

**Recent Developments in
Alzheimer's Disease Research –
Focus on ApoE4**

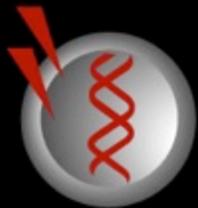
**Yaisa Andrews-Zwilling, Ph.D.
Staff Research Scientist II**

**Gladstone Institute for Translational Research
University of California, San Francisco**

THE J. DAVID GLADSTONE INSTITUTES



**GLADSTONE INSTITUTE OF
CARDIOVASCULAR DISEASE**



**GLADSTONE INSTITUTE OF
VIROLOGY AND IMMUNOLOGY**



**GLADSTONE INSTITUTE OF
NEUROLOGICAL DISEASE**



**GLADSTONE CENTER FOR
TRANSLATIONAL RESEARCH**

Trinidad and Tobago



Goettingen, Germany



Max Planck Institute, Germany



PhD, Husband and Kids!



In Memory of My Biggest Cheerleader



Outline

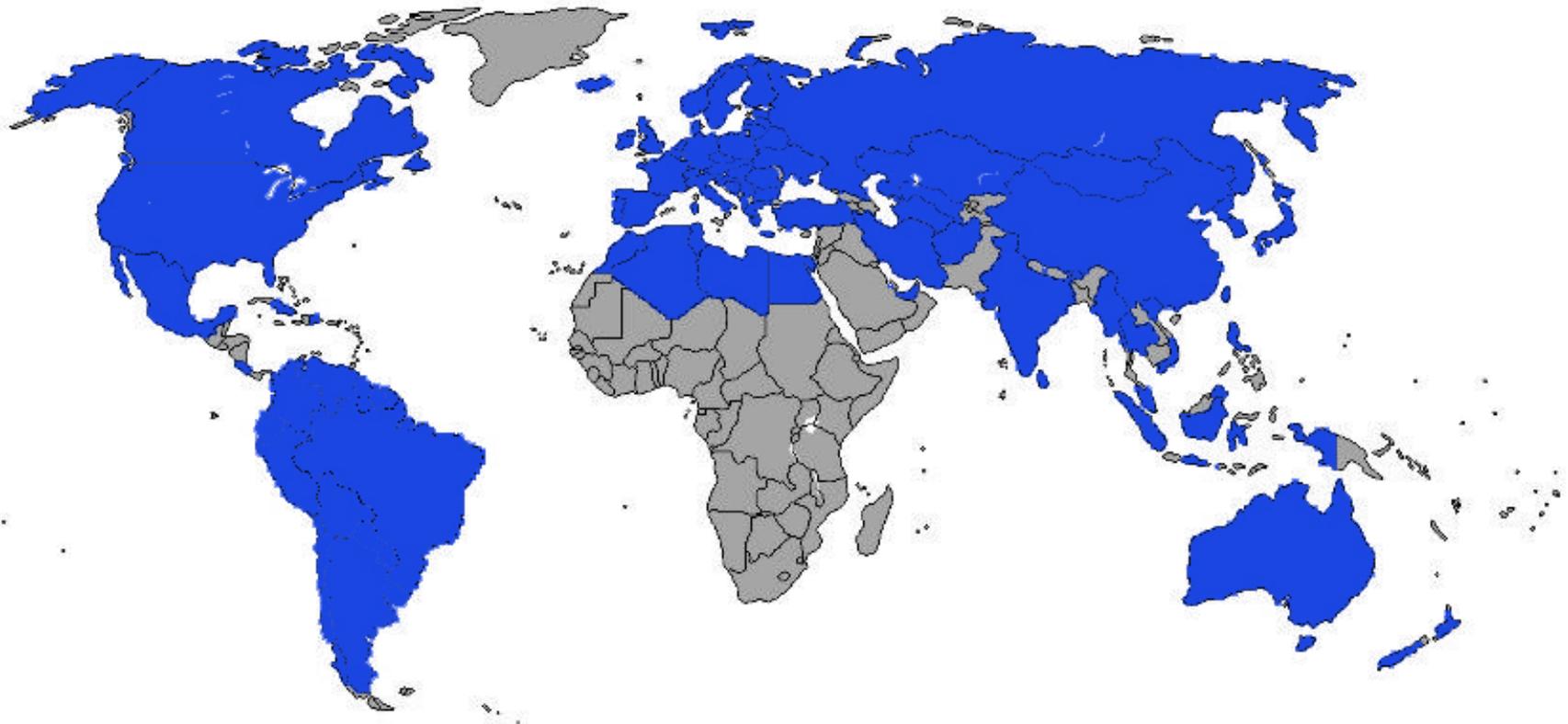
- Our Aging World
- What We Know About Alzheimer's Disease
- Normal vs Diseased Brain
- Apolipoprotein E (ApoE)
- Research
- Drugs
- Prevention

TODAY

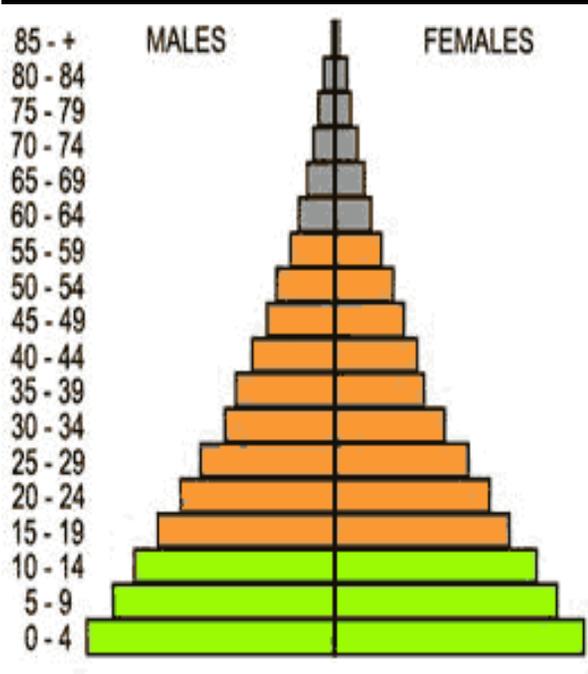


 **> 20% over age 65**

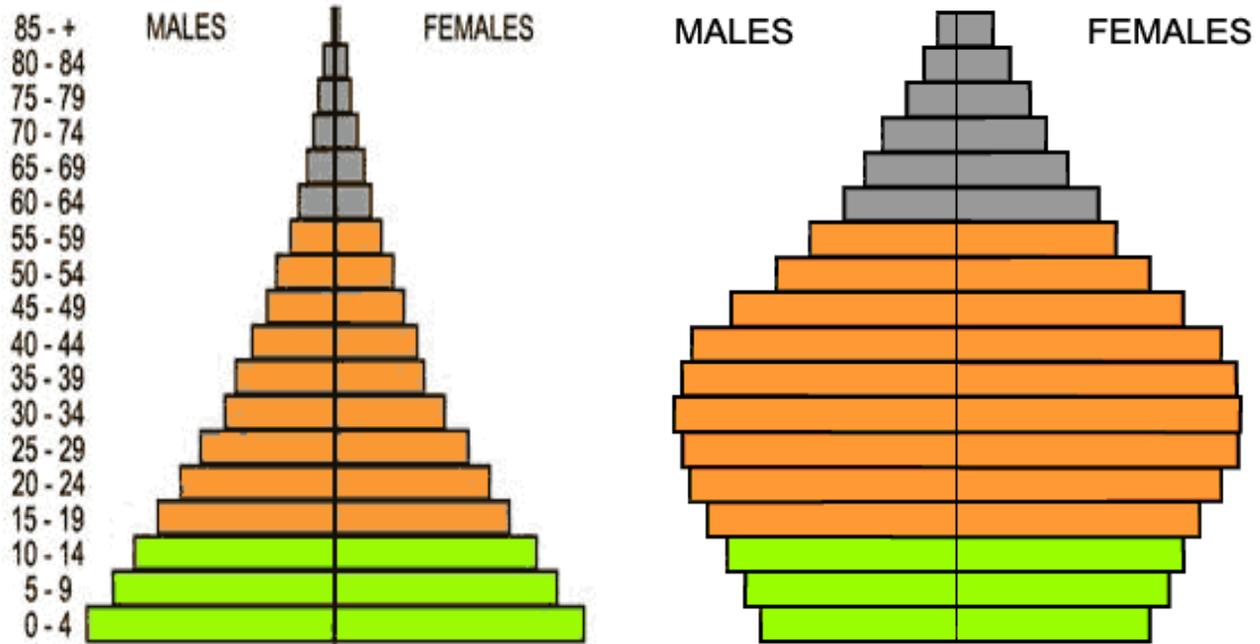
2050



■ > 20% over age 65

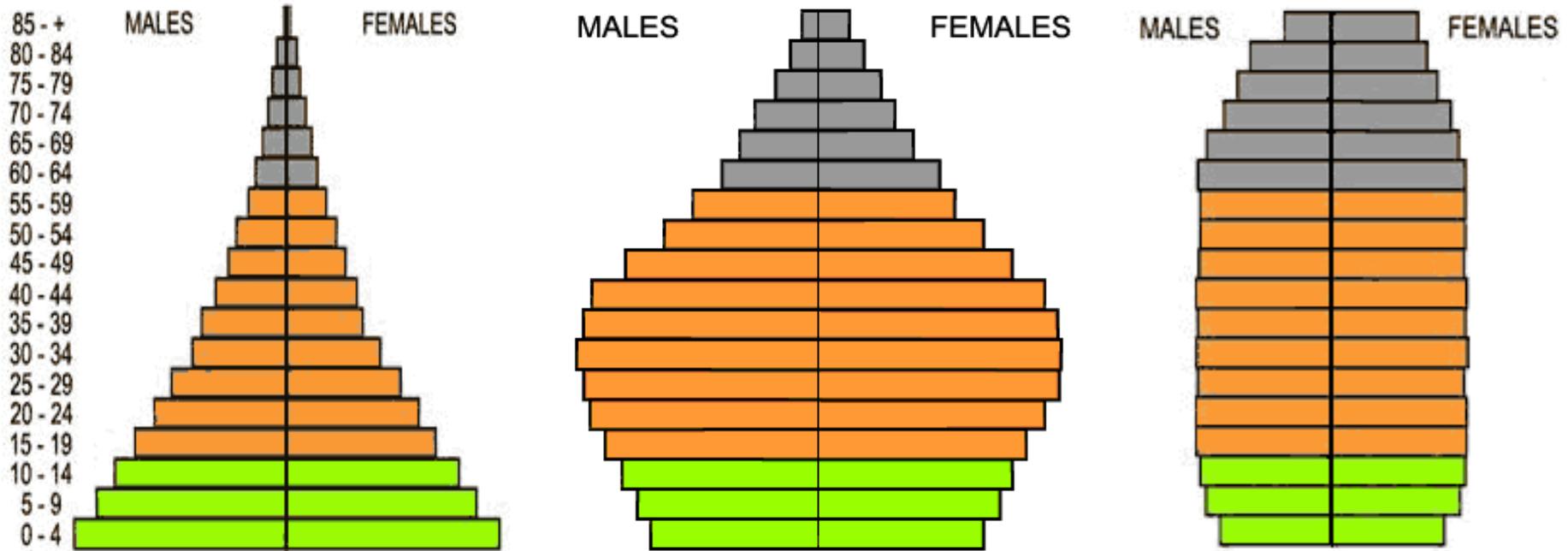


10,000 B.C – 1950



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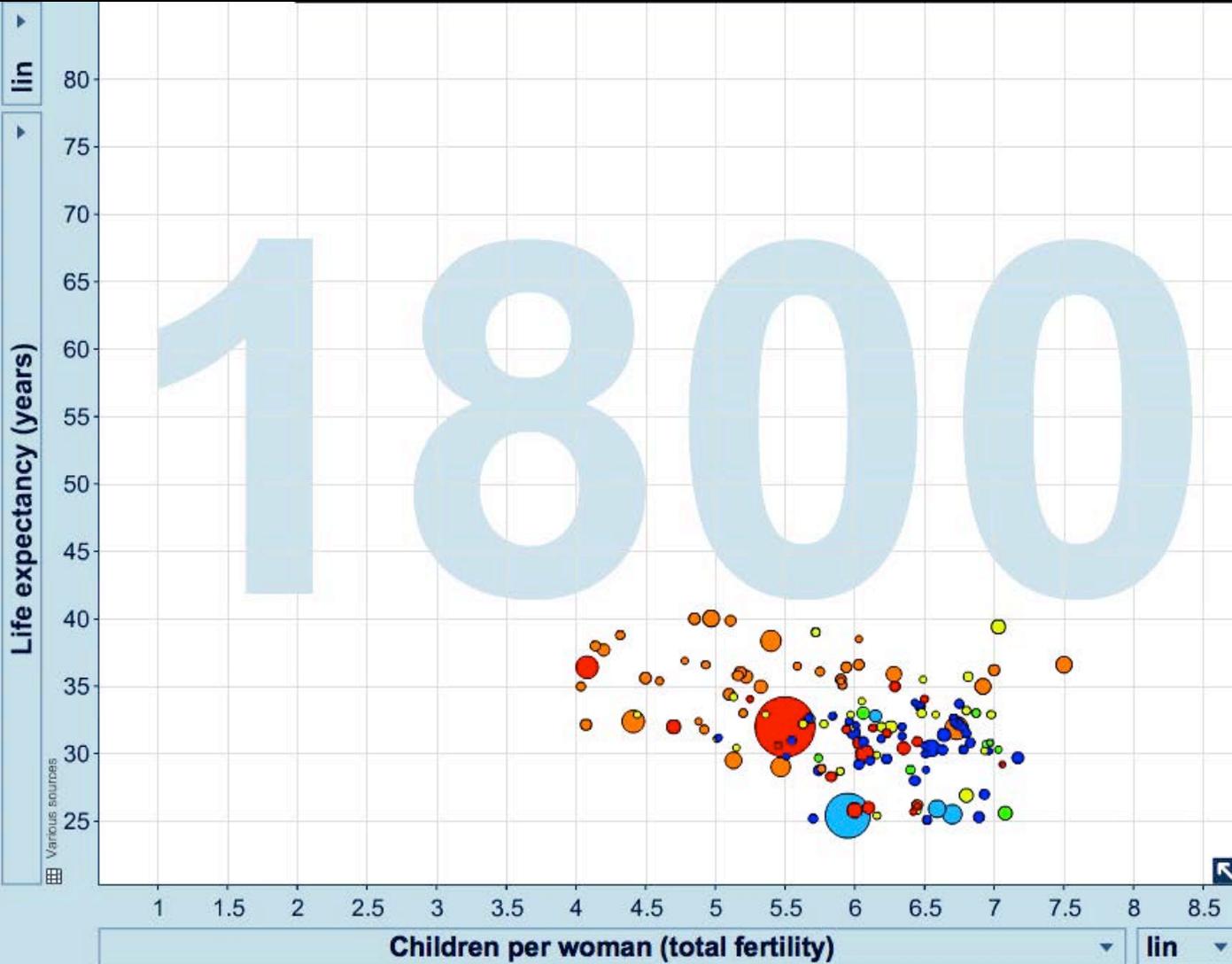
Today



10,000 B.C – 1950

Today

2050



Geographic regions ▾

Select

- Afghanistan
- Albania
- Algeria
- Angola
- Argentina
- Armenia
- Aruba
- Australia
- Austria
- Azerbaijan
- Bahamas
- Bahrain
- Bangladesh

