

# What's Preventing Us from Preventing Alzheimer's Disease?

**Gary Small, MD**

*University of California, Los Angeles*

*Division of Geriatric Psychiatry*

*UCLA Longevity Center*

*Semel Institute for Neuroscience and Human Behavior*

# Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - The off-label use of curcumin/anti-inflammatory medicines for improving memory in normal aging and mild cognitive impairment will be discussed.
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

# Acknowledgments

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Do we have any control over our brain health as we age?

If so, what can we do to forestall symptoms of Alzheimer's disease?





**Born: 1875**

**Died: 1997**

**Madame Jeanne Calment**



**Sardinia, Italy**



**Loma Linda, California, USA**



**Okinawa, Japan**

# Formula for Successful Aging

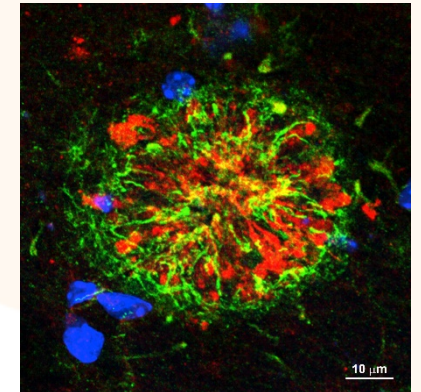
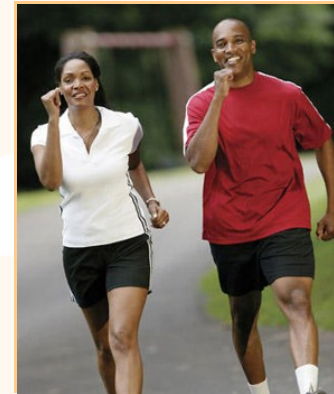
- 1. Physical Activity**
- 2. Mental Exercise**
- 3. Stress Management**
- 4. Healthy Diet**

**Brain Health**  **Quality Longevity**



# Inflammation and Brain Aging

- Normal inflammation protects us from infection/injury
- Brain inflammation increases with aging
- Less inflammation protects brain health
- Anti-inflammatory strategies
  - A good night's sleep
  - Consuming omega-3 fats (fish, nuts)
  - Physical exercise



# Alzheimer's Disease is in the News and on our Minds



THE WALL STREET JOURNAL.



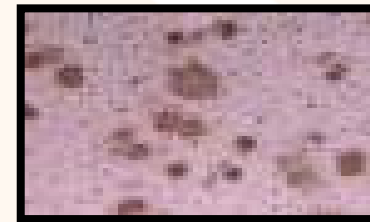
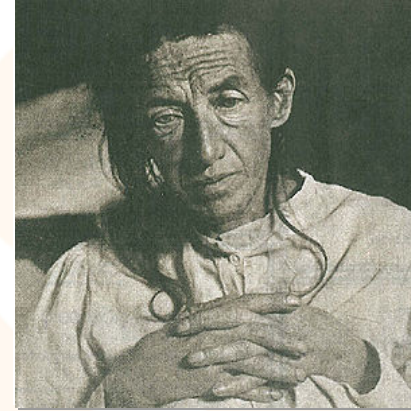
# Increased Life Expectancy and Epidemic of Alzheimer's Disease

- Life expectancy at birth in the United States
  - In 1900: 47 years
  - Today: 78 years
- Age is *the* single greatest risk factor for Alzheimer's disease
- Risk escalates dramatically with age:
  - 65+: 10%
  - 85+: 50%

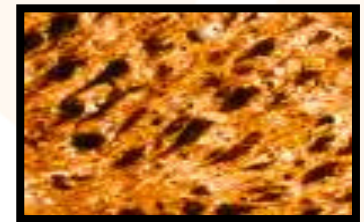


# What is Alzheimer's Disease?

- 1906: Alois Alzheimer presented case of middle-aged woman who progressed rapidly until her death 4 years later
- Autopsied brain tissue showed waxy protein fragments and twisted fibers that define the disease
- 1968: Scientists discovered same plaques/tangles caused “senility”



