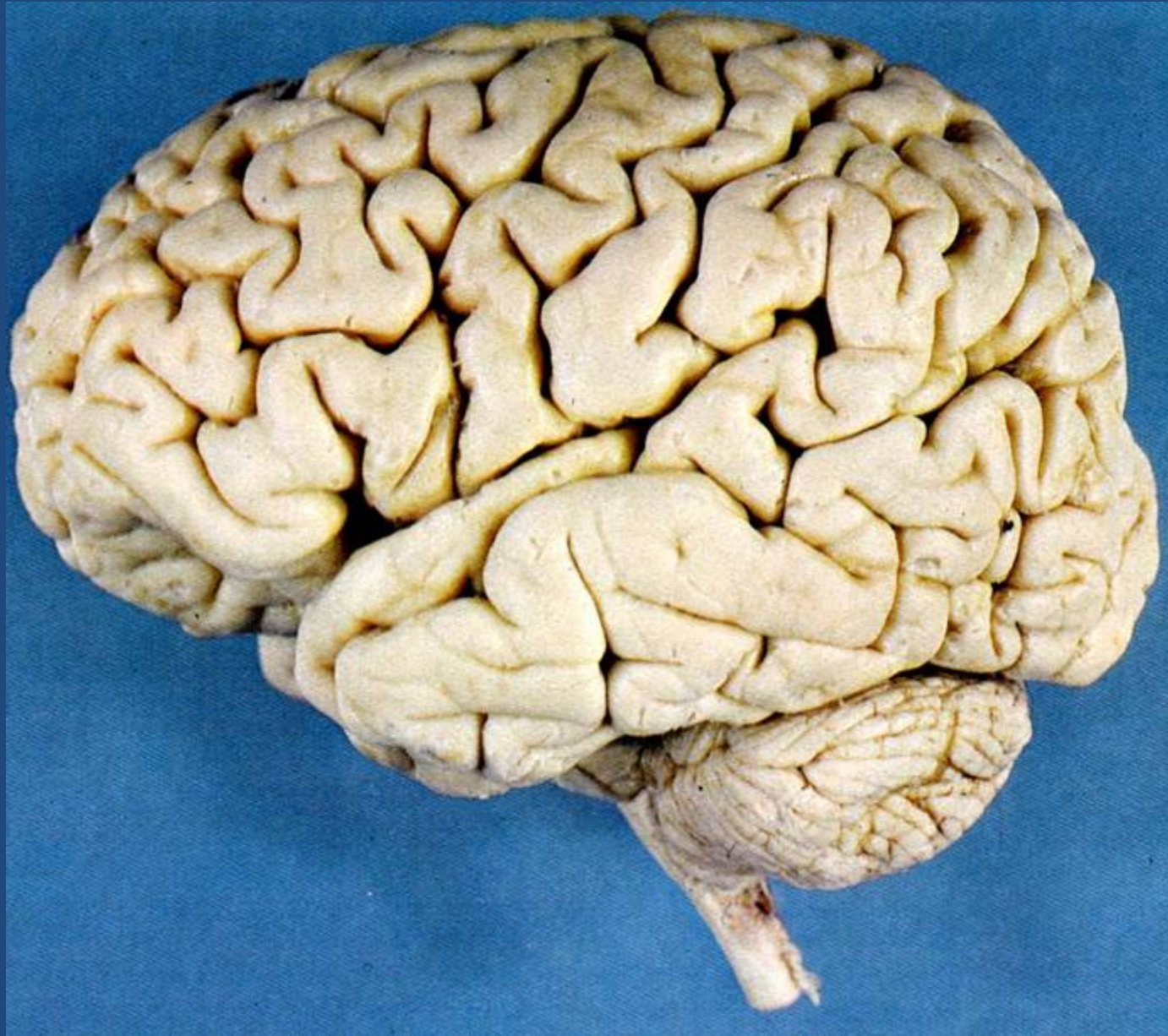
HIPPOCAMPUS

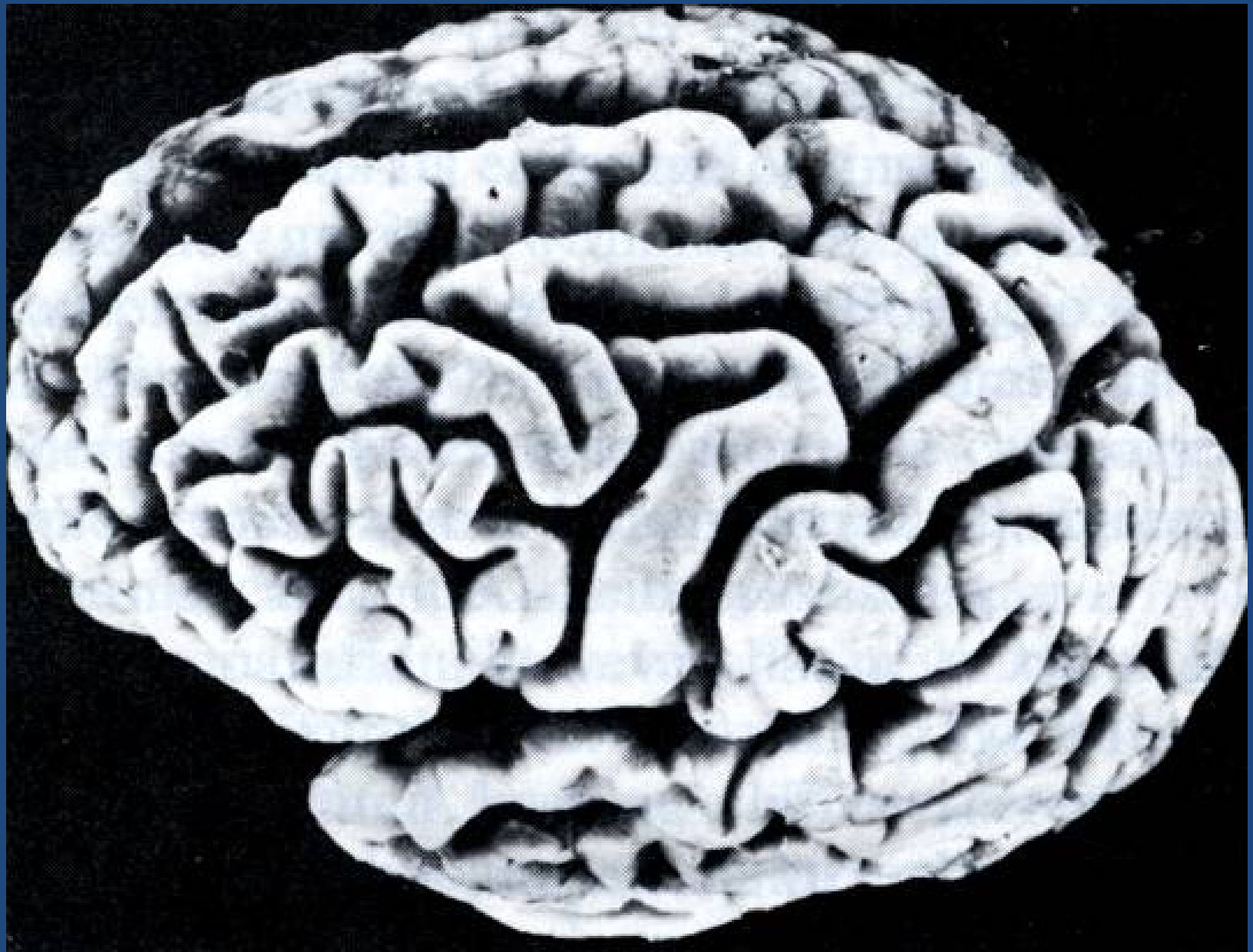


HIPPOCAMPUS FUNCTION

- CONVERTS SHORT-TERM TO LONG TERM MEMORY?
- CAN BE INVOLVED IN DEPRESSION
- VERY HEAVILY ATTACKED IN ALZHEIMER'S DISEASE