Deselect all

Size Various sources

Population, total ▾

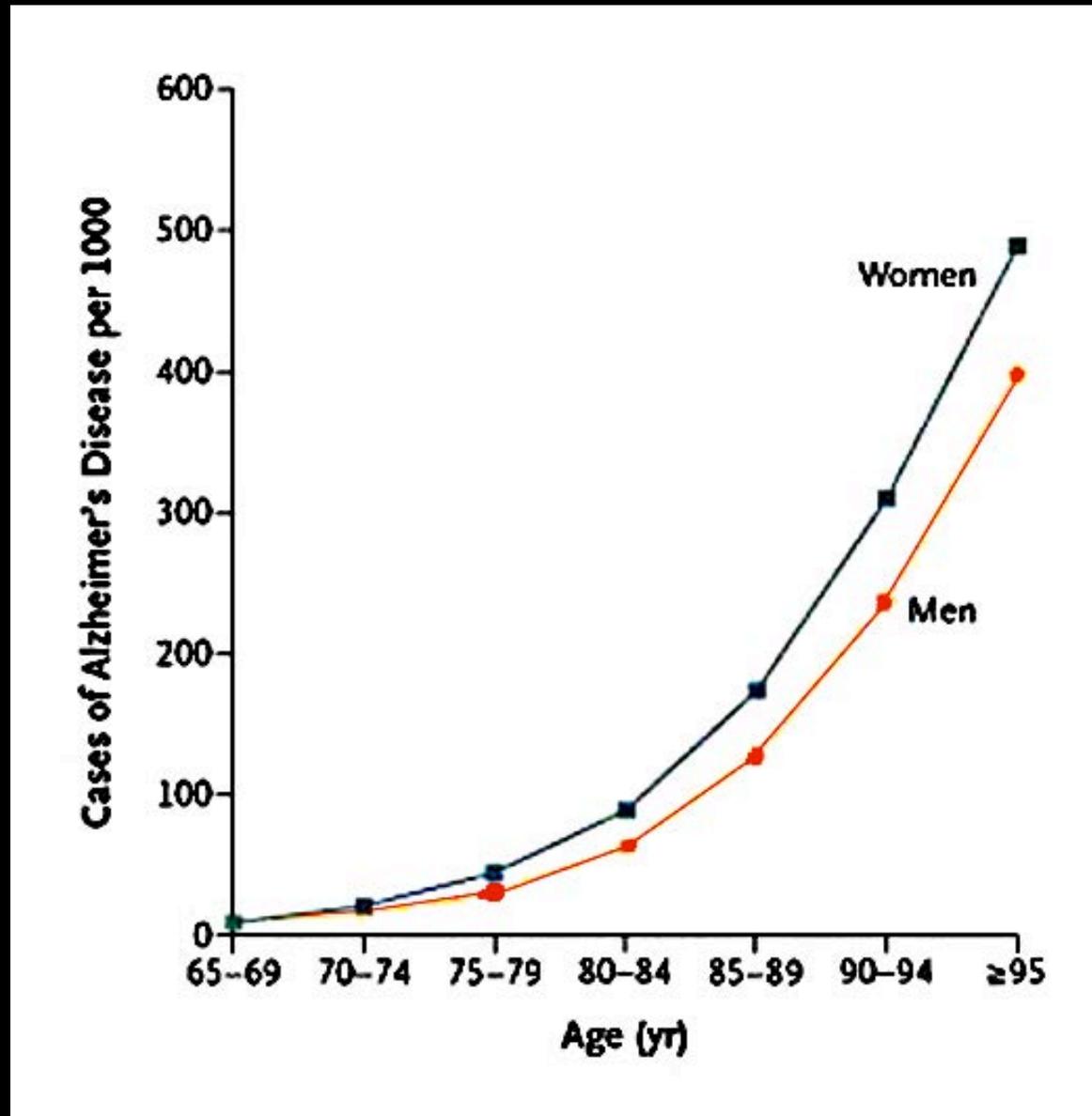
0 1.36 B

Play ▶ 1800 1820 1840 1860 1880 1900 1920 1940 1960 1980 2000 Trails



“What Drag It Is Getting Old”

Age is the Biggest Risk Factor for AD



Biomedical Research

- Precision medicine
- New treatments for AD, PD, ALS, osteoporosis, etc.
- Better ways to detect who's at risk for what, early

BUT – Government funding for research on age-related diseases is too small; we need academia and the private sector to step up, to translate basic research discoveries into validated targets and effective therapeutics

Alzheimer's Disease (AD)

Most common devastating form of dementia

- Affects 5.3 million Americans**
- Number will double in 10 years and more than triple to 15 million by 2050**
- Impact on families cannot be measured in dollars**
 - \$172 billion (2010)**
 - Costs by 2030 to increase 85%!**

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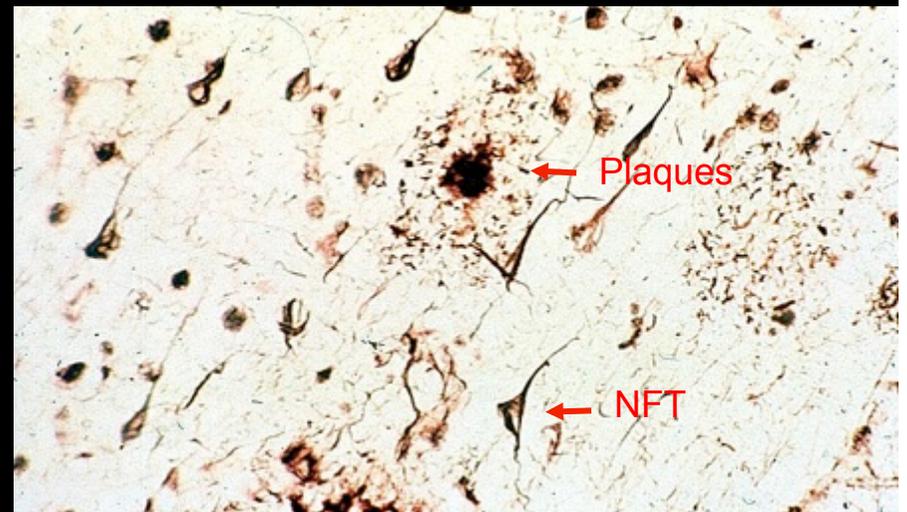
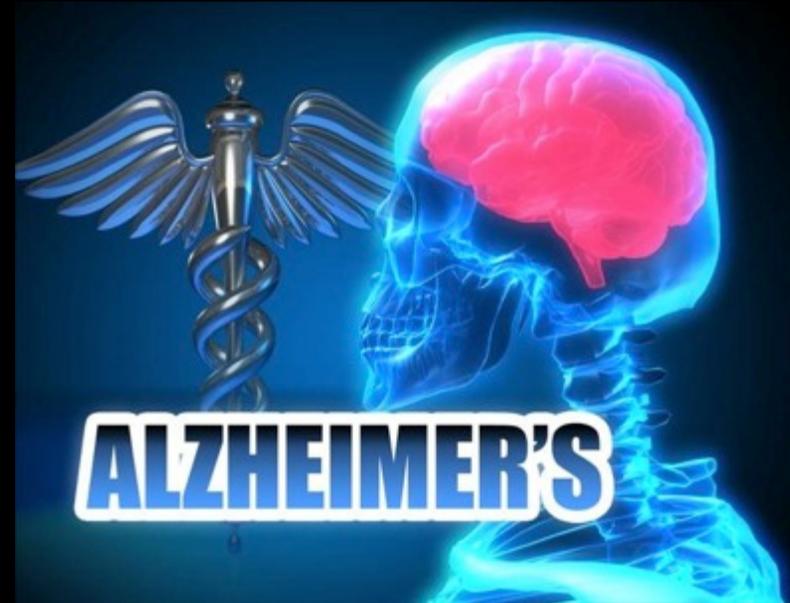
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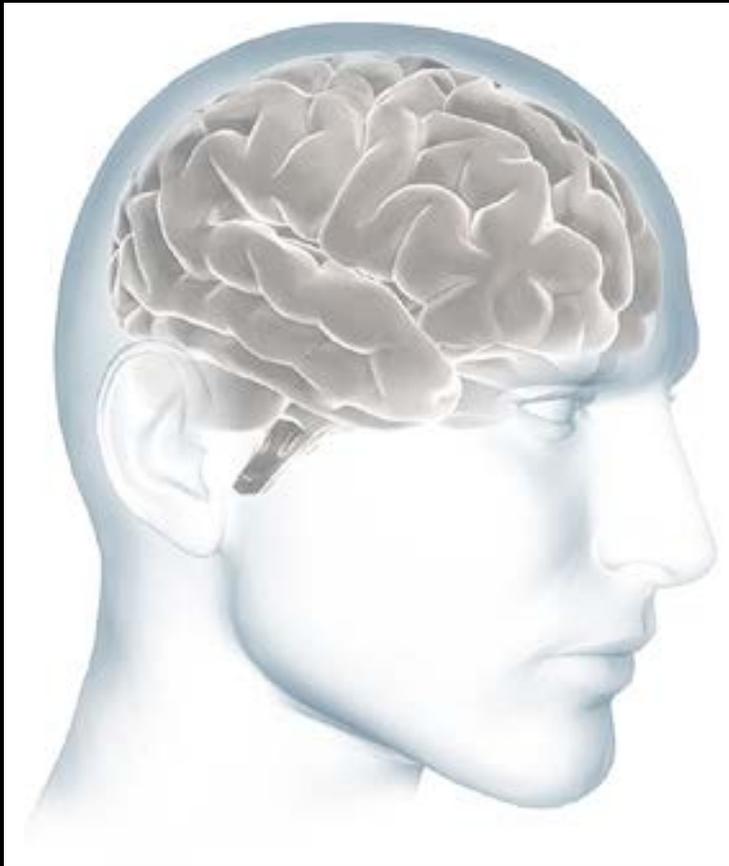
Presently no effective medication that will cure or reverse the cognitive decline

Characteristics of Alzheimer's Disease

- Progressive, degenerative brain disease with a gradual onset, characterized by a loss of memory
- Atrophy or loss of brain cells in specific parts of the brain
- Development of plaques ($A\beta$) and tangles (tau)
- Depletion of neurotransmitters

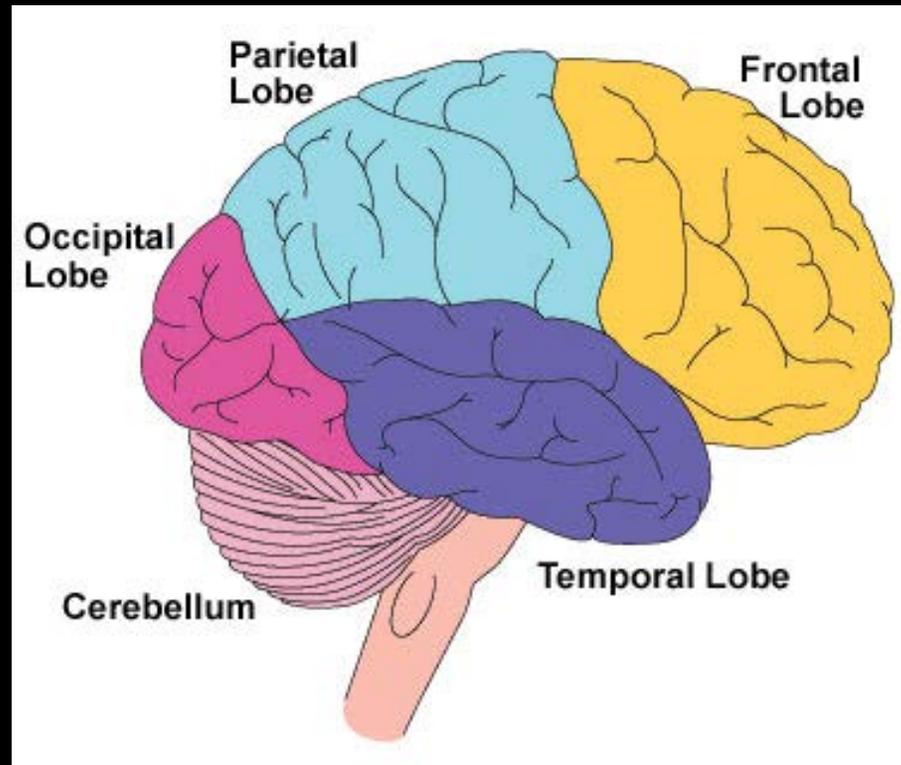


The Healthy Brain



- Your brain is your most powerful and complex organ in your body
- It controls your emotions, it helps you think, it helps you feel; you can say the brain is you

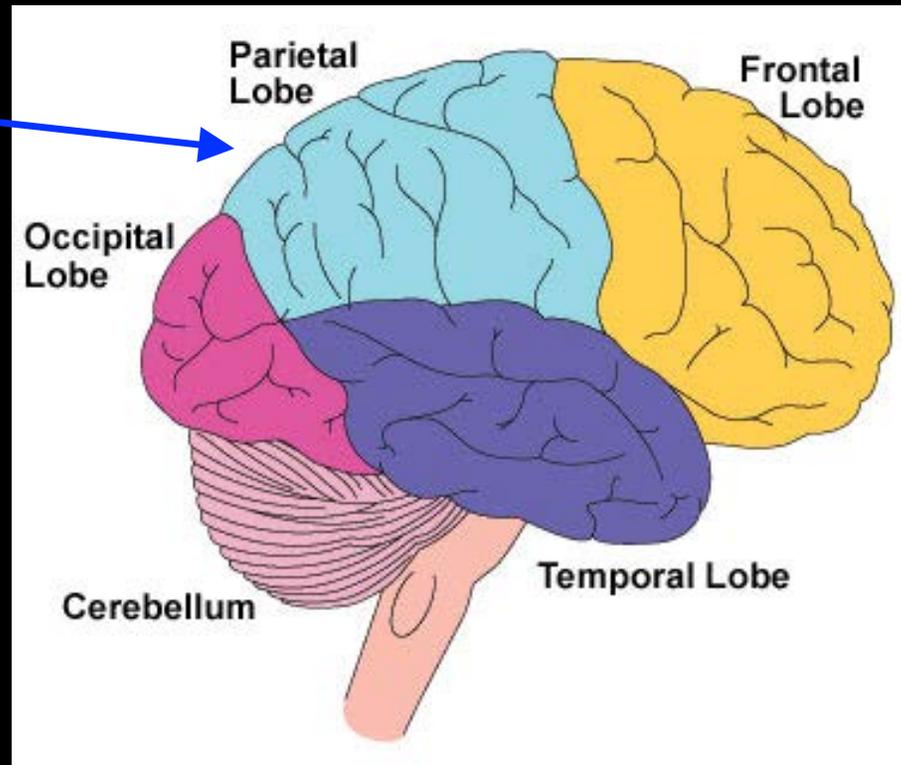
Lobes of the Brain



Lobes of the Brain

Parietal lobe:

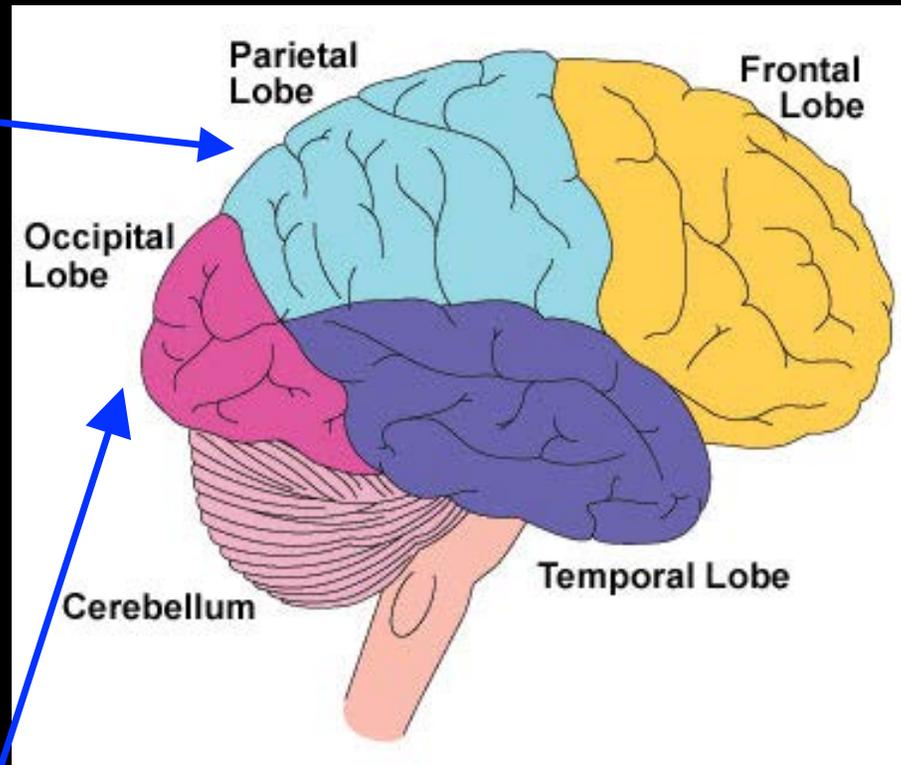
- attention
- touch
- pain
- temperature
- spatial and visual perception
- interprets language, words



Lobes of the Brain

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Occipital lobe:

- vision

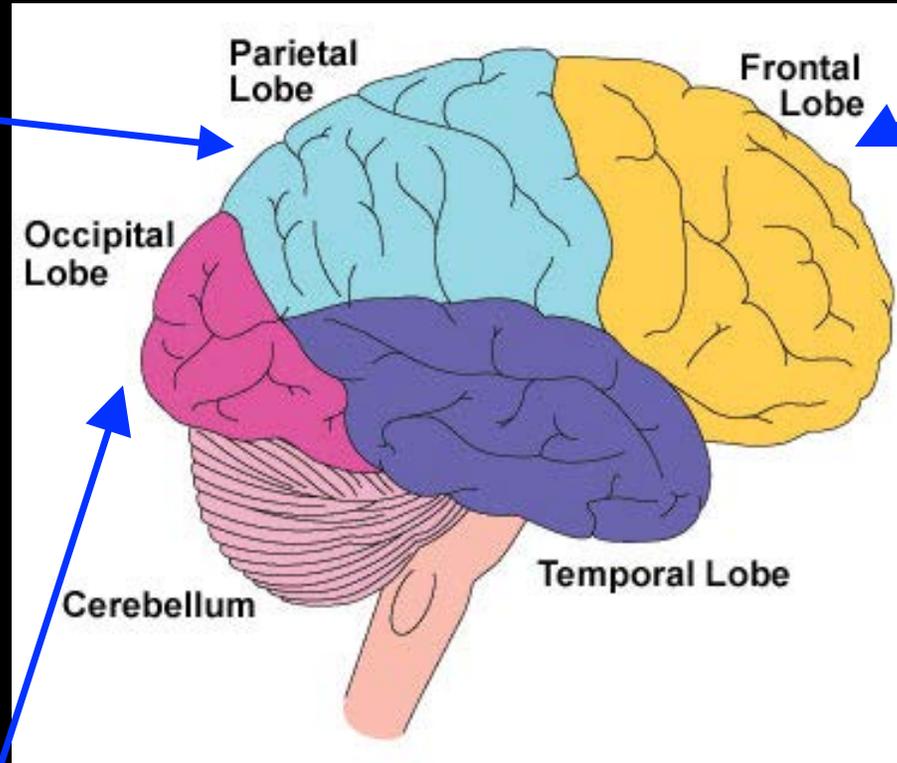
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Frontal lobe:

- planning
- judgment
- thinking
- emotions
- speech
- personality
- intelligence

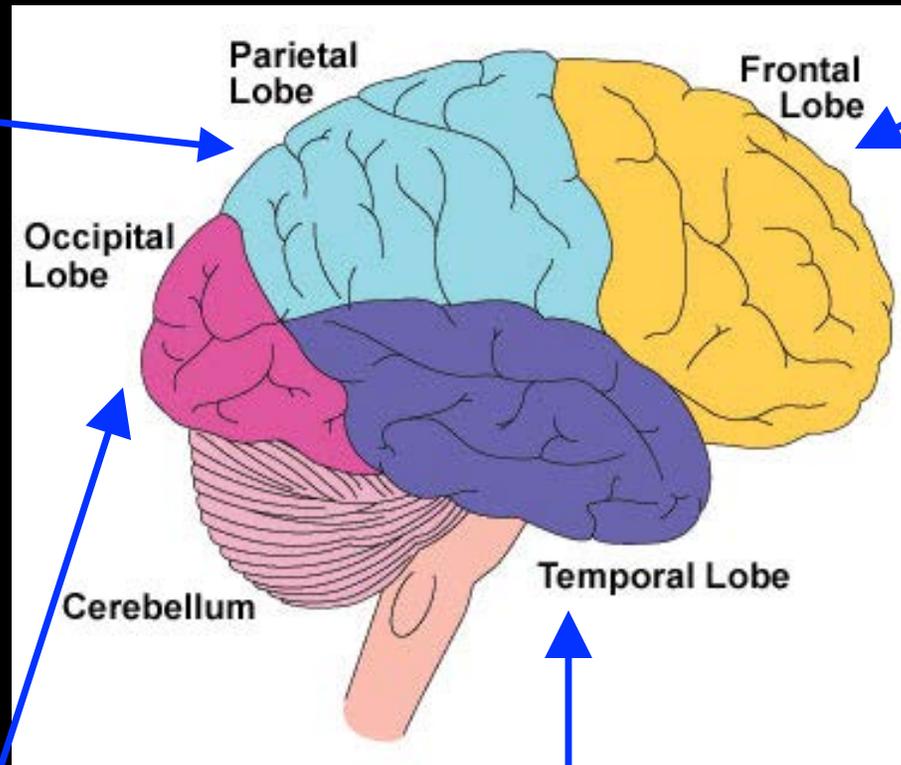
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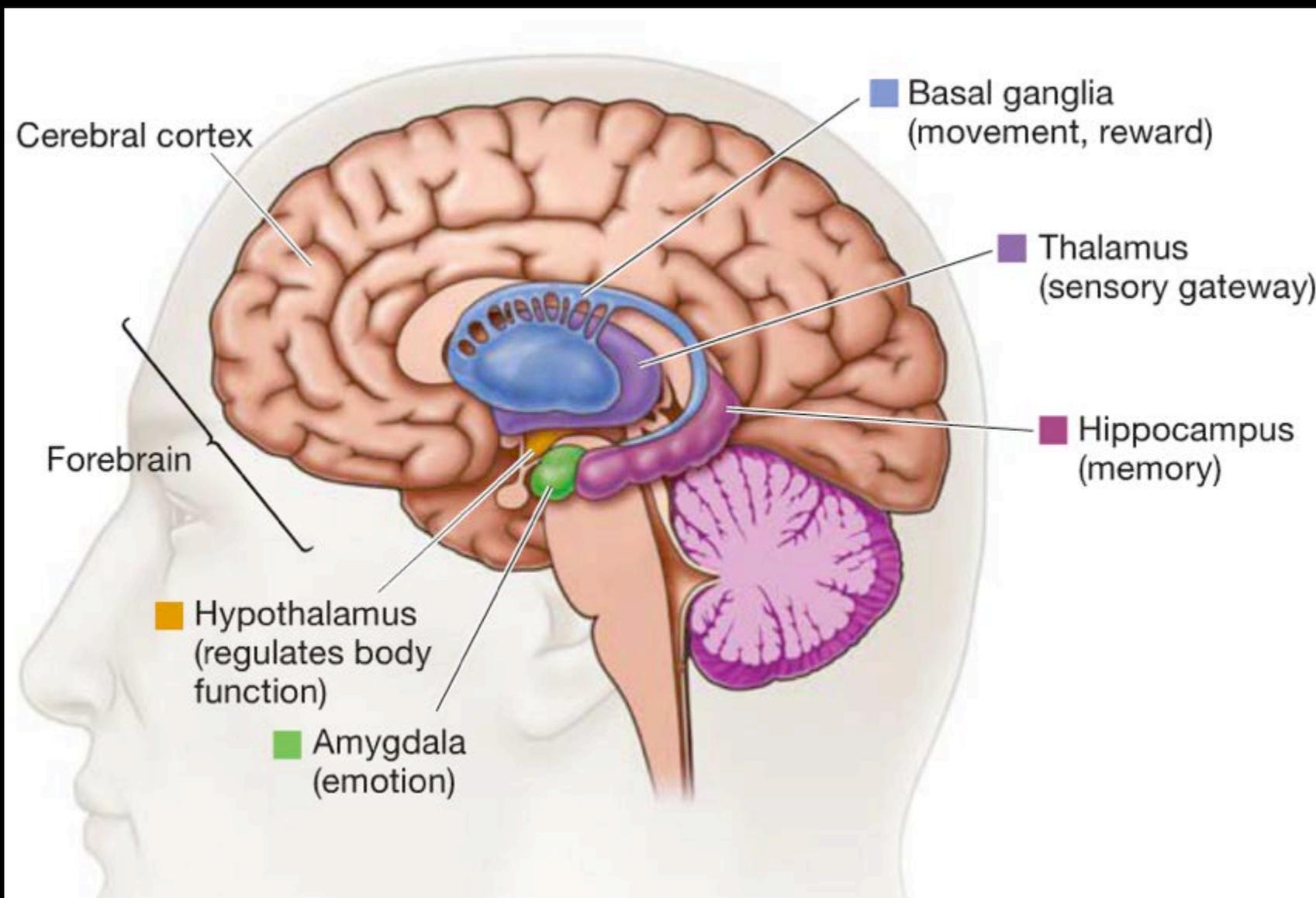
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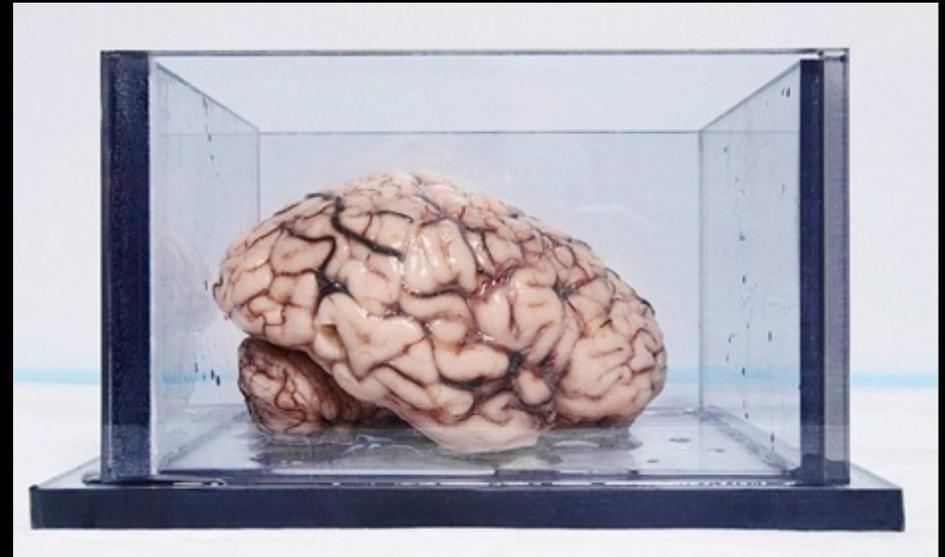
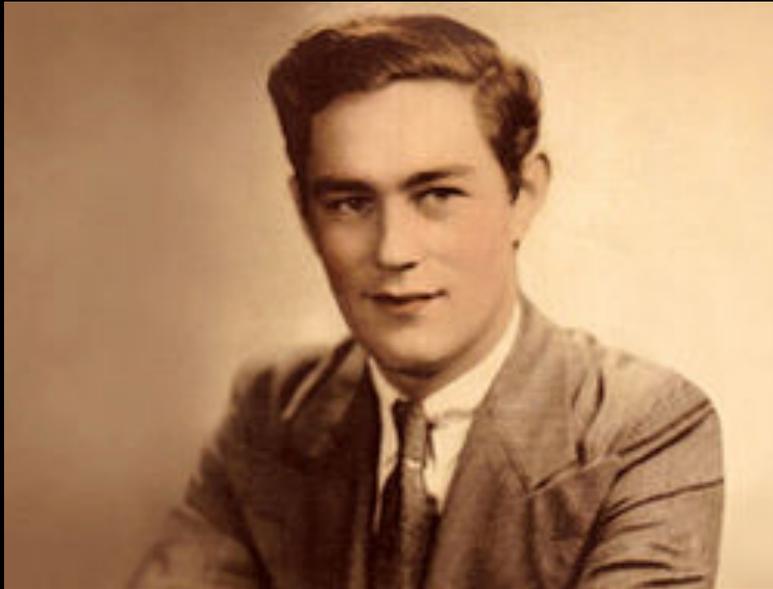
Temporal lobe:

- memory
- hearing
- understanding language

Subcortical Structures of the Brain



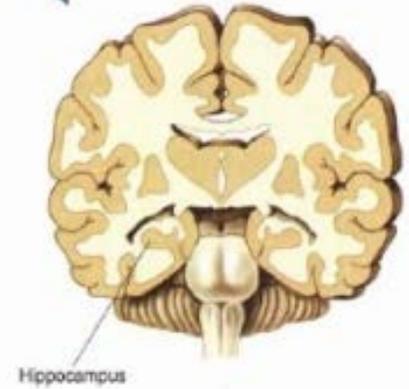
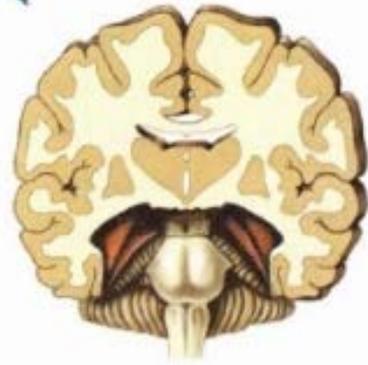
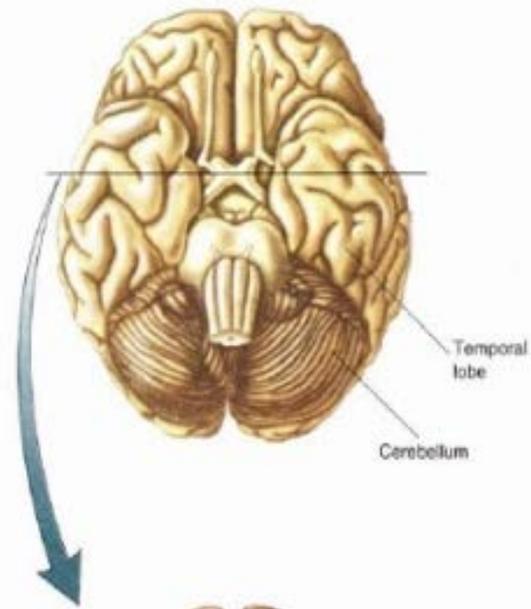
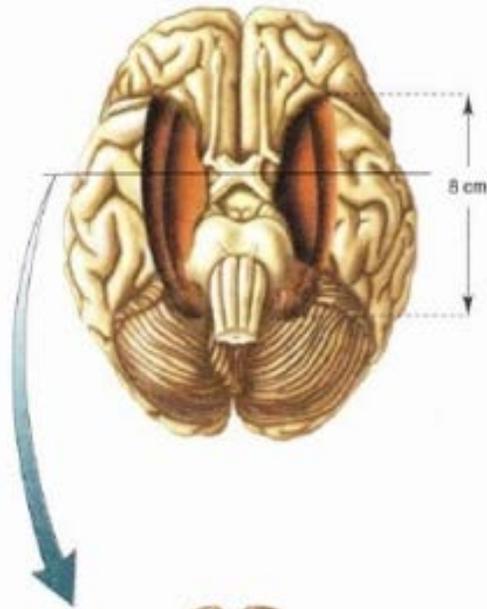
Henry Gustav Molaison (1926-2008)



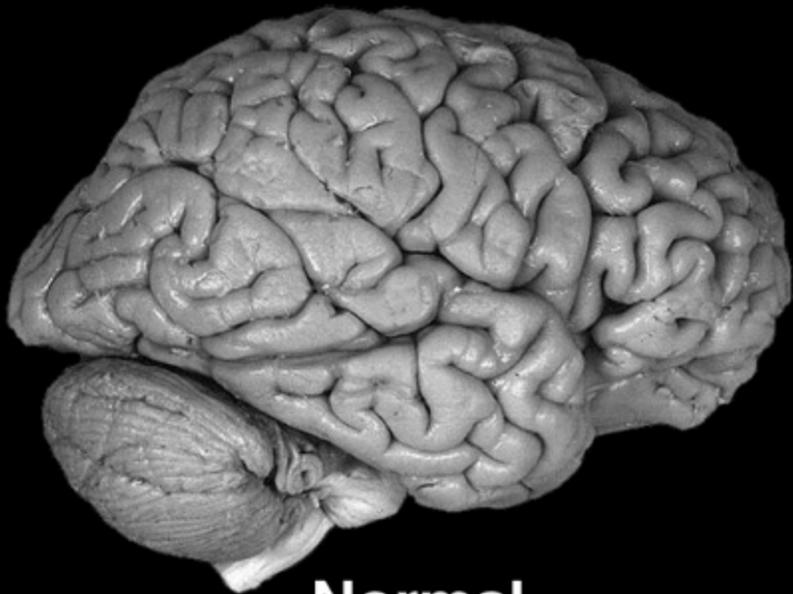
HM had his hippocampus and amygdala surgically removed in an attempt to cure his epilepsy