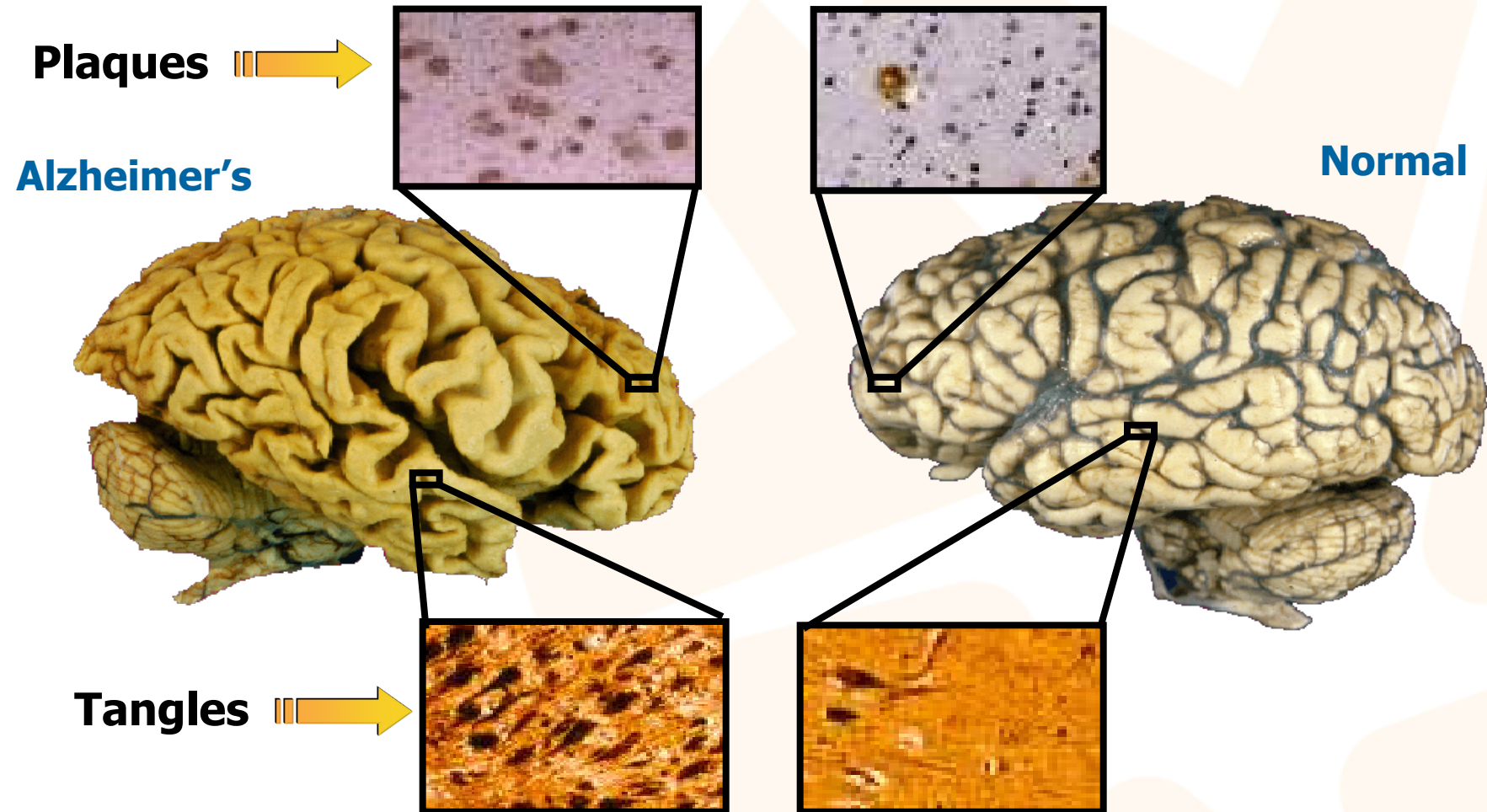
**Plaques**



**Tangles**



# Amyloid Plaques and Tau Tangles in Alzheimer's