AD preferentially attacks association
cortex and the emotional brain



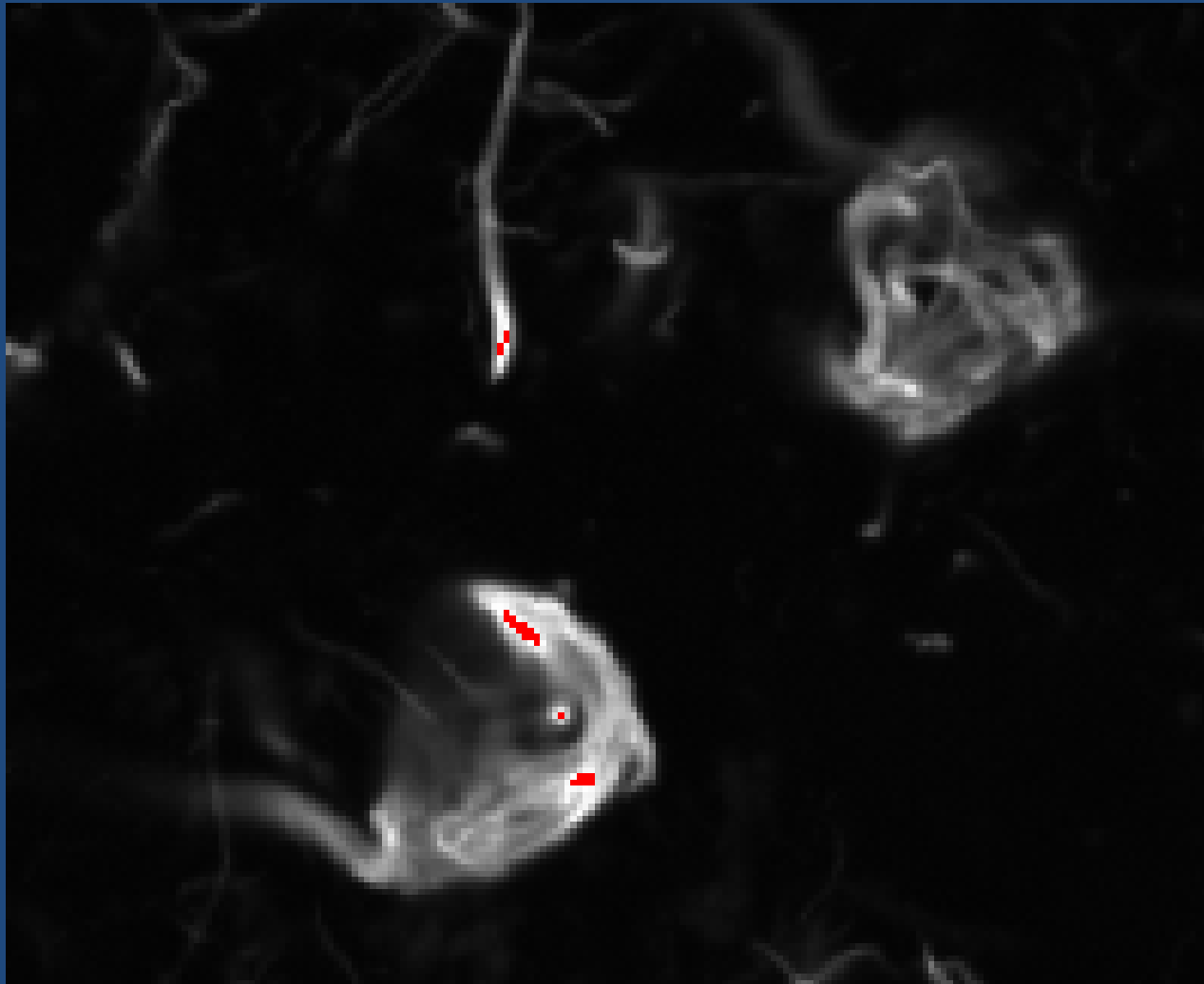


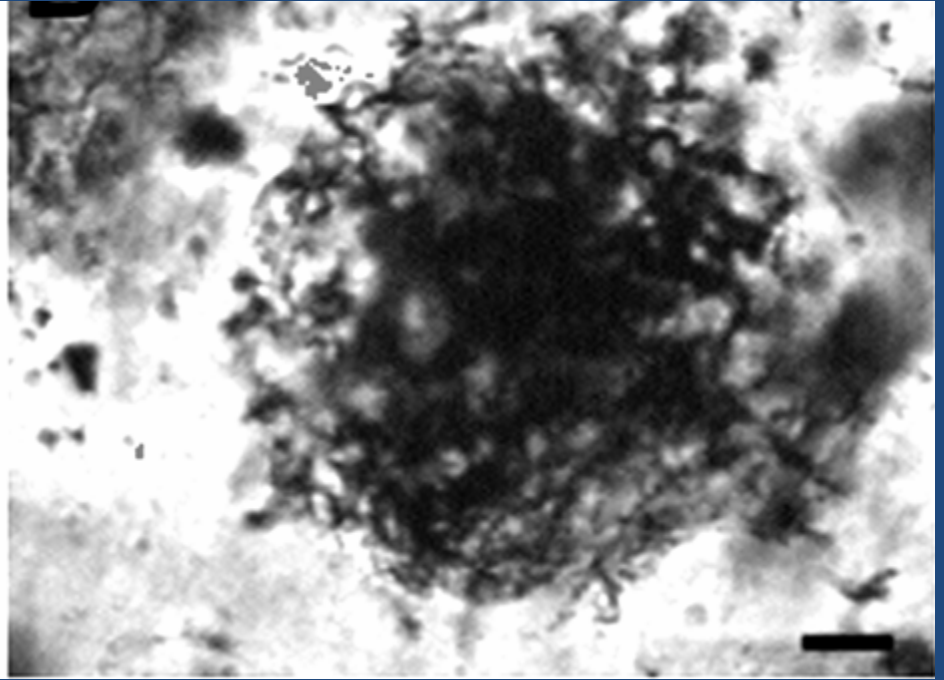
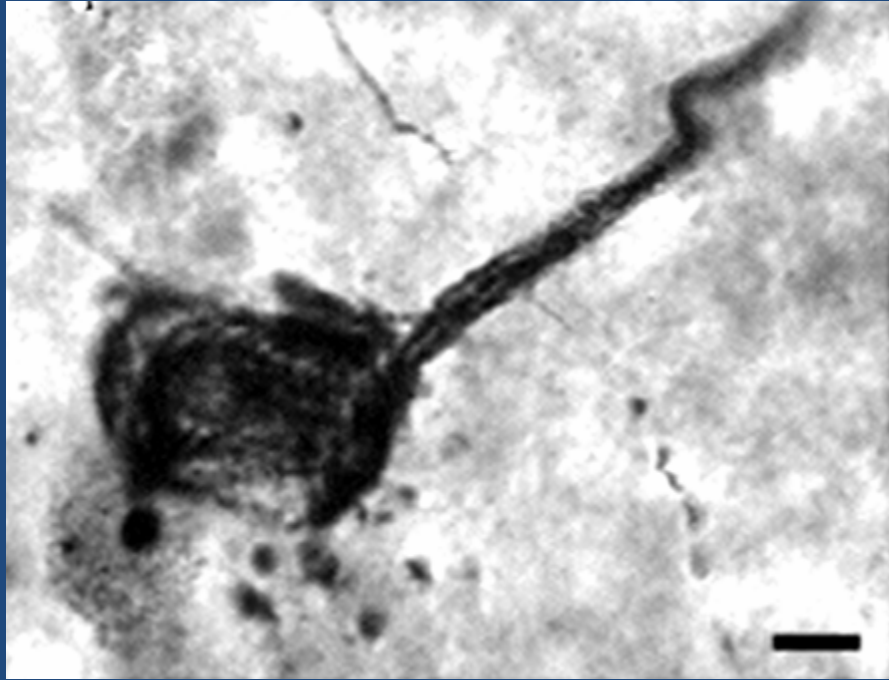
So emotional brain centers are
heavily attacked by the disease
process