HM

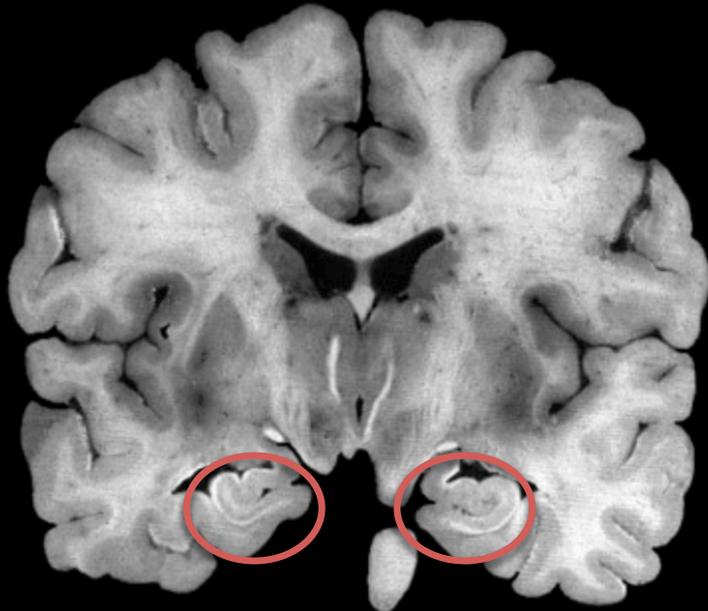
Normal Brain



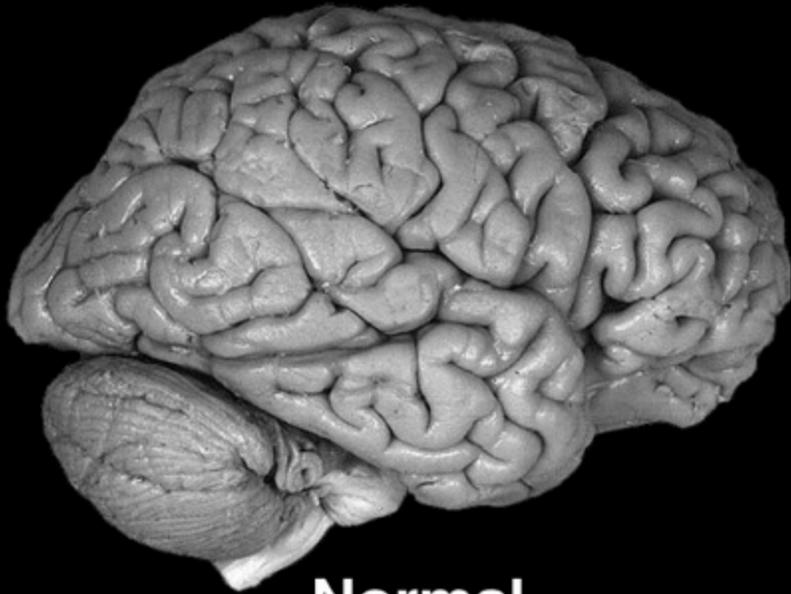
Normal Brain Anatomy



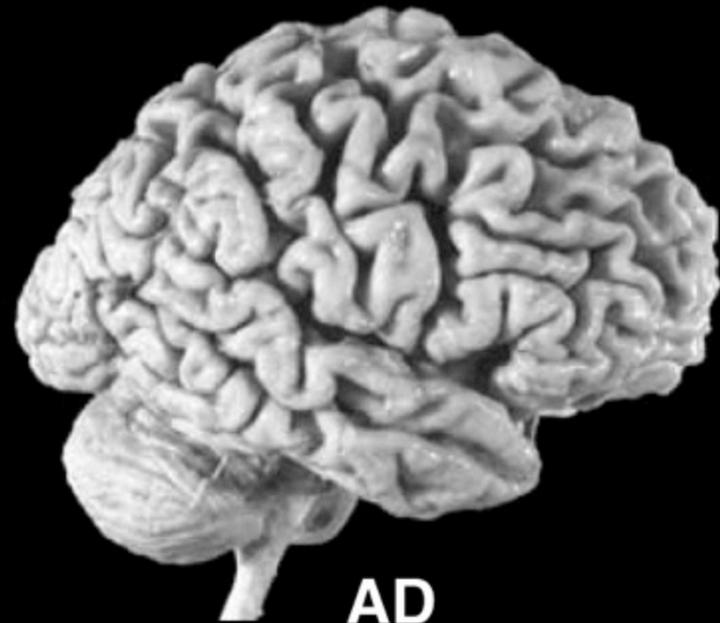
Normal



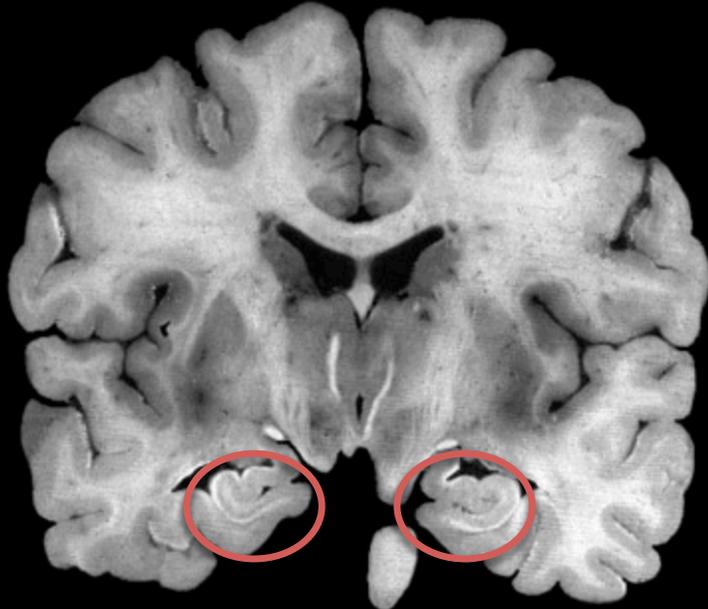
Brain Atrophy in Advanced Alzheimer's Disease



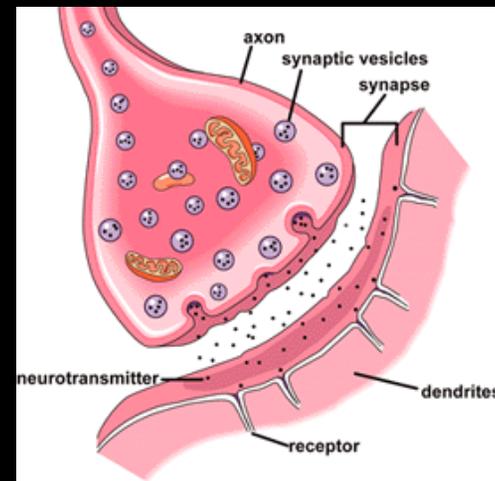
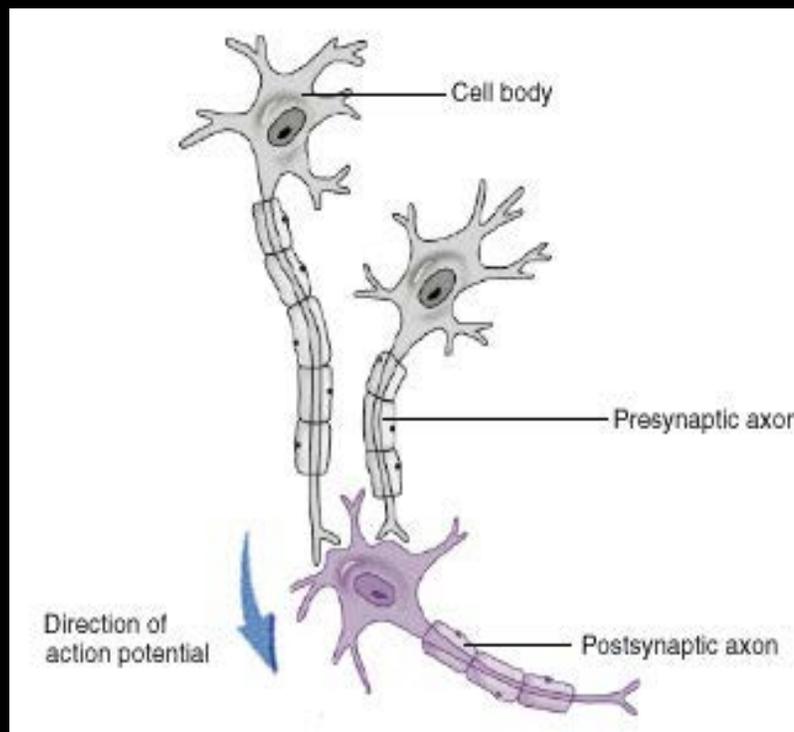
Normal



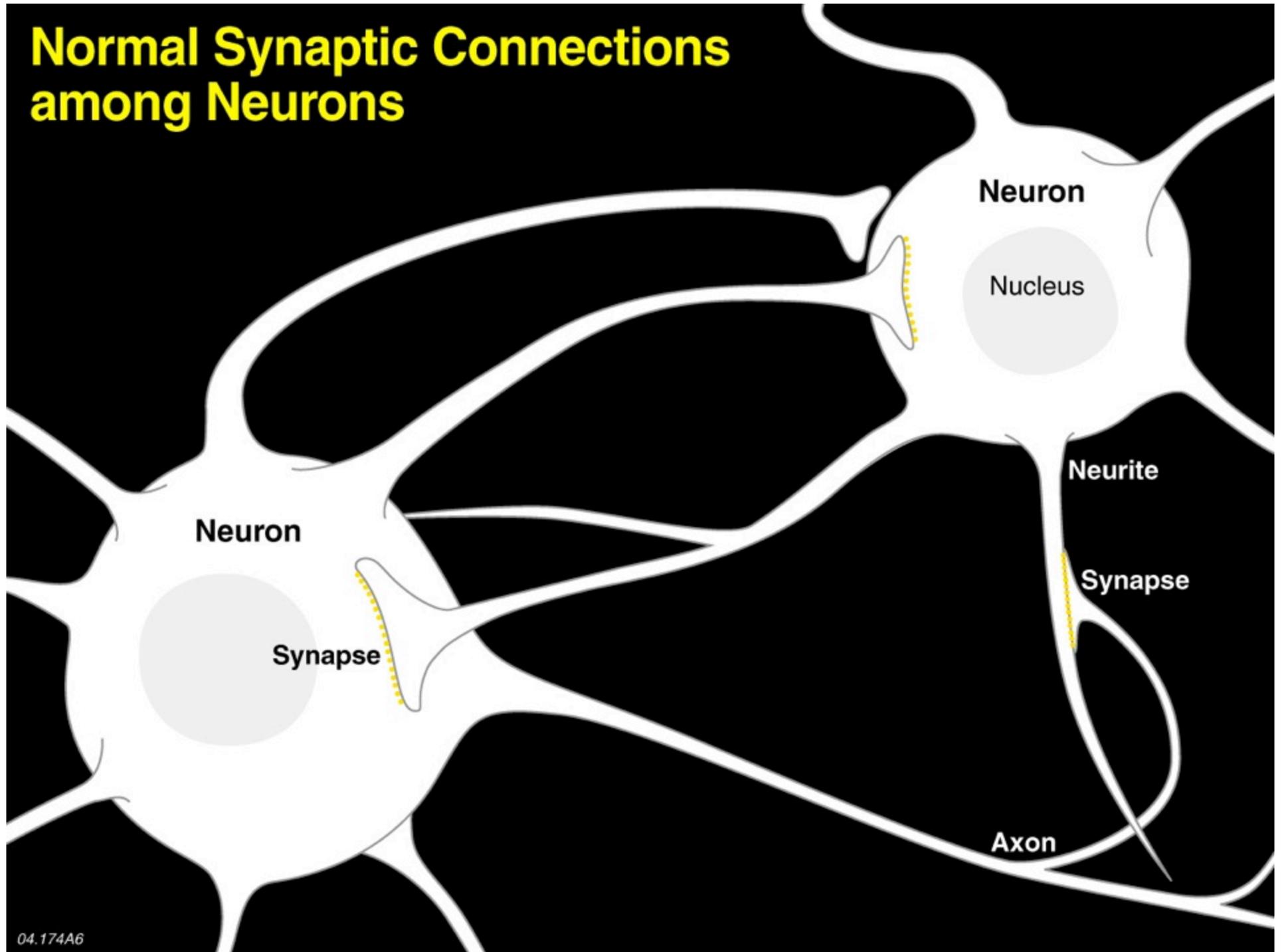
AD



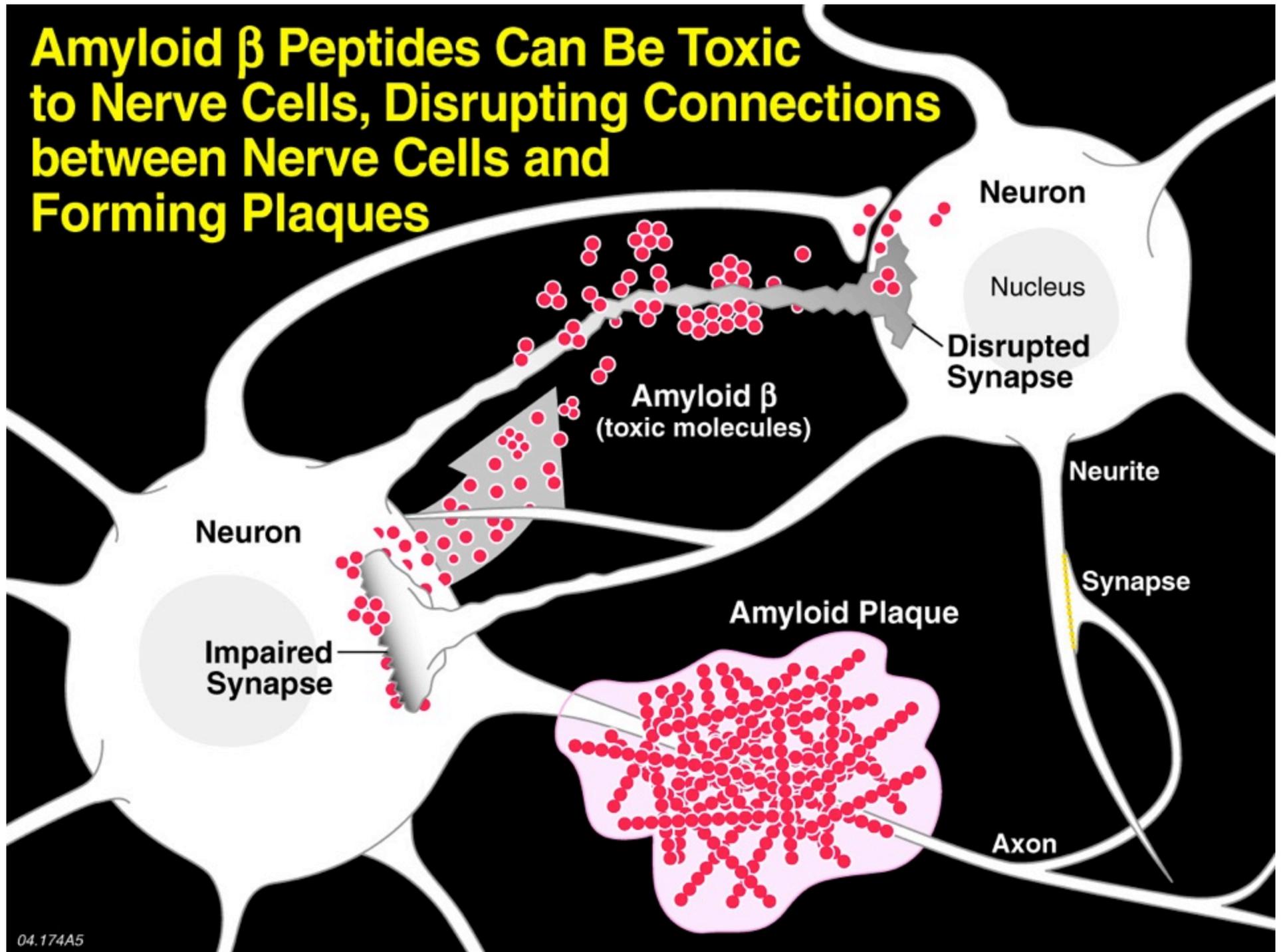
Structure and Function of Nerve Cells (Neurons)



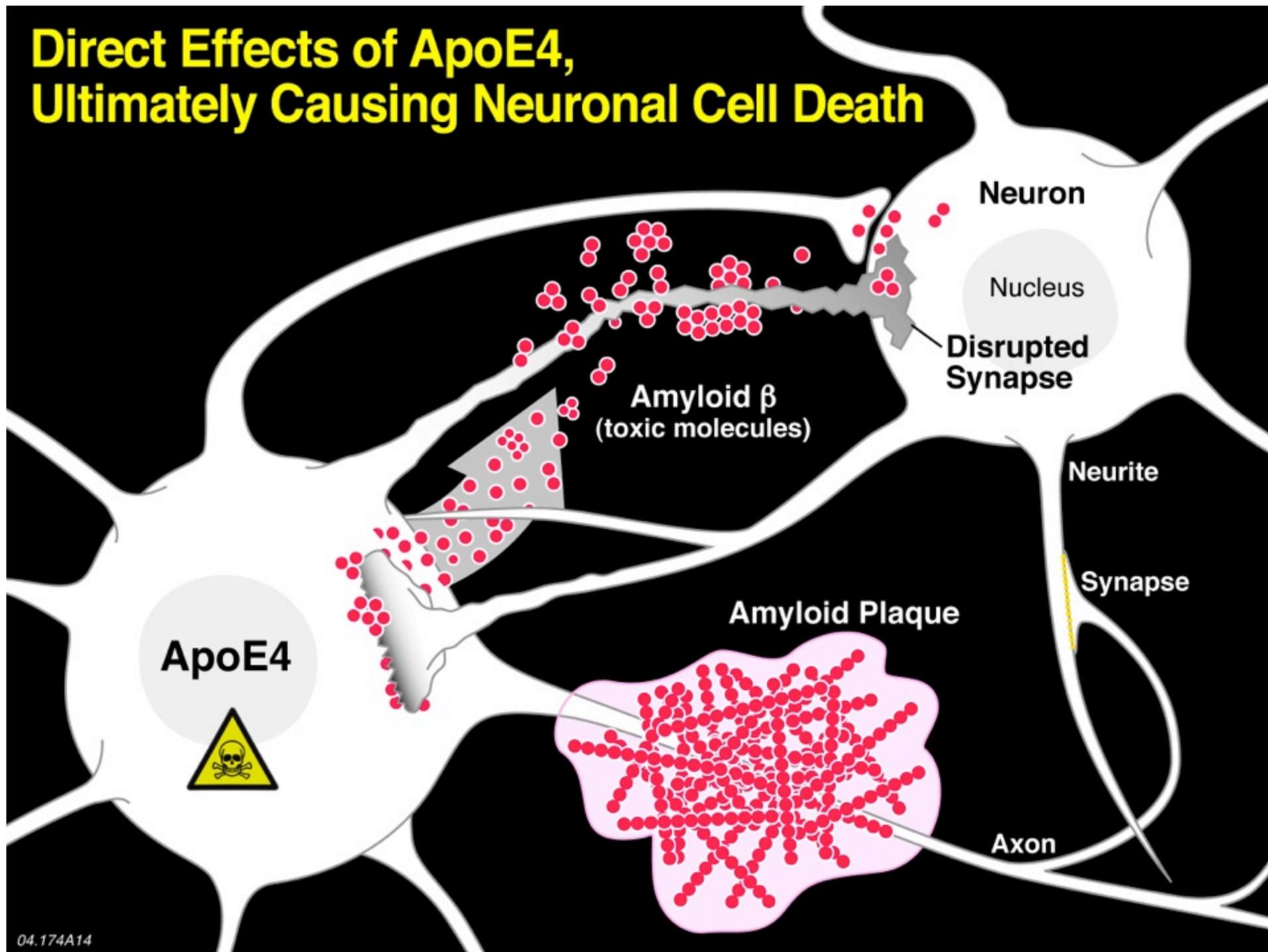
Normal Synaptic Connections among Neurons