Disease and Normal Aging



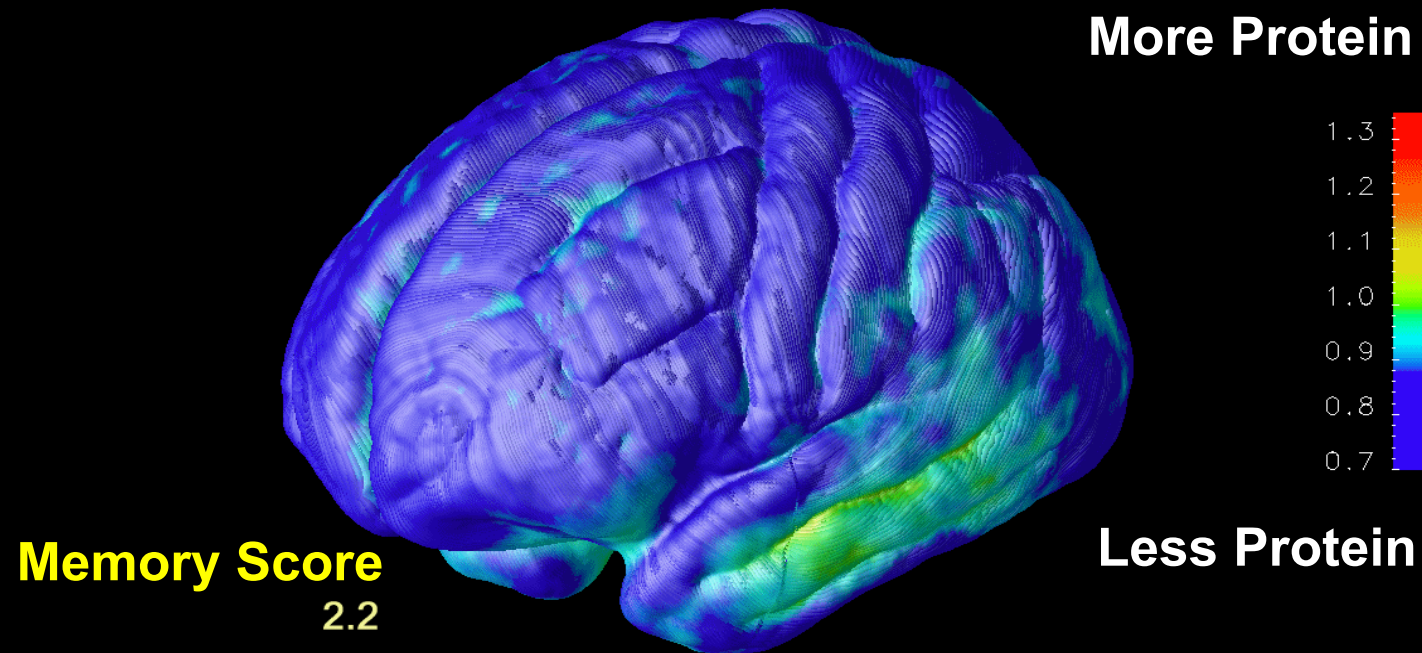
# PET Scanner



PET = positron emission tomography.