Exactly what is the etiology of AD?

Neurological changes in Alzheimer's disease

- Severe loss of neurons
- Severe loss of the connections among neurons
- Degeneration is most dramatic in brain regions associated with emotion and this relates to memory
- The brains contain tangles and amyloid plaques





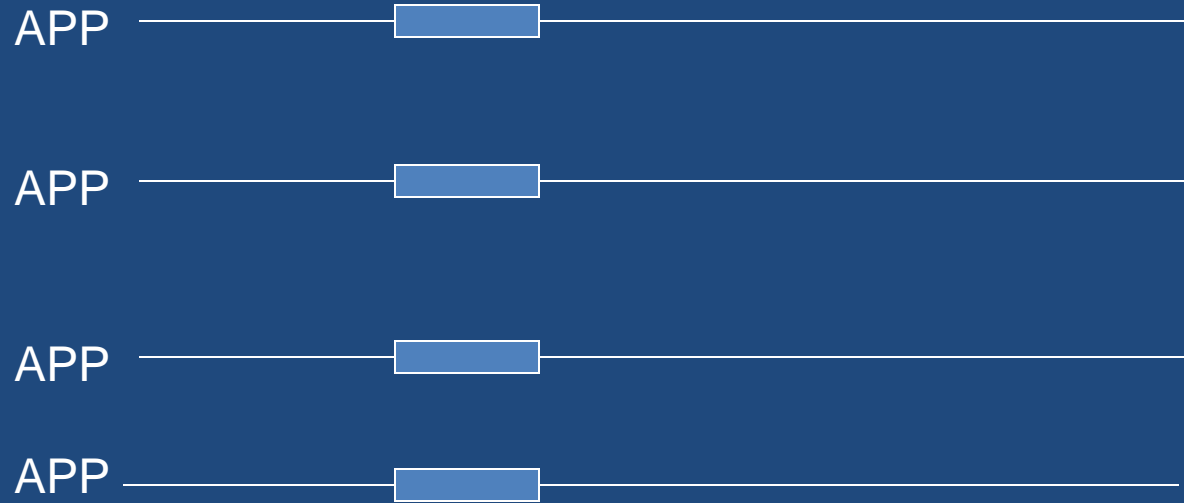
Where do plaques come from?

They are made of small pieces of a protein called amyloid precursor protein

Amyloid precursor protein

- Called APP FOR SHORT
- A small piece called “beta A4” is cut from APP and beta A4 makes the plaques
- Enzyme systems called secretases do the cutting