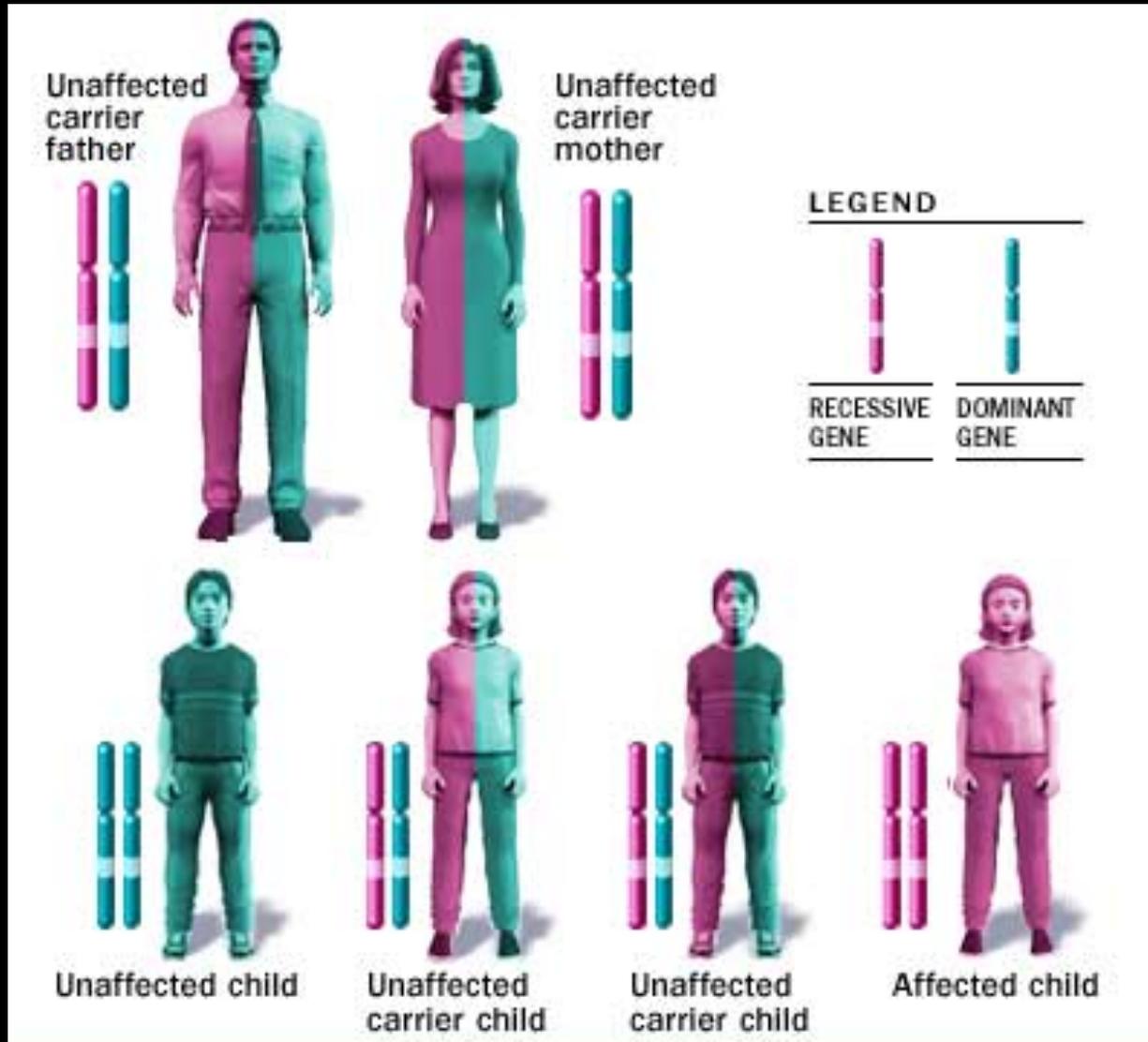
Amyloid β Peptides Can Be Toxic to Nerve Cells, Disrupting Connections between Nerve Cells and Forming Plaques



Direct Effects of ApoE4, Ultimately Causing Neuronal Cell Death



Genetic Inheritance



Genetic Inheritance

African-Americans have higher incidence rates of late-onset Alzheimer's compared to whites living in the same community

Genetic risk factors seem different in African Americans and white Americans

Genetic Inheritance – ApoE4

**ApoE is the strongest genetic risk factor for
Alzheimer's Disease**

**But ApoE genotype alone does not explain the
increased frequency of AD in older African
Americans**

Genetic Inheritance – ABCA7

- **A 2013 study revealed:**
- **ABCA7 gene - was once thought to be weakly associated with AD risk in whites may almost double the risk of developing AD in African-Americans**
- **African-Americans are 1.8 times more likely to develop late-onset Alzheimer's than those who didn't have the gene**

Two Major Forms of ApoE in Humans

ApoE3 (Good “E”)

- Most common, so-called “normal” form

ApoE4 (Bad “E”)

- “Abnormal” form, associated with Alzheimer’s disease

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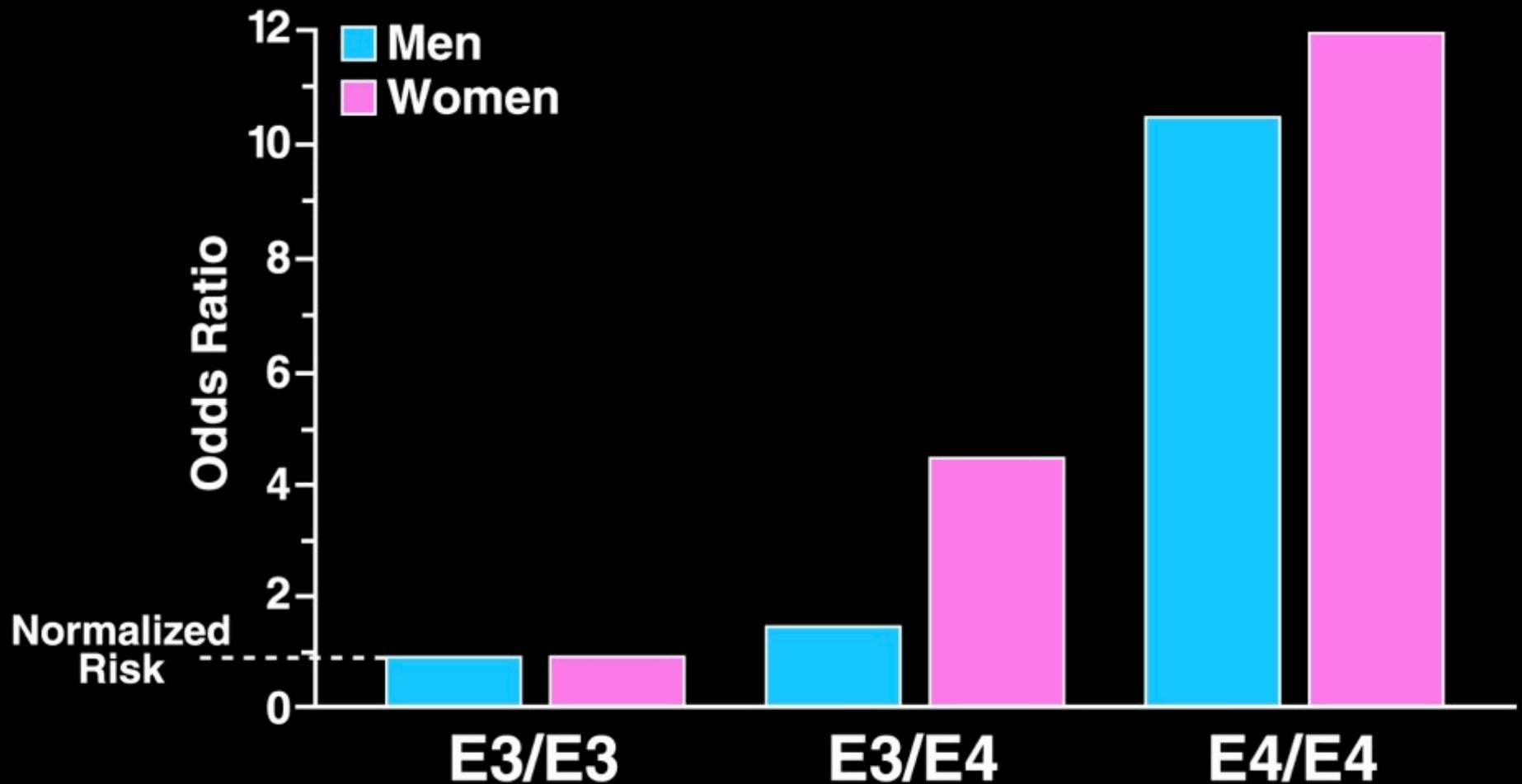
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- Not rare (25% of population)
- 65–80% of patients with Alzheimer’s disease have this form of apoE
- Increases risk
- Decreases the age of onset
 - No apoE4: 75–80 years of age
 - With apoE4: 65–68 years of age

Effect of *APOE* Genotype on the Risk of Developing Alzheimer's Disease around the Age of 60



Adapted from Farrer *et al.*, 1999

How Might ApoE4 (Bad “E”) Adversely Affect the Nerve Cells (Neurons) in the Brain?

Injurious Agents:

Aging

Head Trauma

Poor O₂
Delivery

```
graph TD; A[Aging] --> C((Neuronal Damage)); B[Head Trauma] --> C; D[Poor O2 Delivery] --> C;
```

Neuronal
Damage

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Effective Repair/
Protection of Nerves

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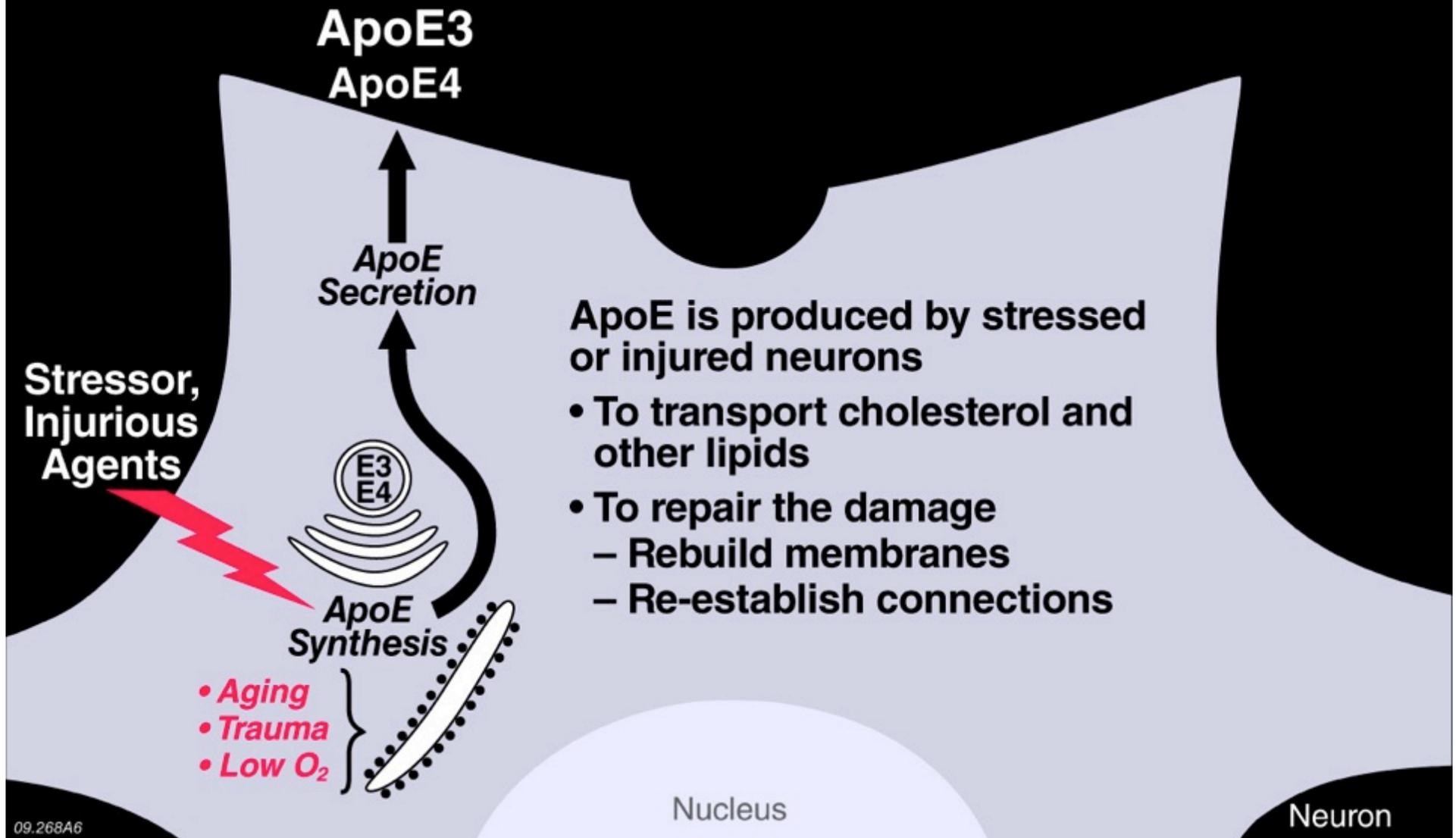
ApoE4

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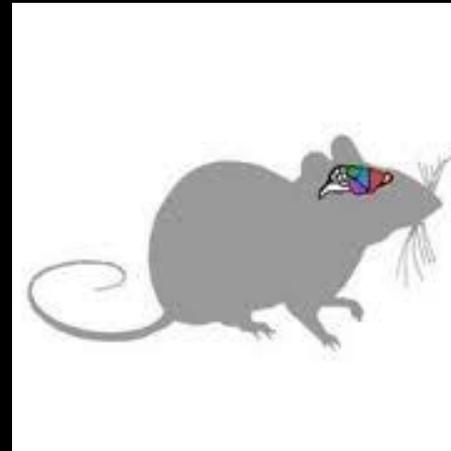
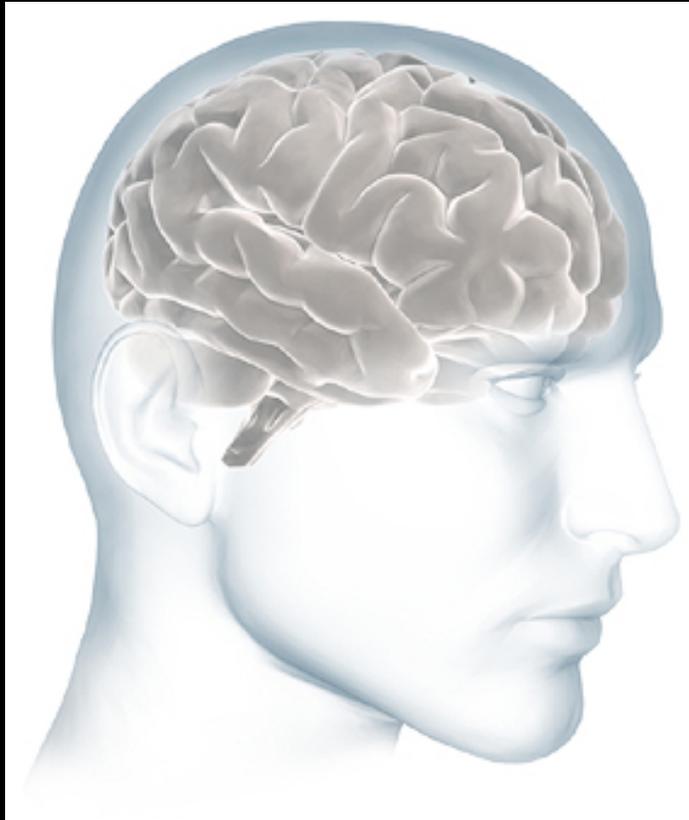
Poor Repair/Protection