# Brain Amyloid and Tau Proteins Accumulate as Memory Worsens

FDDNP-PET scans of 20 volunteers  
(8 normal, 6 MCI, 6 Alzheimer's)



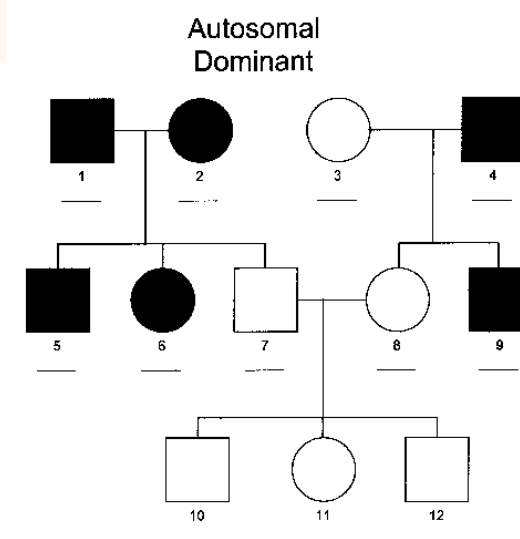
MCI = mild cognitive impairment.

Braskie MN, et al. *Neurobiol Aging*. 2010;31(10):1669-1678.

Small GW, et al. *Arch Neurol*. 2012;69(2):215-222.

# Genetics and Alzheimer's Disease

- Genetic mutations that cause the disease early in life in half of relatives
  - Presenilin genes (chromosomes 1 and 14)
  - APP gene (chromosome 21)
- Apolipoprotein E-4
  - Common allele (gene form) in 20% of population
  - Increases risk but
    - Some with APOE-4 never get the disease
    - Some without APOE-4 get the disease
    - Used for research and not a predictive test

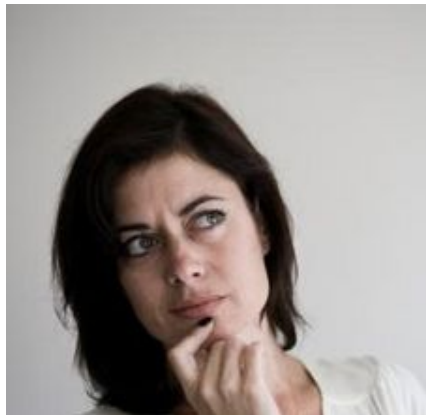
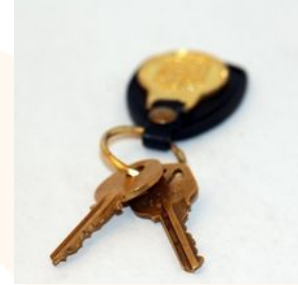