Beta amyloid is cut from amyloid precursor protein

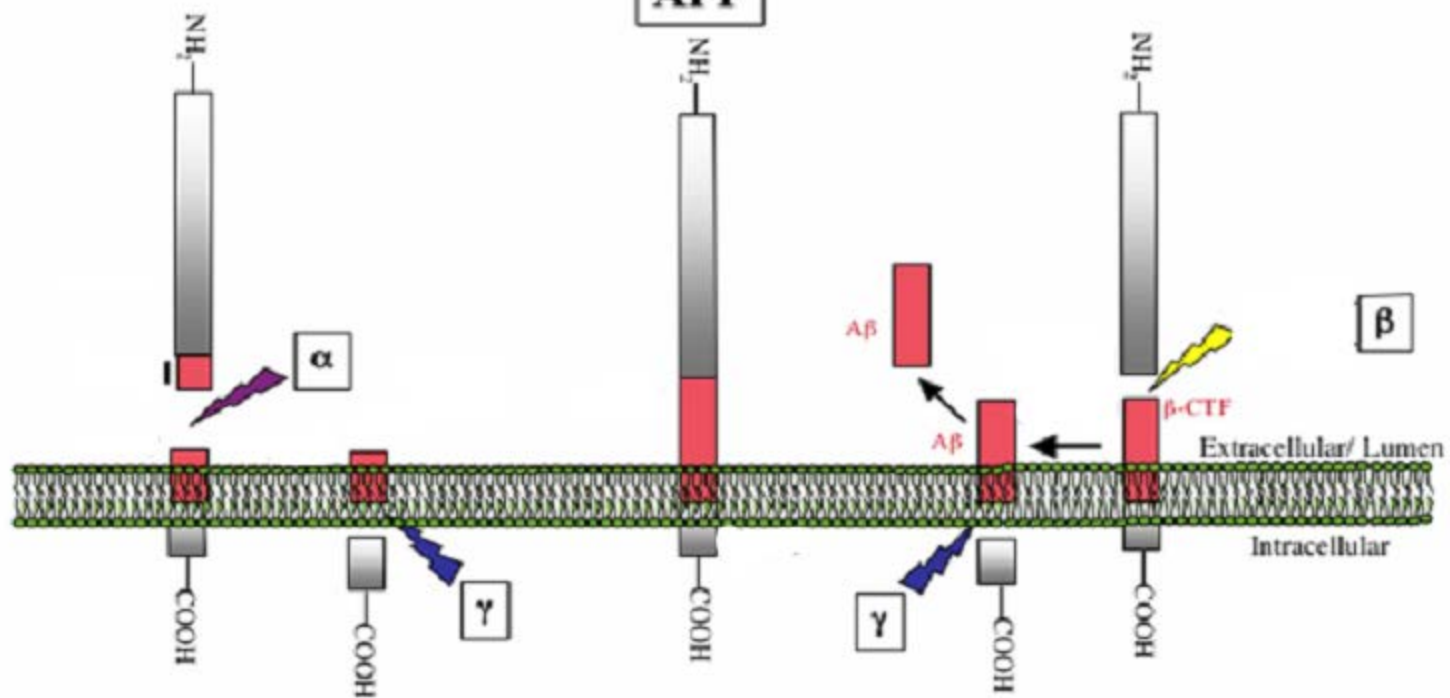


Plaque made of
thousands of
copies of beta
amyloid

non-amyloidogenic

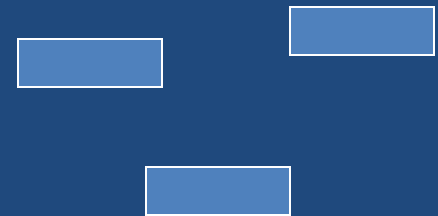
APP

amyloidogenic

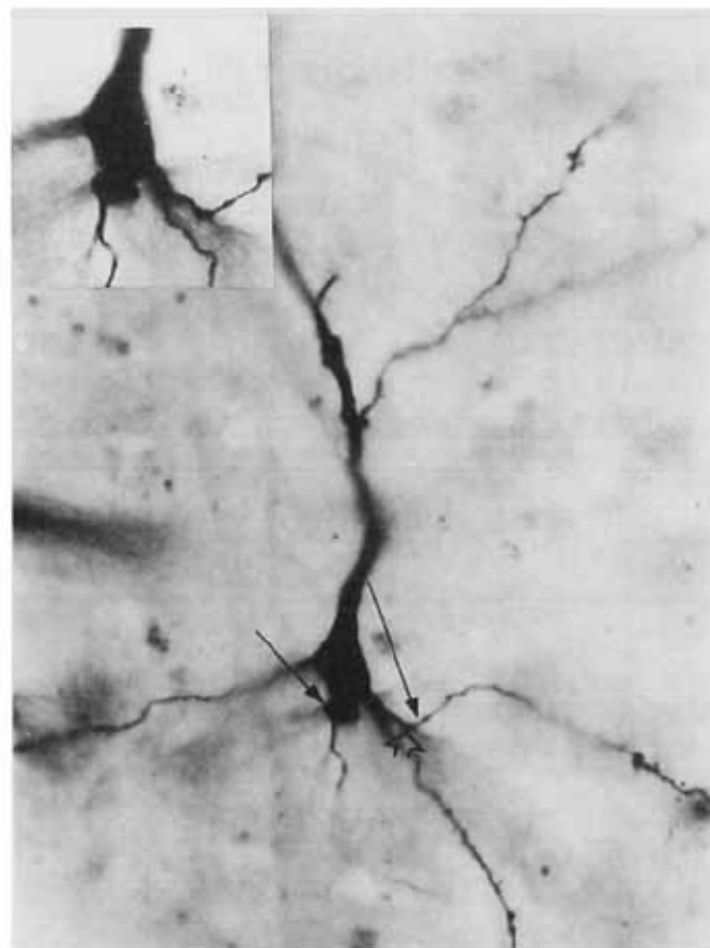
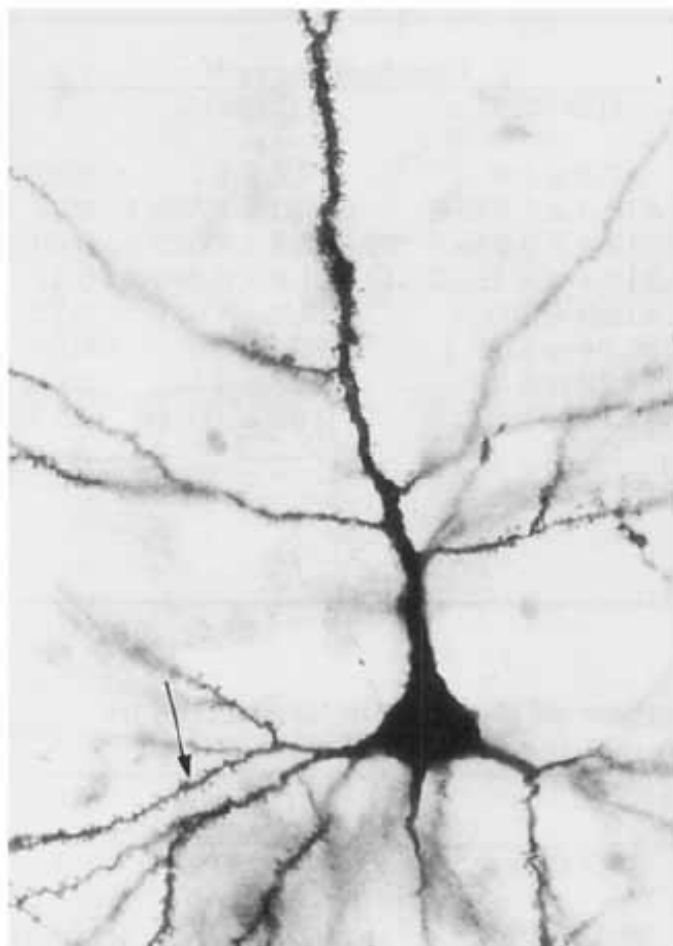


Beta-amyloid

- Also exists in a **soluble oligomeric form**
 - toxic to synapses
 - May be the actual substance that kills neurons
 - Brain may bundle it in plaques to protect themselves so a plaque would be a toxic waste dump.



- DEMENTIA CORRELATES WITH SYNAPSE LOSS rather than the number of plaques or tangles.



Risk factors

- Age
- Apolipoprotein E4
- Trauma
- Lack of brain exercise
- What's bad for the heart is bad for the brain (and vice versa)

New news

- Mediterranean diet slows down AD development: very promising
- Being bilingual seems to help
- The gene for alpha secretase can now be upregulated....in mice that is....

The alpha secretase gene

- The gene is called ADAM 10
- ADAM 10 is activated by an enzyme called “SIRT1”.
- SIRT1 is related to longevity

SIRT 1 experiments in mice

- Increased SIRT1 DECREASES beta amyloid while...
- Decreased SIRT1 does the opposite

How can you activate SIRT1 in your own brains?

- Red wine (but don't drink if you don't drink) provides resveratrol, which activates SIRT1
- Lower caloric intake
- Melatonin ?