Alzheimer's Disease

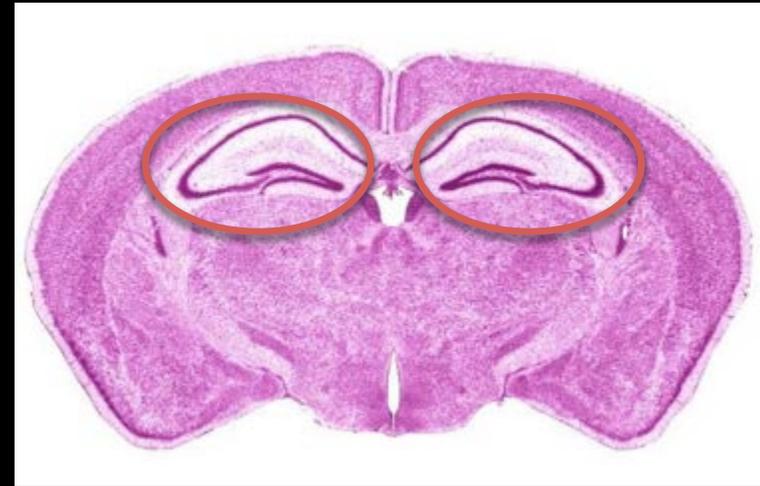
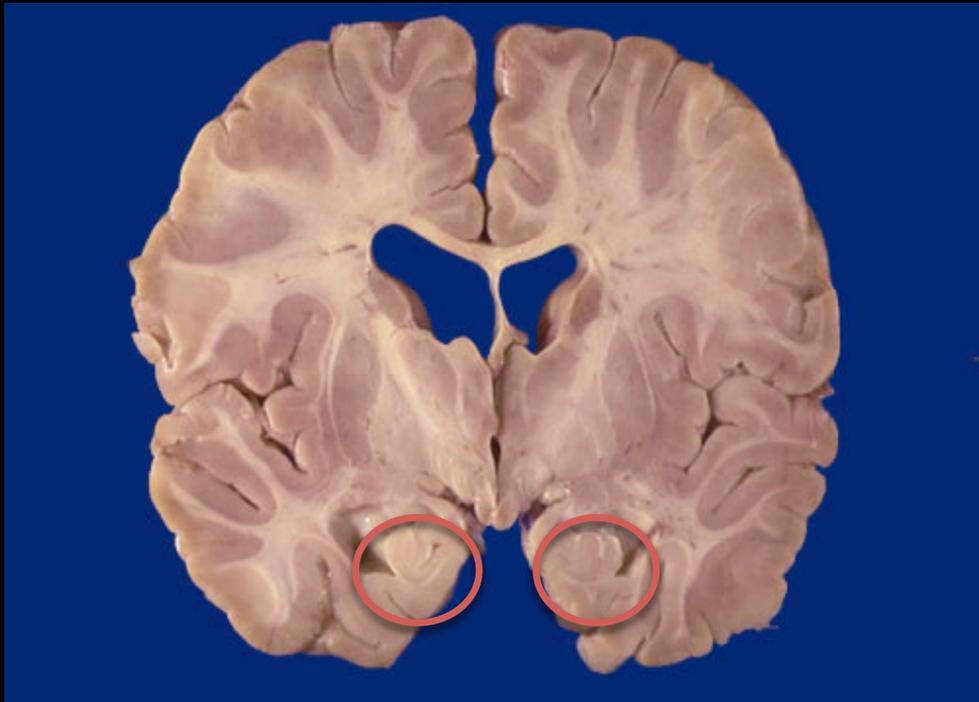
Nerve Cells That Are Stressed or Injured Turn on Synthesis of ApoE



Animal Models to Research AD



The Hippocampus is One of the First Areas to be Affected in AD



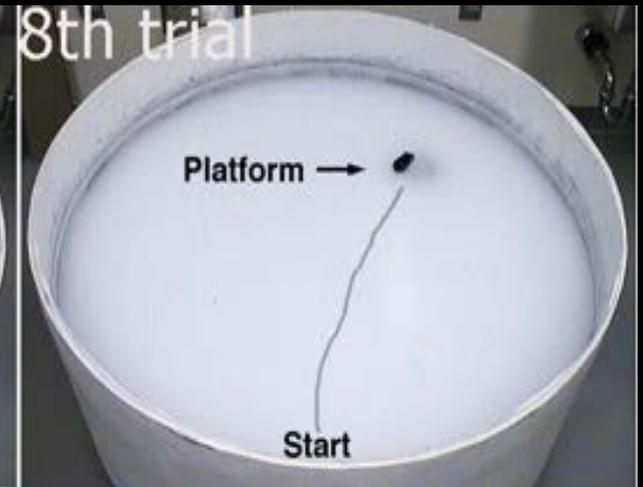
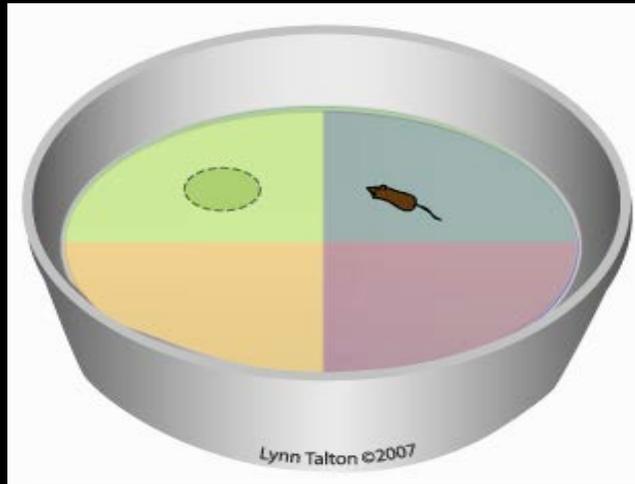
The Hippocampus is Responsible for Memories

How Do We Know This About ApoE?

Transgenic Mice Expressing ApoE in Neurons



How Do Scientists Test Memories in Mice?



Purpose:

Uses visual and spatial learning and memory.

Detects hippocampal memory deficit.

Water Maze Test

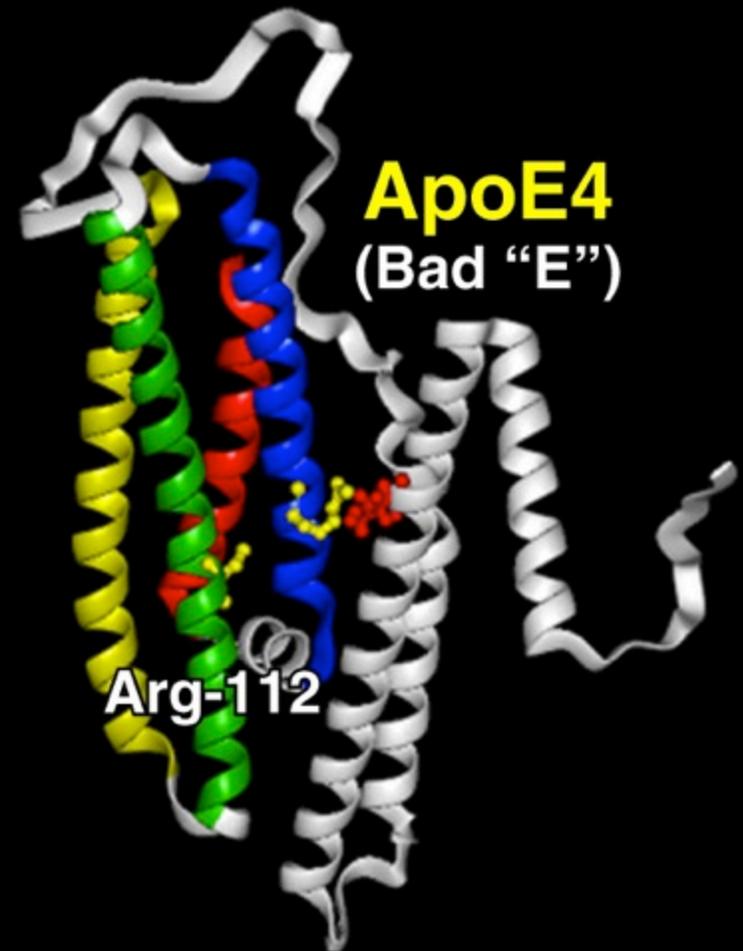
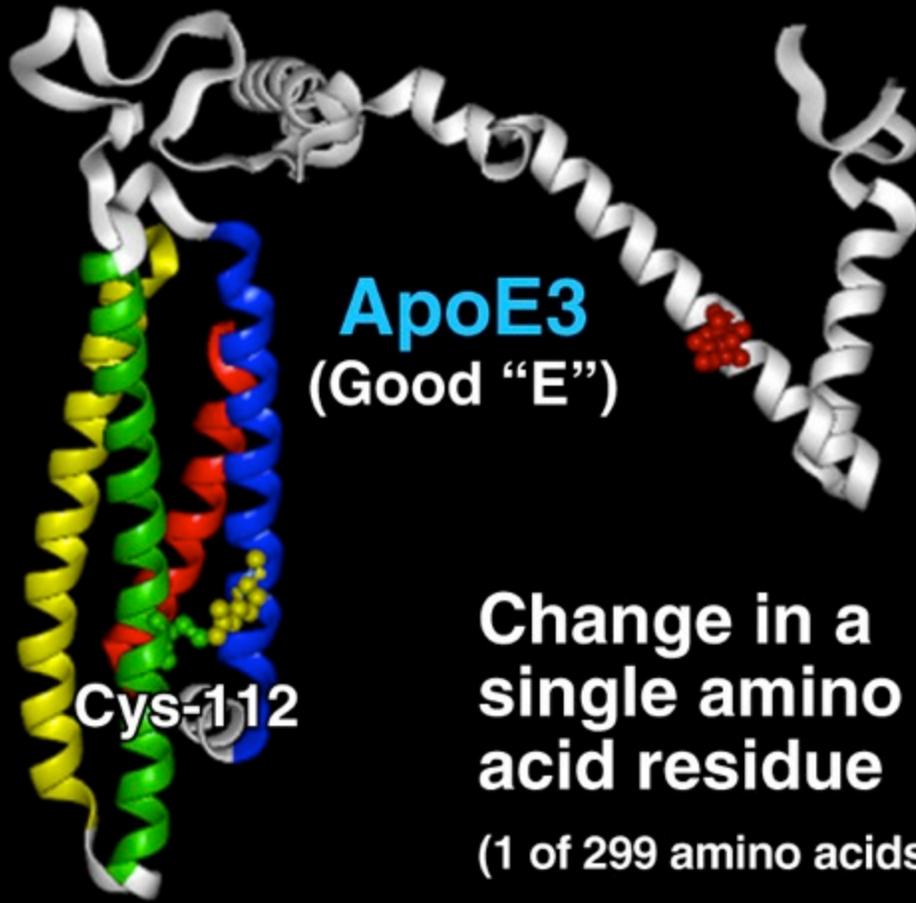


How Might ApoE4 (Bad “E”) Be Causing the Neuropathological Effects?

A major clue:

- The structure of apoE4 is different from apoE3
- ApoE4 has a structure that leads to pathology

Difference between ApoE3 and ApoE4

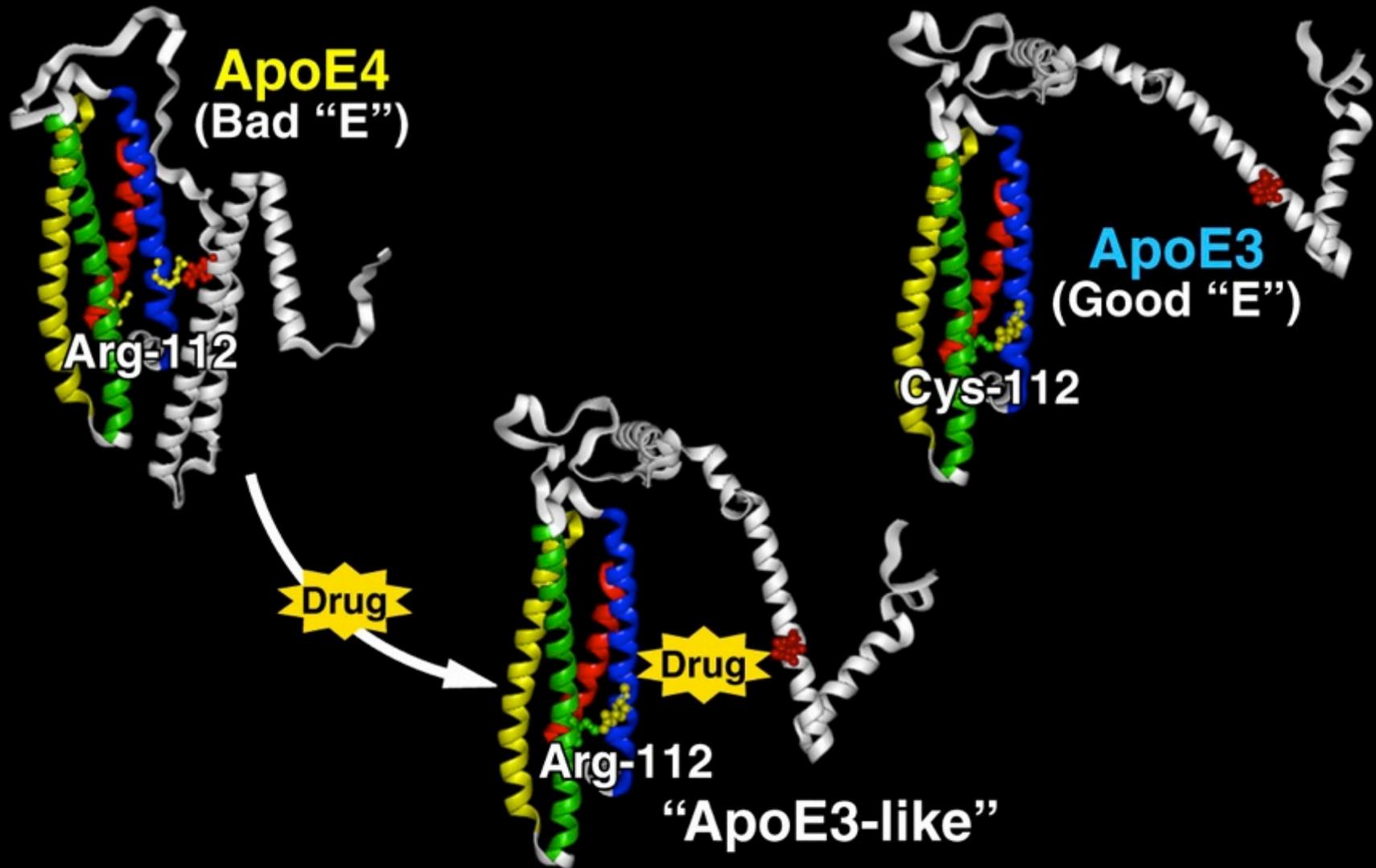


Change in structure and function is profound.

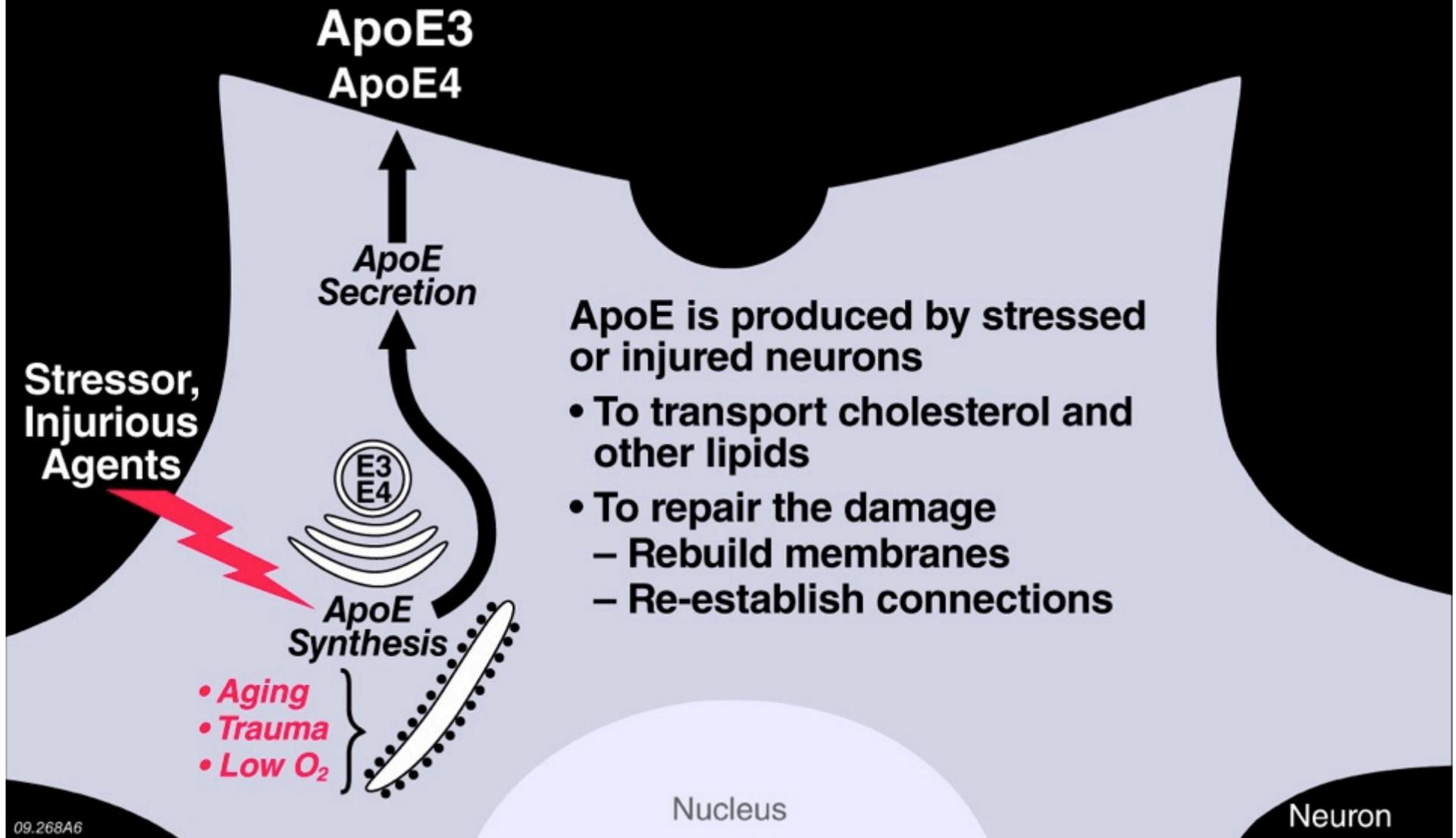
What Can We Do about the Detrimental Effects of ApoE4 (Bad “E”)?