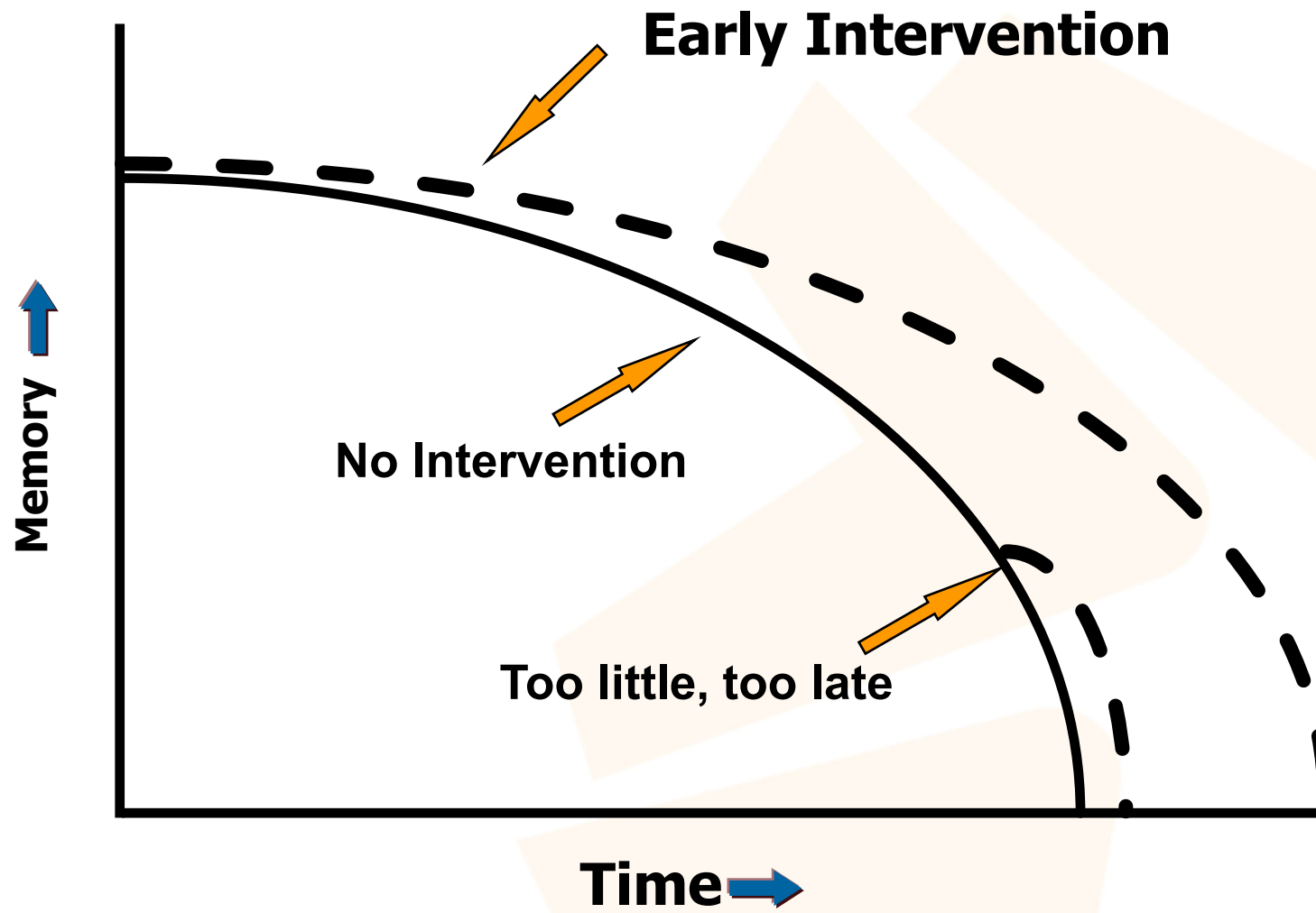
# Some Definitions

- **Memory**
  - Learning
  - Recall
- **Cognition**
  - Memory
  - Attention
  - Visual/spatial skills
  - Reasoning
- **Dementia**
  - Cognitive loss
  - Interferes with everyday life
- **Alzheimer's disease**
  - Most common dementia cause
  - Gradual onset/progression
  - Plaques and tangles

# The Most Common Memory Complaints

- Names and faces
- Where we put things
- Forgetting an appointment or plan
- Forgetting a word or name we should know that is on “the tip of your tongue”