Marriage of Medicine and Cell Biology Series Week 2, part 2

*“The Man Who Mistook His Wife for a Hat,”
the modular brain,
and the elements of dementia*

EDWARD VALENSTEIN

OCTOBER 19, 2011

Plan

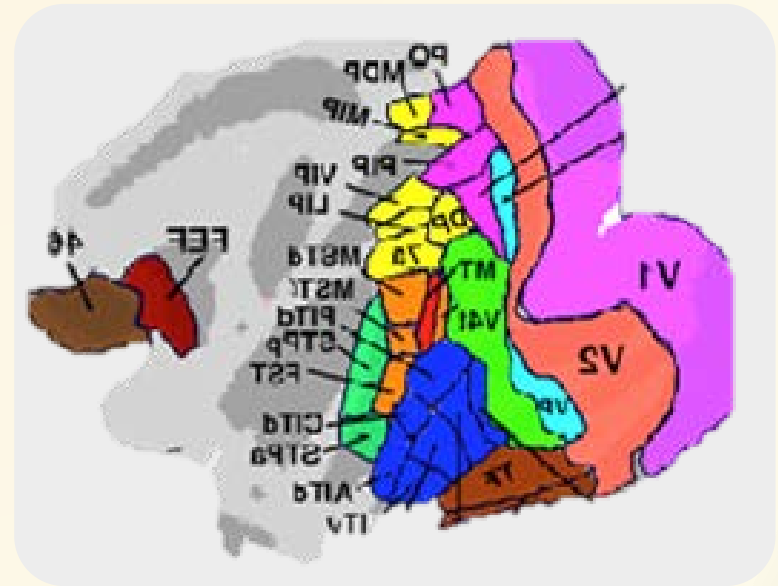
- The Man Who Mistook His Wife for a Hat
- The modular brain in visual perception
- Definition and causes of dementia
- Domains of function and the assessment of dementia
 - Frontal lobe function(s)
 - Clinical features
 - Concepts
 - Animal models
- Early detection and treatment/prevention of dementia

The Man who Mistook His Wife for a Hat

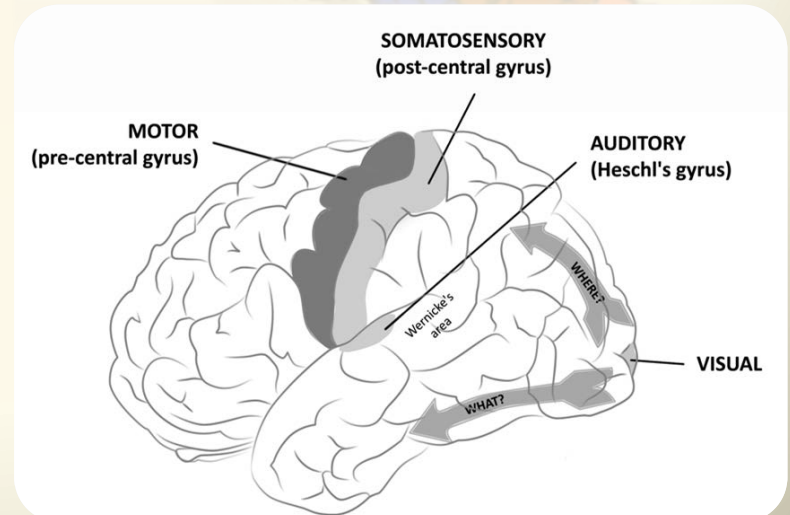
- Oliver Sacks, in 1985 wrote about a musician who
 - Could not recognize faces or expressions on faces
 - Made errors in identifying objects: a foot for a shoe, his wife's head for a hat, etc.
 - Lost the ability to read music
 - Saw only one object at a time when looking at a scene
- Condition called *visual agnosia*
 - Failure of recognition through vision, with intact recognition by other modalities (touch, hearing)
 - Many varieties...

Visual processing

- Visual streams
 - Dorsal “where” stream for spatial localization
 - Ventral “what” stream for object identification
- Clinical disorders
 - Dorsal stream
 - Simultanagnosia
 - Ventral stream
 - Prosopagnosia
 - Many others
- Brain modularity



From Felleman & Van Essen, 1991
(reversed)



Conscious visual perception

- All components (shape, color, motion, location etc.) are “bound” to form a seamless visual perception.
- How? Possibilities include:
 - High-order visual association cortex receiving input from both “what” and “where” streams
 - Frequency “tuning” to coordinate components of vision

QUESTIONS?

Diagnosis of Dr. Sack's case

- Unknown, but we can speculate
- Posterior cortical atrophy?
 - Usually a form of Alzheimer's disease

What is dementia?

- Loss of mental functions (decline from previous function)
- Loss is sufficient so that the patient cannot function independently
- Not explained by delirium or major psychiatric disorder
- Lesser deficits still compatible with independent living are called mild cognitive impairment (MCI).

Causes of dementia

- Neurodegenerative disease
 - Alzheimer's
 - Most common cause of dementia (incidence of 1% at age 60, then doubles every 5 years; 16% at age 80)
 - Lewy body dementia
 - Parkinson's
 - Frontotemporal dementia
 - Corticobasal degeneration
- Vascular dementia
- Traumatic brain injury
- Many others...

Evaluation of Dementia by Domain

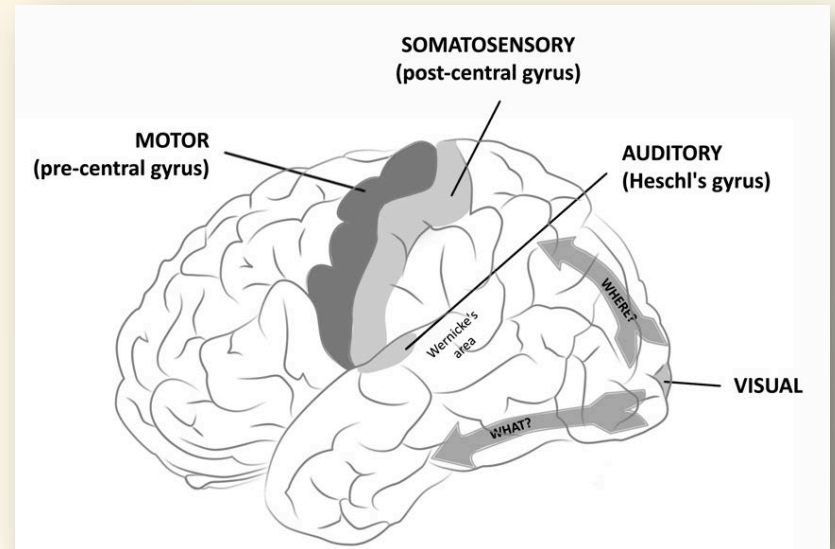
- Domains selected because
 - Can identify behaviors specific to a domain
 - Can demonstrate selective loss of these domain-specific behaviors in disease
- Mental Status exam:
 - Arousal
 - Attention
 - Memory
 - Cognitive (posterior cortical) function
 - Frontal lobe (“executive”) function