**Can we find a small molecule (drug?)
that converts apoE4 (bad “E”) to an
apoE3-like molecule and abolishes the
detrimental effects on neuropathology?**

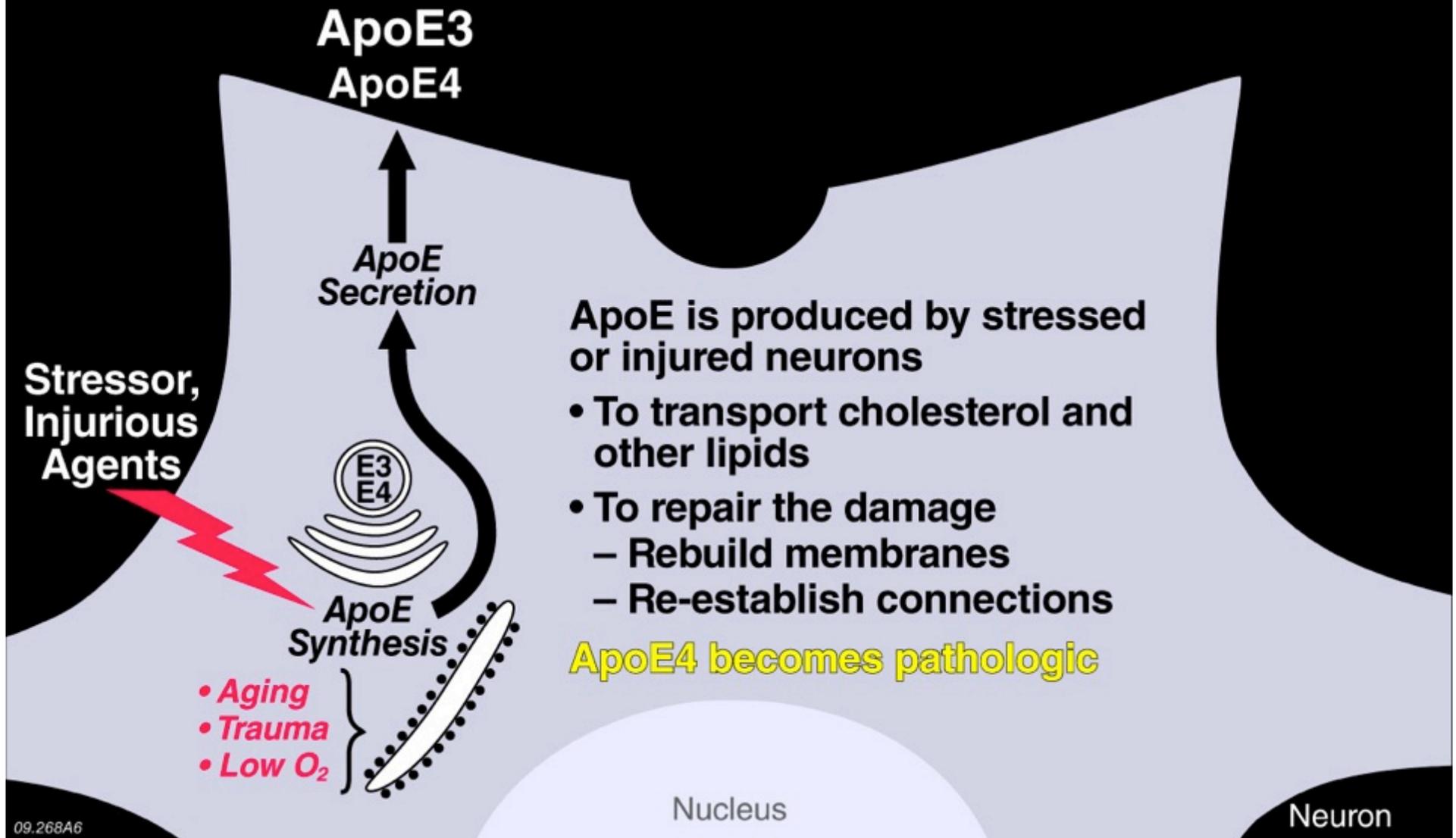
Converting **ApoE4** (Bad “E”) to an ApoE3-like (Good “E”) Molecule to Block Adverse Effects



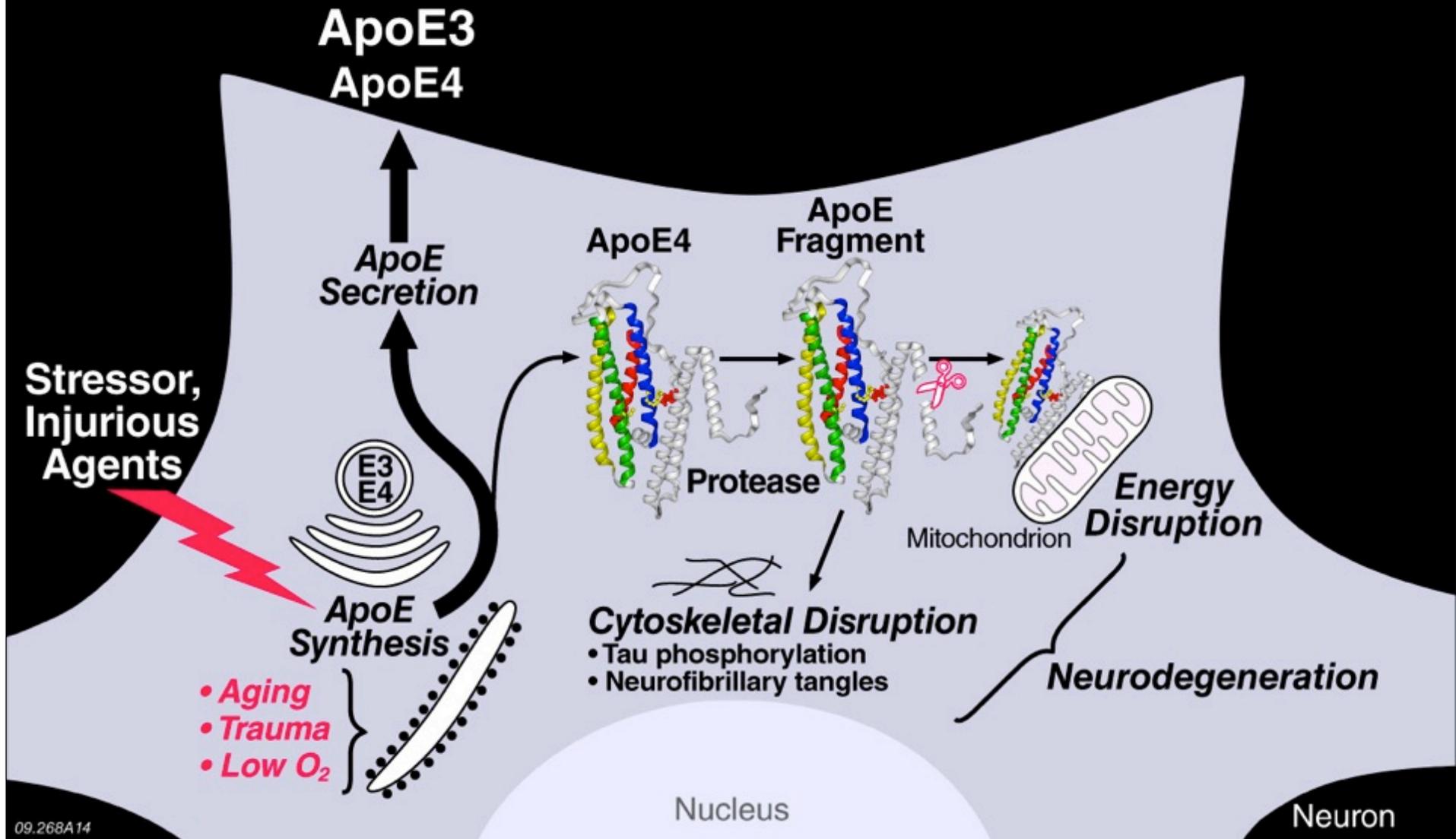
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Nerve Cells That Are Stressed or Injured Turn on Synthesis of ApoE



Detrimental Roles for ApoE4 in Neuropathology: Therapeutic Targets for Intervention

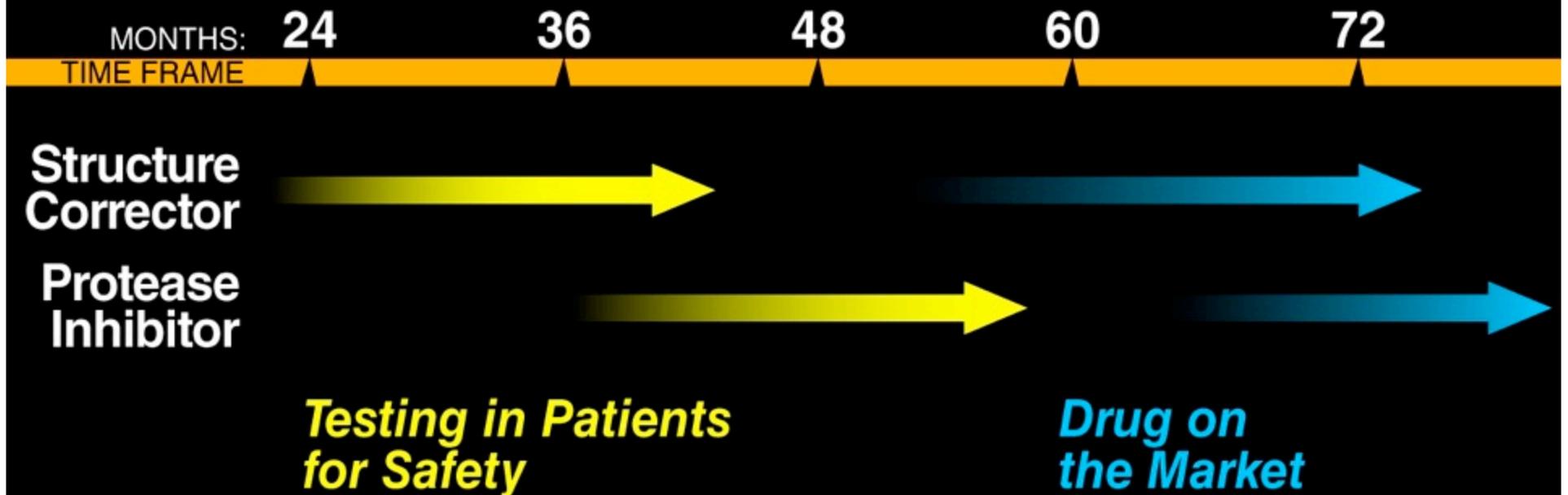


The Hope

Goal

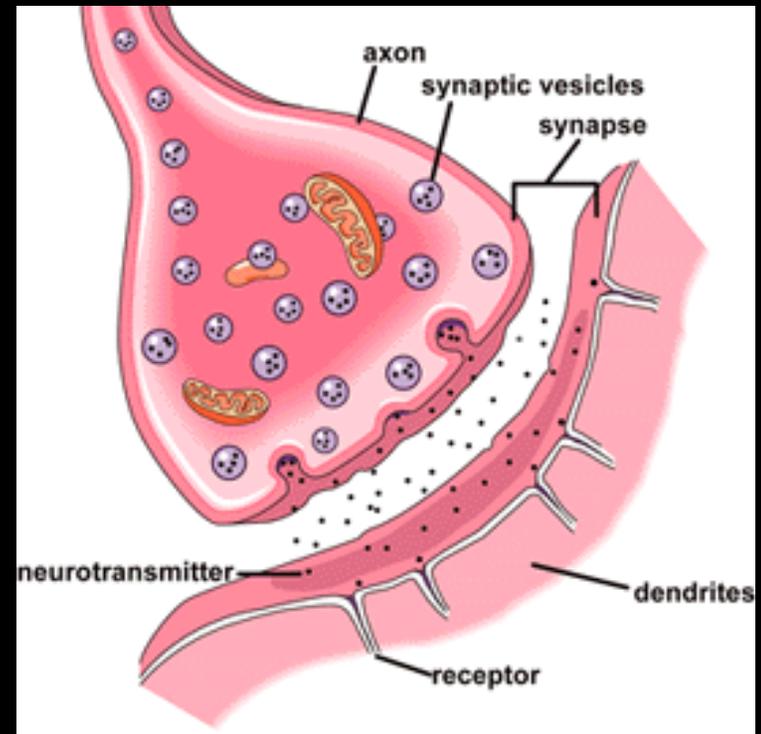
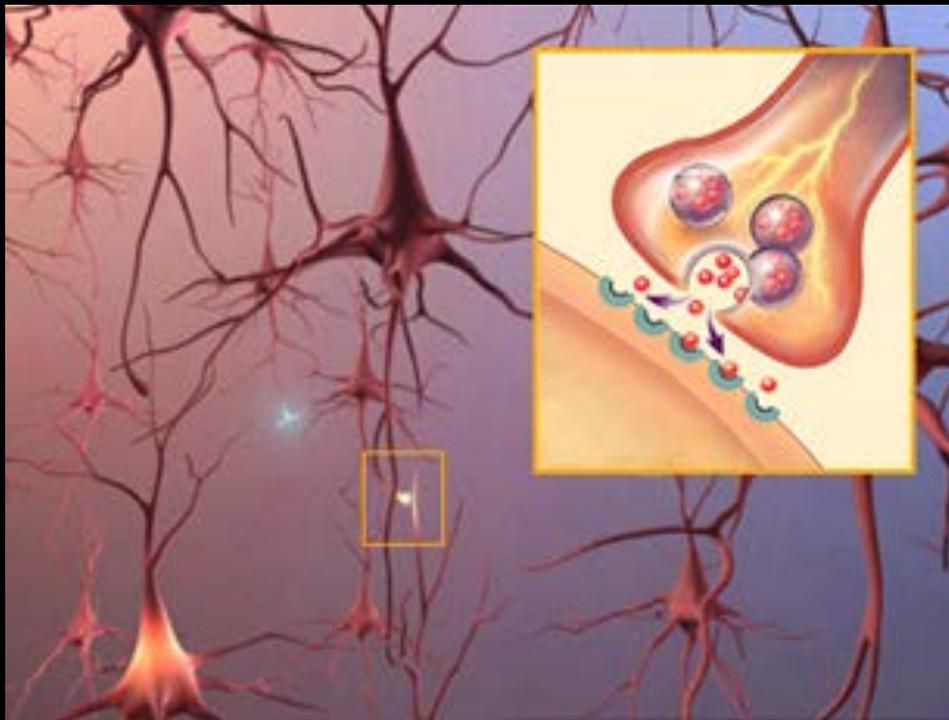
Drug to Attack ApoE4-associated Neuropathology

- Prevent the disease
- Reverse the disease (?)