Memory

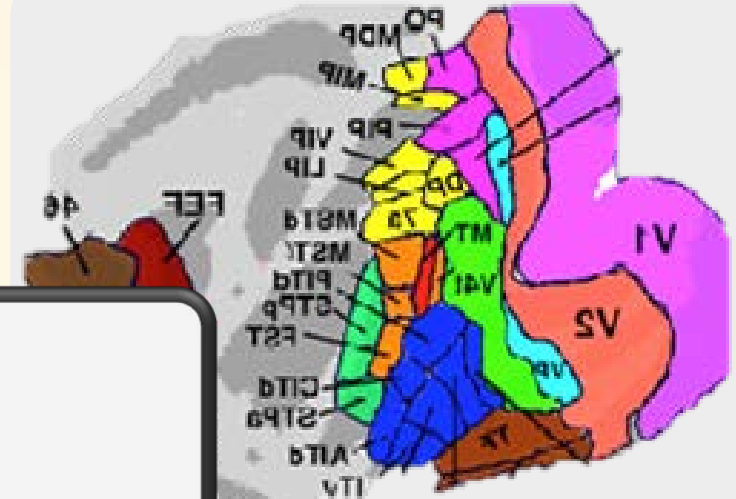
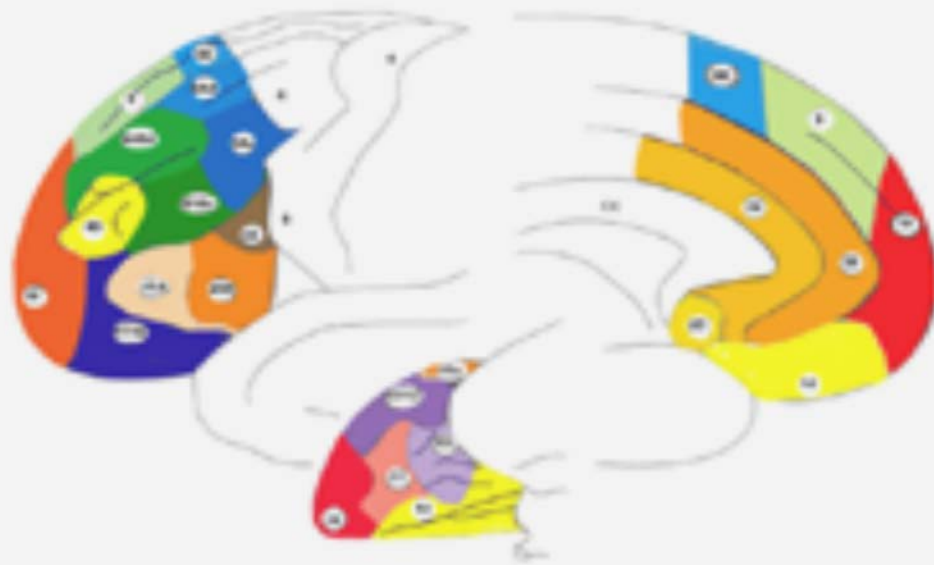
- Damage to very specific brain structures causes a specific amnesic syndrome
 - Loss of episodic (personal) memories
- These same structures are affected early in Alzheimer's disease
- Memory disturbance is an early feature in most patients with AD

Posterior cortical dysfunction

- Perception
 - Visual
 - Auditory
 - Somatosensory
- Left hemisphere (\pm)
 - Language
 - Praxis (in right-handers)
- Right hemisphere (\pm)
 - Visuospatial
- Most patient with AD have posterior cortical dysfunction affecting
 - Language
 - Praxis
 - Visuospatial function



Frontal lobe and executive function



Phineas Gage (1848)

“Previous to his injury, although untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart businessman, very energetic and persistent in executing all his plans of operation...”

After the injury “he is fitful, irreverent, ... manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires ... devising many plans of future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible... In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was “no longer Gage.”



John M. Harlow, M.D., 1866

Brickner's patient (1934,6)

- 39yo stockbroker, 1 yr progressive headache, leading to mental obtundation
- Found at surgery (Walter Dandy) to have a large meningioma of the falx, compressing both frontal lobes
- 2-stage removal that included resection of all frontal tissue anterior to Broca's area on the left, and more extensive removal on the right.

Brickner's patient (1934,6)

Preserved function

- No motor deficits; normal language
- Oriented, understood his medical history
- Intellectual ability:
 - Could play checkers expertly
 - Could explain meaning of proverbs
 - Could lucidly discuss his own predicament
- Could learn to operate a complex printing machine

Deficits

- Emotions
 - Inappropriate; shallow affect
- Social behavior
 - Boastful
 - Witty at the expense of others
 - Impotent
- Planning
 - No initiative
 - Spoke about returning to work; but made no effort to do so

EVR (Eslinger & Damasio, 1985...)

- 30 yo male, had been excellent student, role model for friends and siblings, who was a church elder and had risen to a supervisory position in his company.
- Then noted to be unreliable, could not complete his usual work, experienced marital difficulties, was suspended from job.
- Large orbitofrontal meningioma resected

EVR (cont'd): post-op

Preserved

- Neuro exam normal except for mild left arm incoordination and anosmia
- VIQ 120; PIQ 108
- Retested 125, 124
- Memory quotient 140,148 (nl)
- Psychometric eval:
 - Normal Halstead-Reitan battery
 - Normal MMPI
- Psychiatric eval: “no evidence of organic brain syndrome or frontal dysfunction”

Deficits

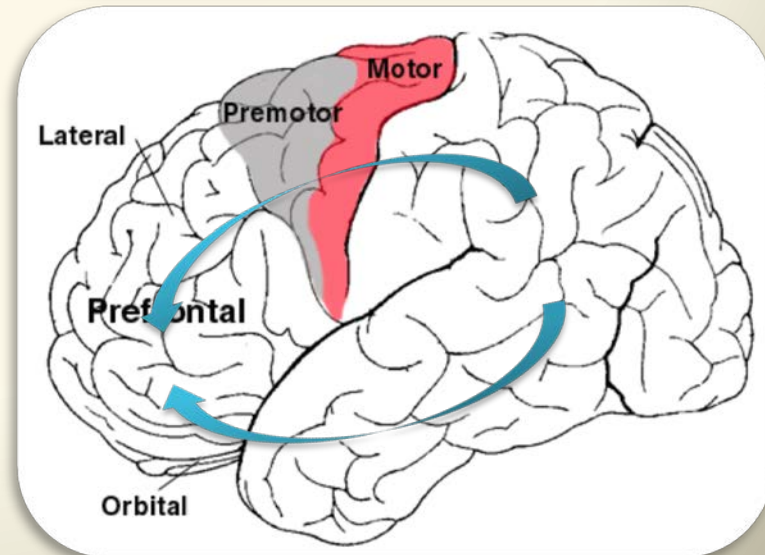
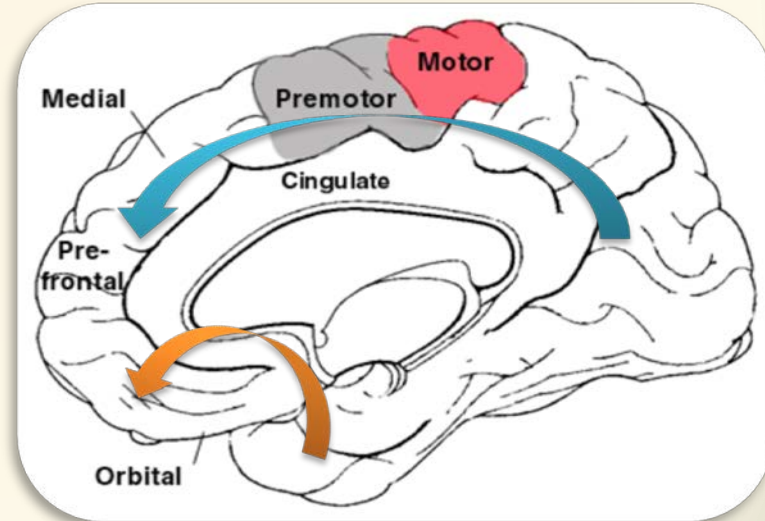
- Partnered with a dubious businessman → bankrupt.
- Got fired from multiple other jobs.
- Divorced.
- Remarried
- Divorced