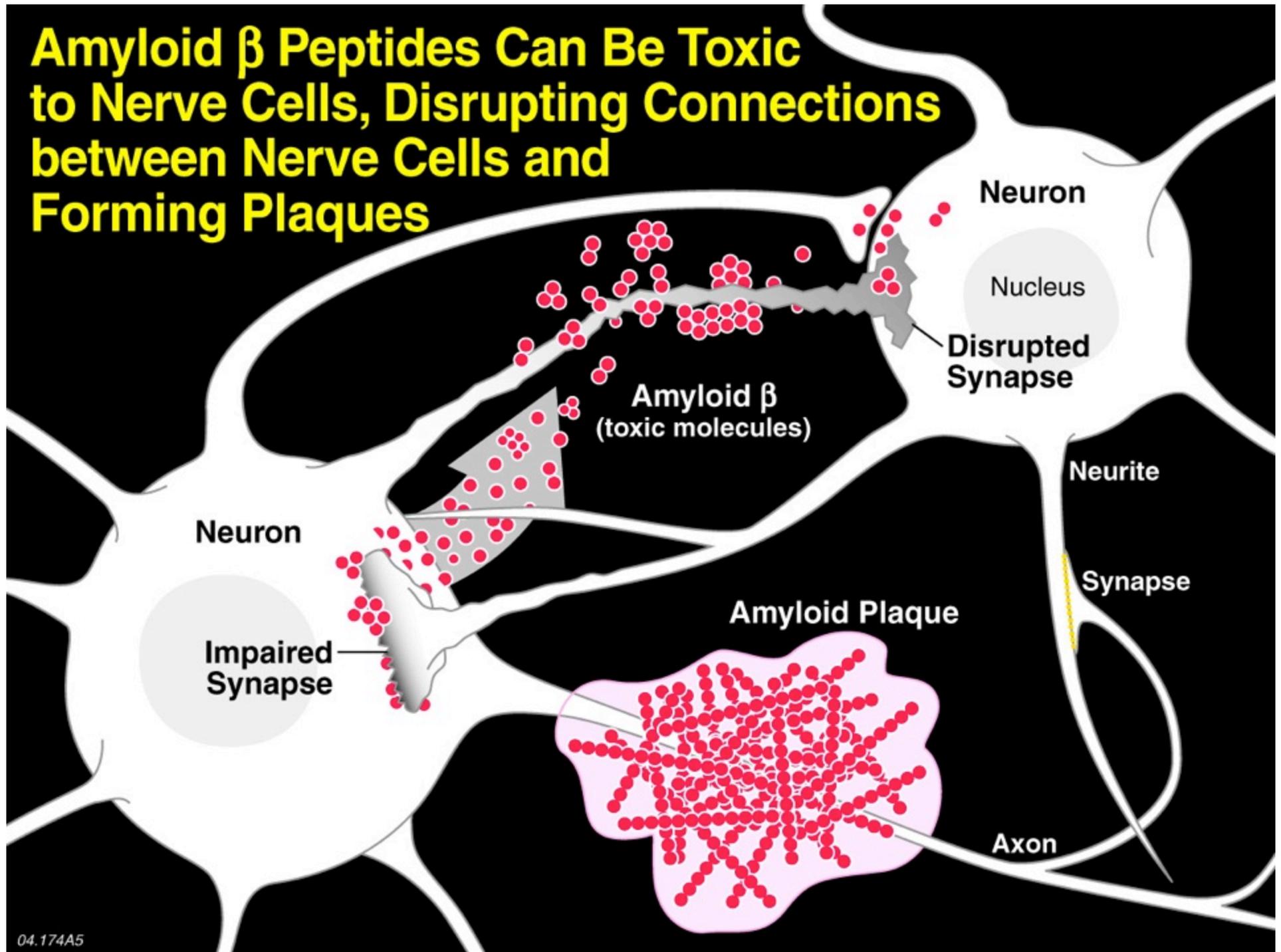


How Do Other Alzheimer's Disease Drugs “Work”?

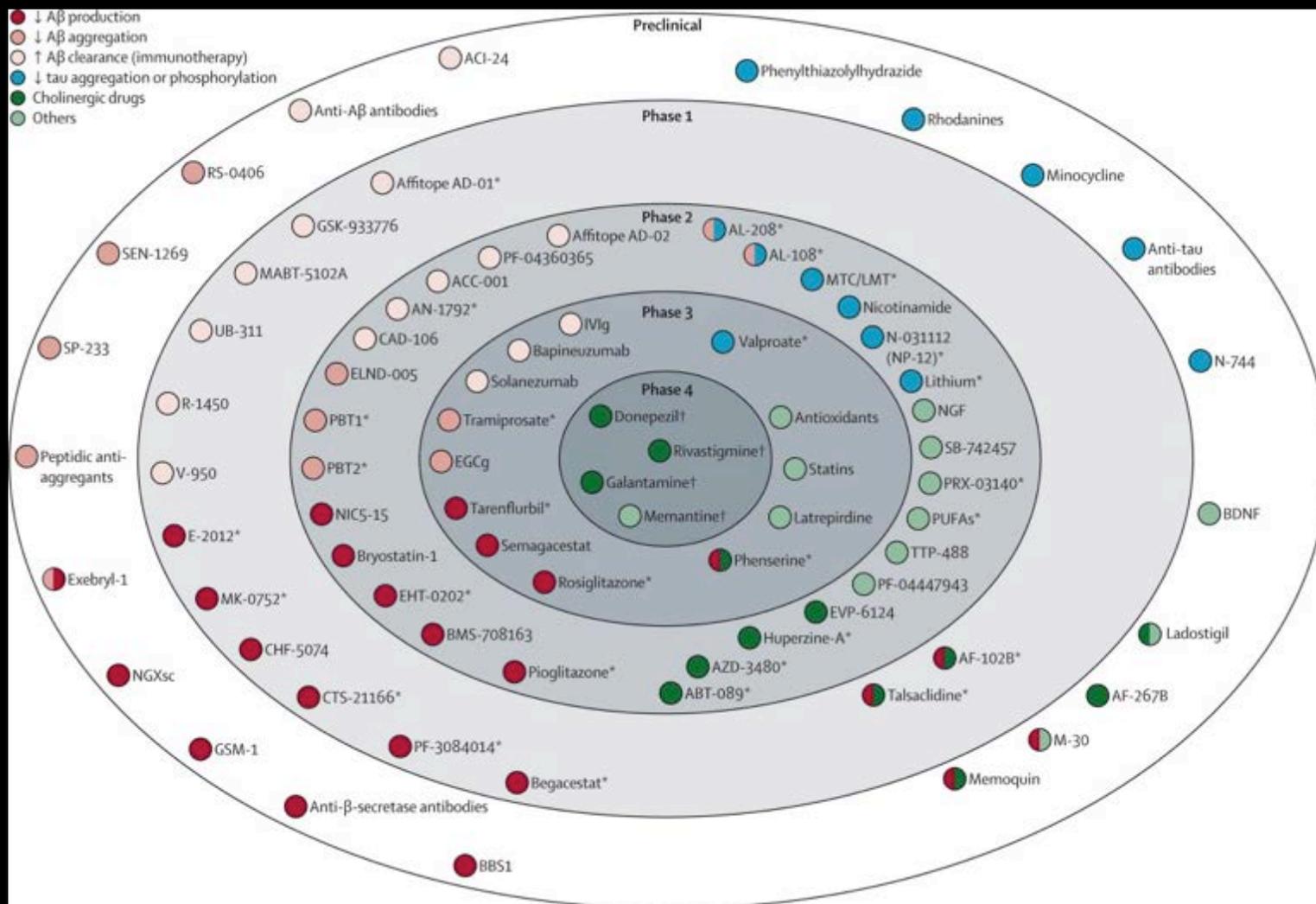
How Do Other Alzheimer's Disease Drugs "Work"?



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Drugs in Trials



Alzheimer's disease: clinical trials and drug development Francesca Mangialasche The Lancet Neurology 2010

There have been 101 unsuccessful attempts since 1998, according to the Pharmaceutical Research and Manufacturers of America. Current therapies provide some temporary symptomatic improvement.

What Should Can Do?

Biomedical research - LOTS of biomedical research

- **New treatments for AD, PD, ALS, osteoporosis, etc.**
- **Better ways to detect who's at risk for what, and we need to detect this as early as possible**

African American Statistics

- **Individuals with a history of either high blood pressure or high cholesterol levels are:**
 - **twice as likely to get Alzheimer's disease**
 - **with both risk factors are four times as likely to become demented**
- **African-Americans have a 60% higher risk of type 2 diabetes**
— **a condition that contributes directly to vascular disease**
- **African-Americans have a higher rate of vascular dementia than white Americans**

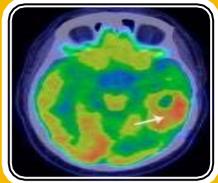
Screening and Assessment Tools

- **African-Americans tend to be diagnosed at a later stage of Alzheimer's disease**
 - **limiting the effectiveness of treatments that depend upon early intervention**
- **African-Americans are seriously underrepresented in current clinical trials of potential treatments for Alzheimer's disease**
- **This has occurred even though evidence of genetic differences and response to drugs varies significantly by race and ethnicity**

Early Identification



Genetic Testing



Brain Scans (PET & MRI)



Cerebral Spinal Fluid

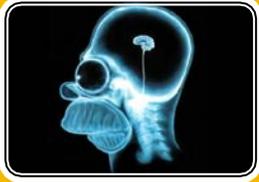


Biomarkers

Prevention and Risk Reduction



Heart health, exercise, cardiovascular disease, obesity, diabetes



Brain stimulation, education, novelty



Nutrition, vitamins, anti-oxidants, Omega 3's



Social & emotional wellbeing

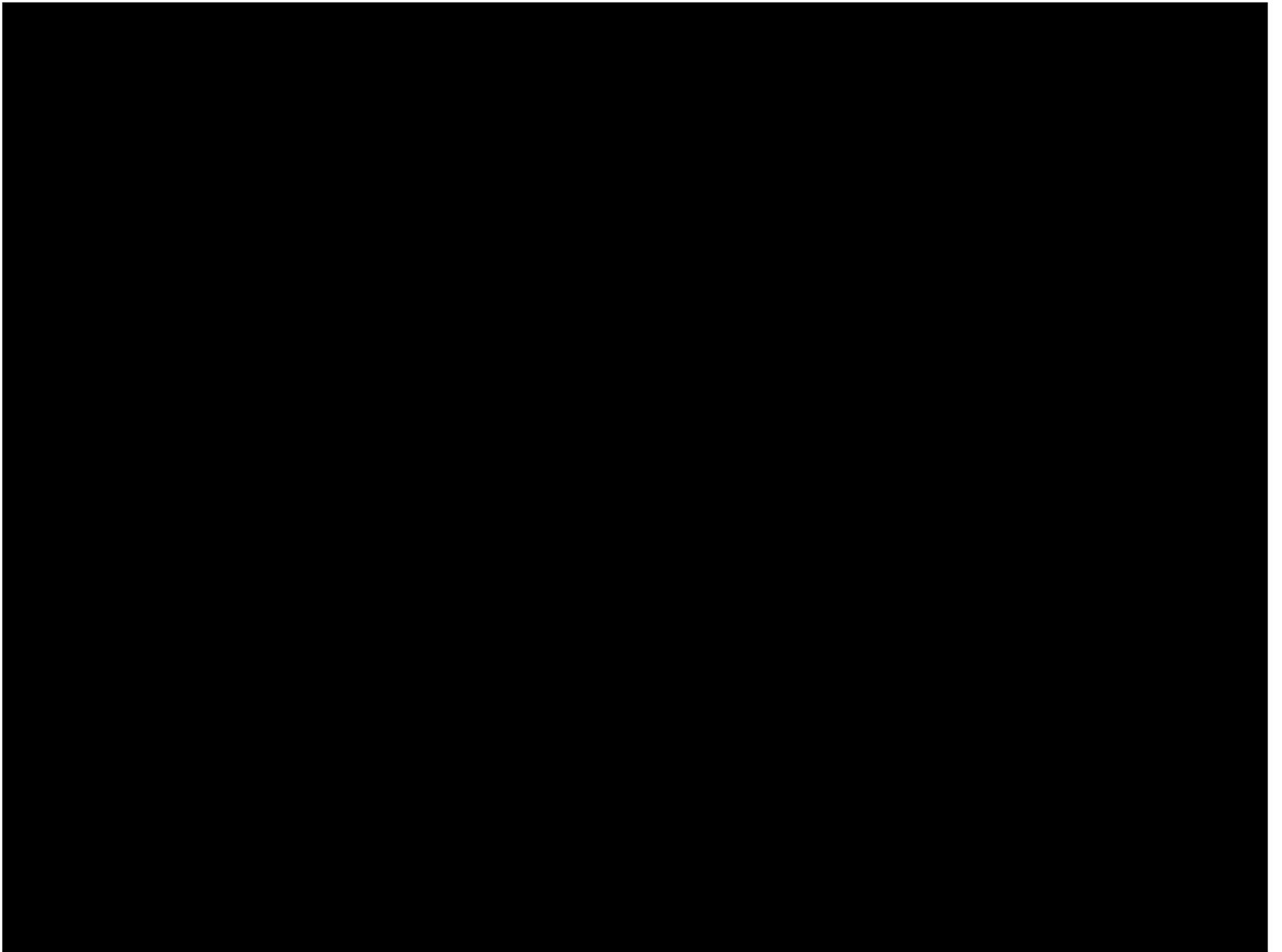
Wine!



Caffeine



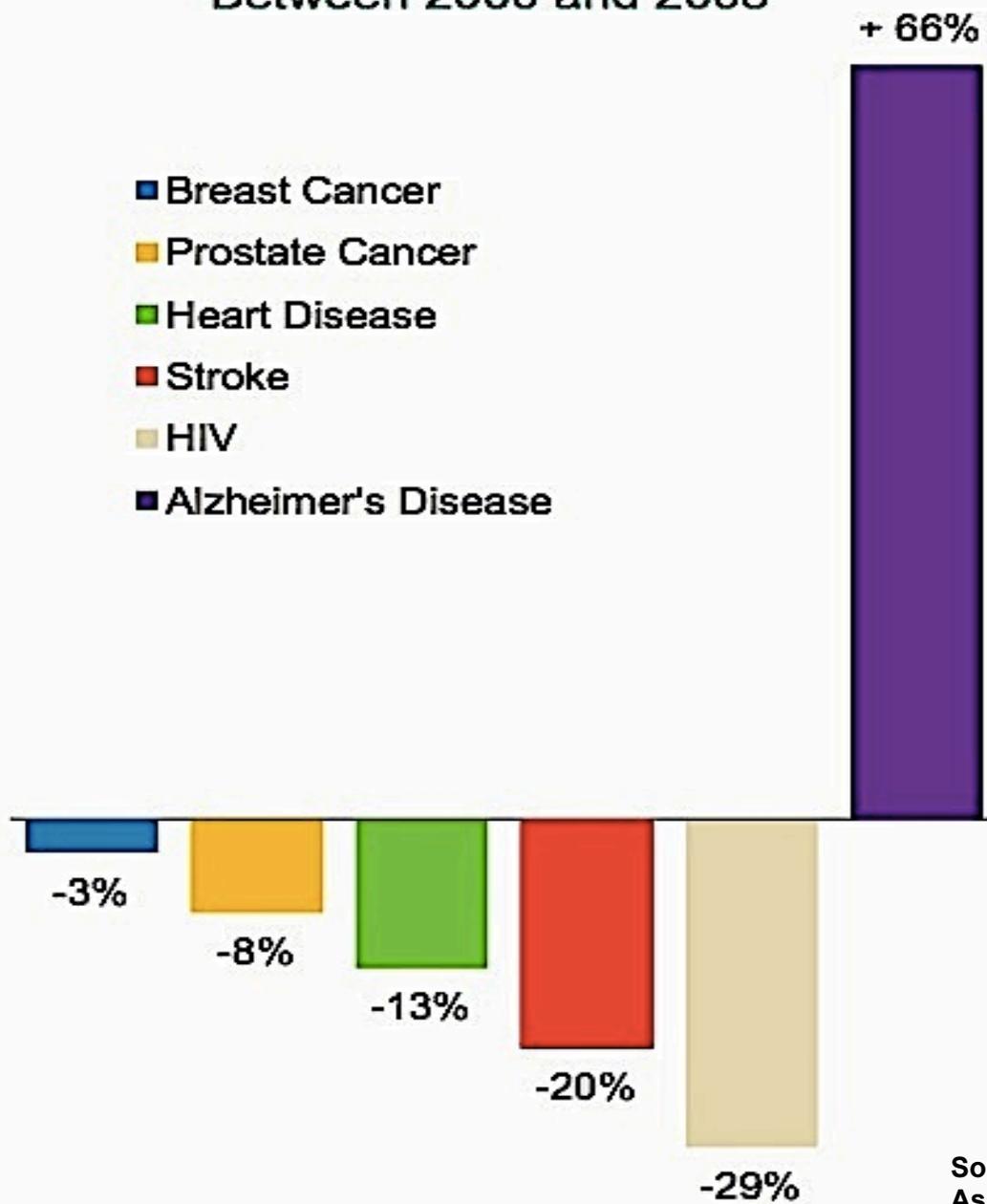
Thank You



The Coming Epidemic

- ~ 5 million with AD in US today
- 13.8 million with AD in US in 2050
- 3 million with PD by 2050
- Estimated cost of AD: \$1 trillion/yr by 2050
- \$606 million/yr from government for AD research
- \$3 billion/yr for AIDS research
- \$6 billion/yr for cancer research

Change in Number of Deaths Between 2000 and 2008



Source: The
Association

Population of U.S. age 80+ (millions)