Characterizing Prefrontal Deficits

- Preserved functions:
 - All or most elementary neurological functions (motor, sensory, reflex...)
 - All posterior cortical functions, including IQ, reasoning
 - Memory, with exceptions
- Deficits
 - Working toward goals (memory for the future)
 - Inhibiting inappropriate actions
 - Regulating social behavior
- What is *normal* frontal function?
 - Posterior cortical: easy stuff
 - Automatic
 - Accurate
 - Frontal stuff
 - Effortful
 - Often in error
 - Poor frontal function as a norm:
 - Children
 - Some adults...

Anatomic basis of frontal lobe function

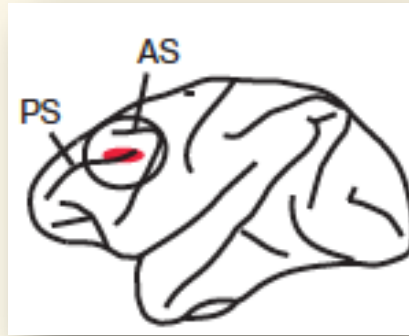
- Relationship to motor cortices
- Connections with posterior cortex (cognition, the external environment)
- Connections with limbic structures (emotion, internal environment)
- Therefore: using all available input (external, internal) to influence decisions about acting



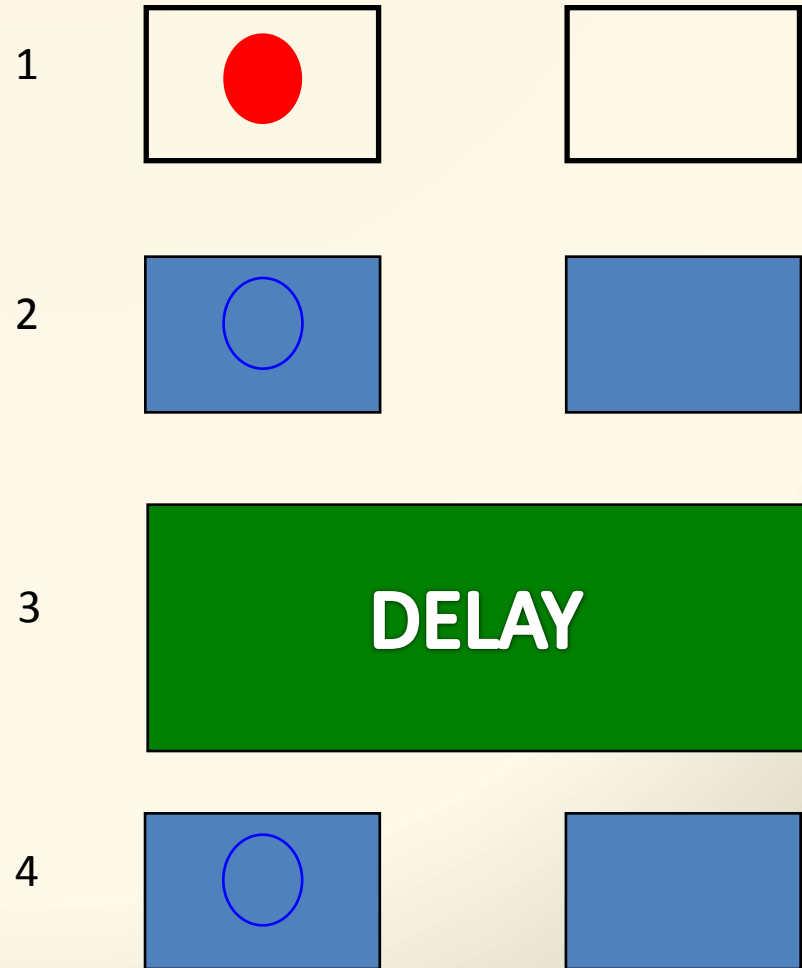
Animal research

- Utilization behavior
- Stimulus-bound behavior
- Out of sight, out of mind
 - Delayed response task

Animal model of frontal dysfunction

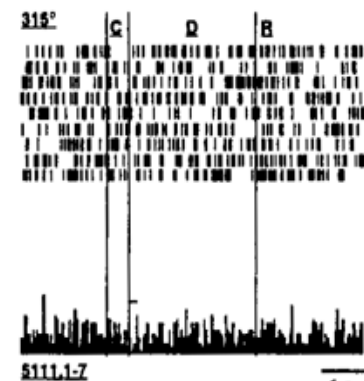
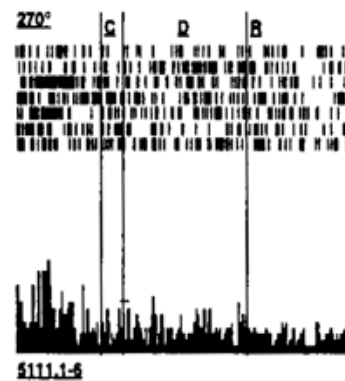
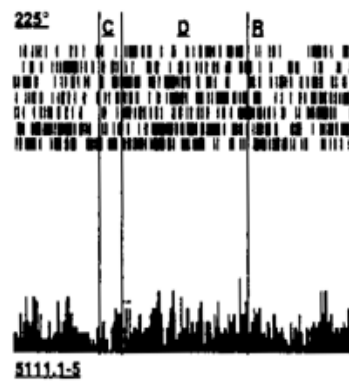
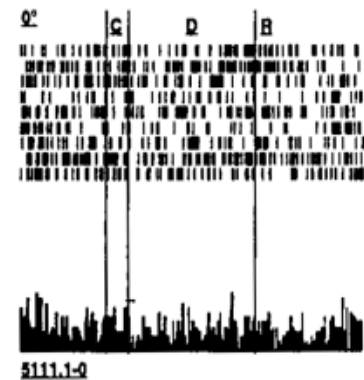
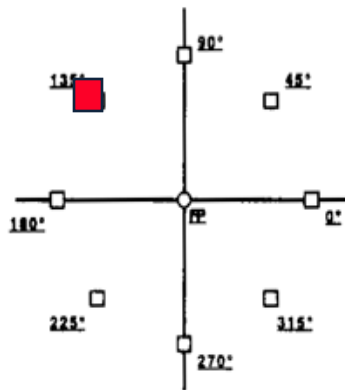
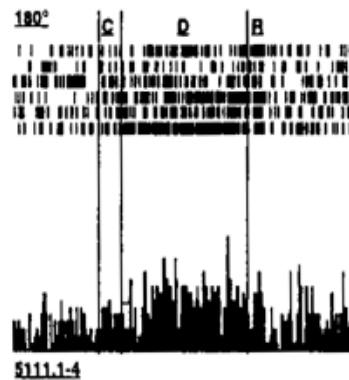
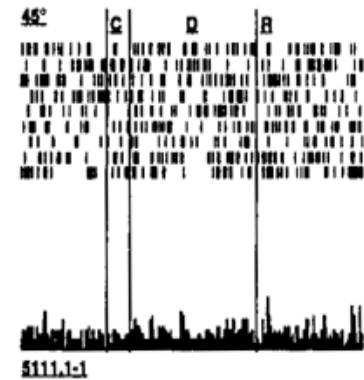
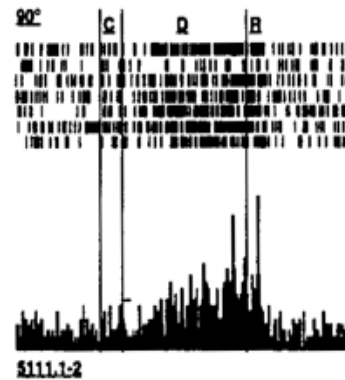
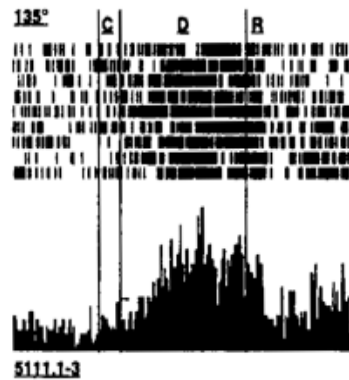


Jacobsen (1930's):
Delayed response
paradigm



Spatial Delayed Response

From
Funahashi,
Bruce &
Goldman-Rakic,
J. Neurophysiol.
61, 331-349,
1989.



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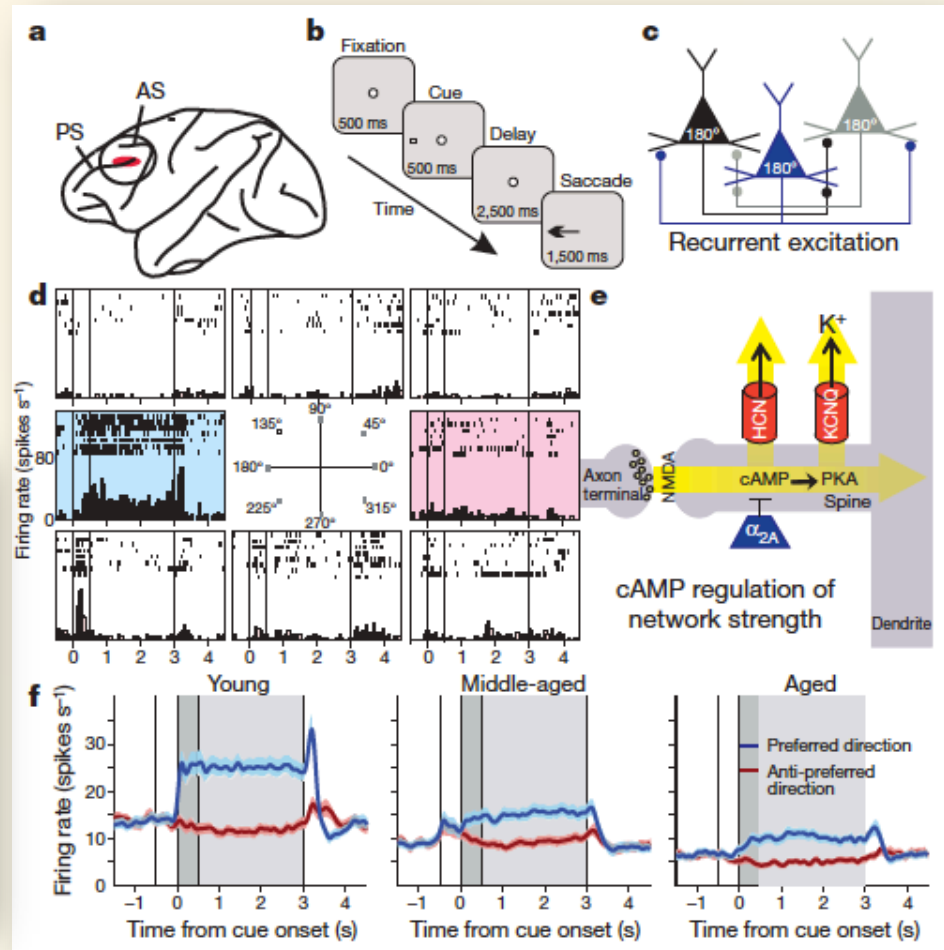
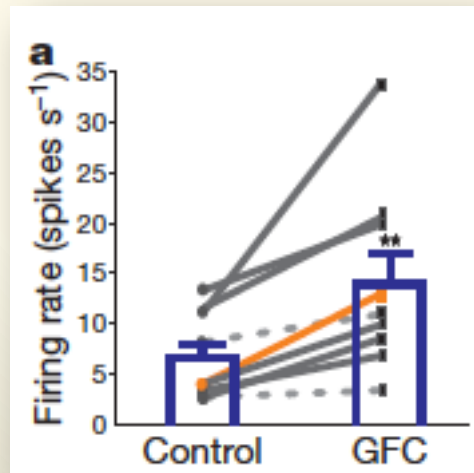
Deficits in normal aging

- Processing speed
- Naming
- Working memory

New and breaking news

Thin dendritic spines in layer III are most vulnerable in aging.
Layer III contains the recurrent excitatory networks that sustain firing during the delay period.

- Gaunfacine
- Potassium channel blockers



Wang M, Gamo NJ, Yang Y, Jin LE, Wang X-J, Laubach M, Mazer JA, Lee D. *Neuronal basis of age-related working memory decline.. Nature Neuroscience*, 476:210, 2011

Prevention/treatment of degenerative dementia: is help on the way?

- Early diagnosis of AD
 - Pre-clinical phase
 - Mild cognitive impairment (MCI)
 - Amyloid-beta in serum, CSF, PET scan
 - APOE4 genotype
 - Risks (multiple head injury, Down's syndrome, family history, diabetes, cardiovascular disease)
- Interventions
 - Improve cholinergic function
 - Drugs (Aricept®, etc.)
 - Stem cell therapy – cholinergic cells in basal nucleus
 - Increase clearance of Amyloid beta

Exercise

- Mental exercise, especially social interactions
- Physical exercise
 - It's good for you, regardless of age
 - Heart
 - Blood pressure
 - Diabetes control
 - It also appears to be beneficial in
 - Preventing/reversing dementia
 - Why?
 - Increases genes regulating synaptic plasticity
 - Increases dendritic length and spine complexity
 - Enhanced neurogenesis in hippocampus
 - Enhanced long-term potentiation
 - Elevates neurotrophin levels
 - Reduced *tau* phosphorylation
 - Enhances mitochondrial activity

How much exercise?

- Not known
- Recommended
 - Increase heart rate to 60% of maximum for age
 - For at least 150 minutes per week
- Is more better?
- Risks
 - Falls, fractures, acute cardiac symptoms