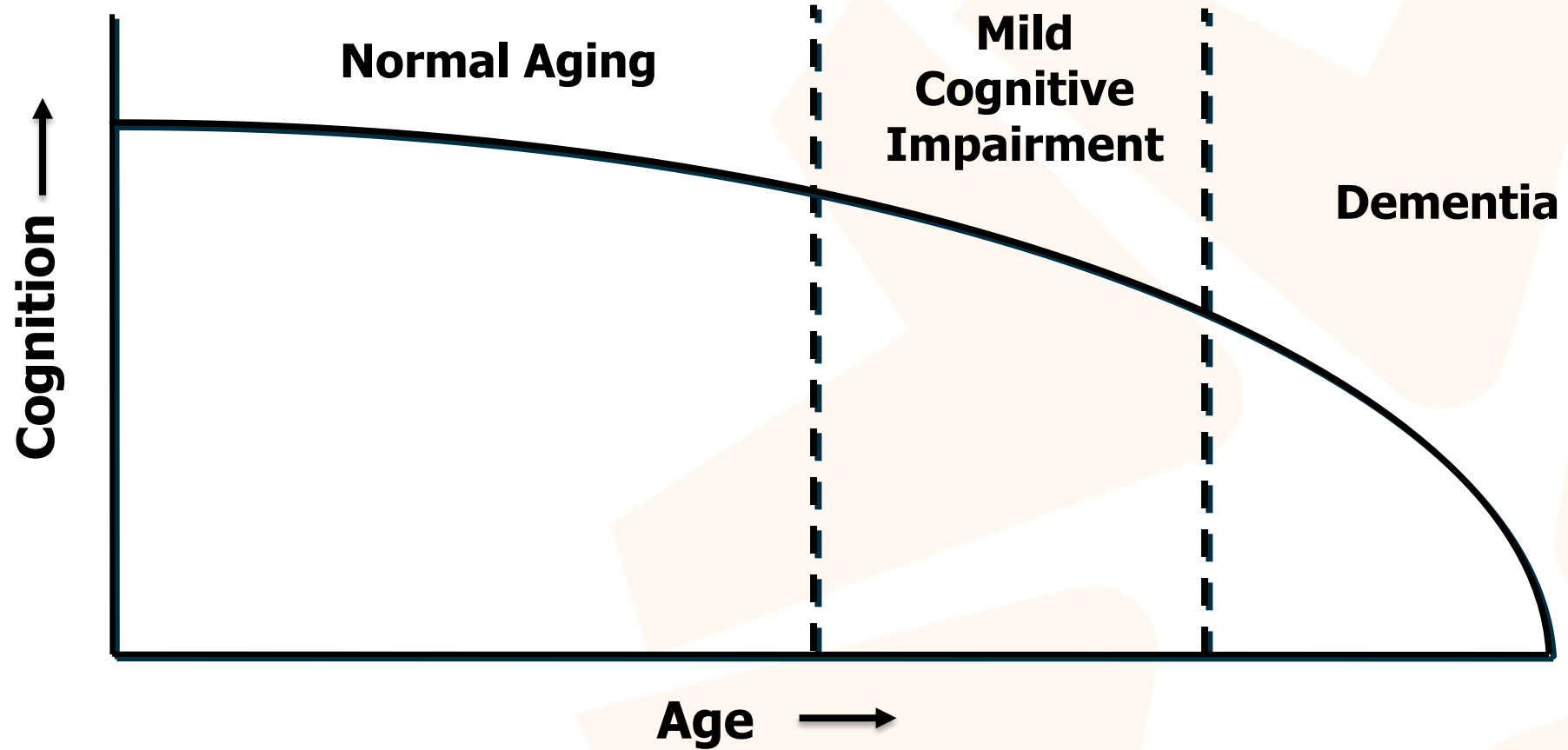




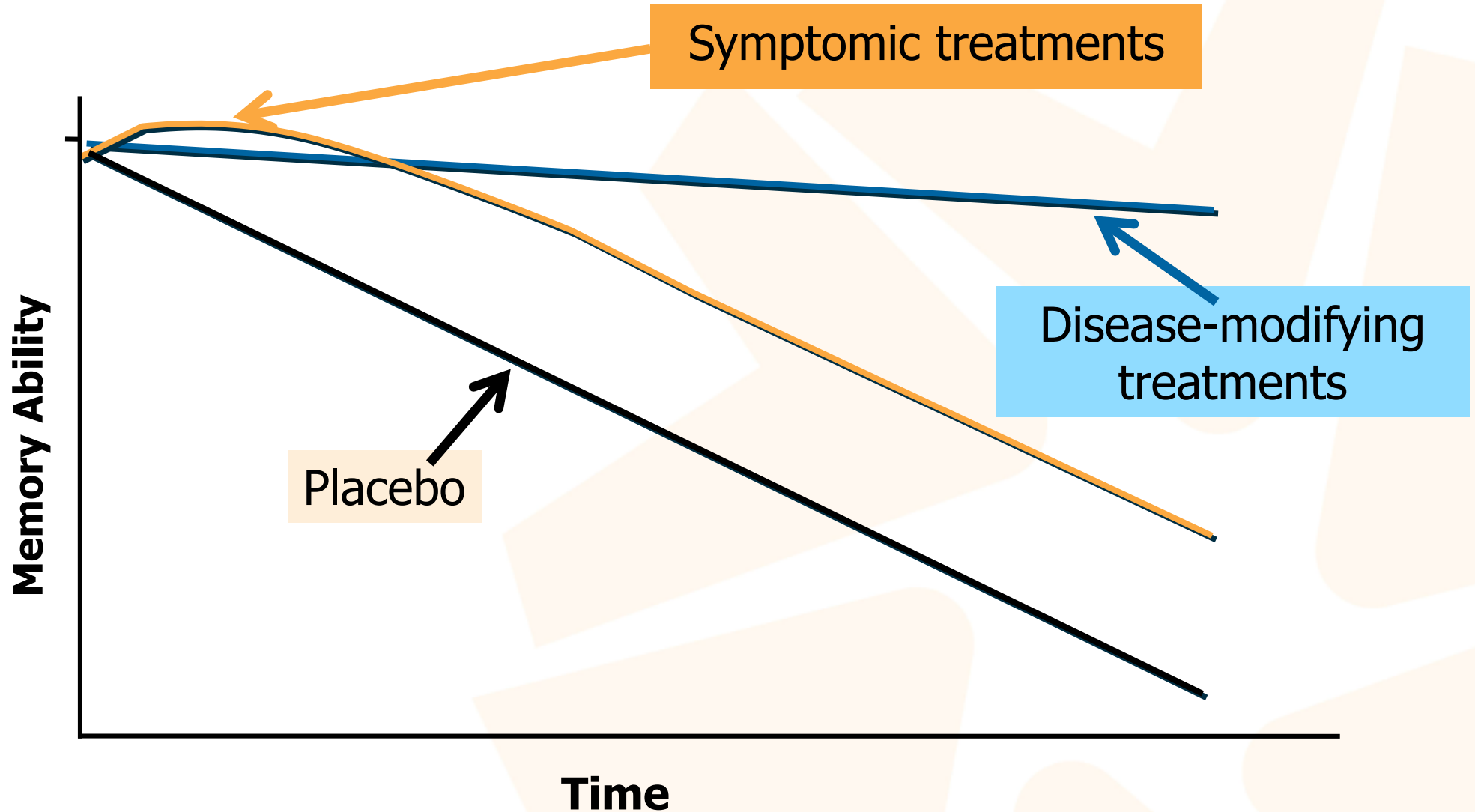
**Grandma Ollie  
and me**



# Stages of Brain Aging



# Alzheimer's Treatments

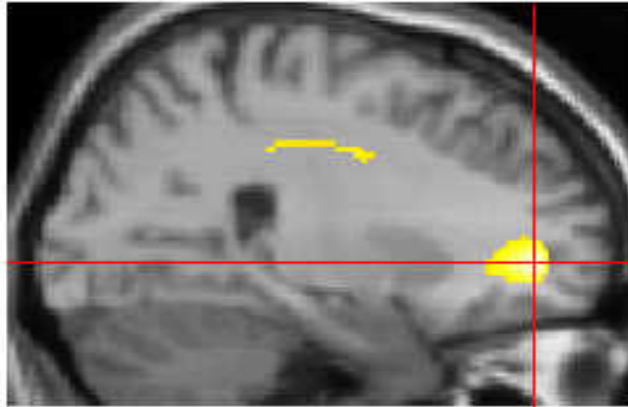


# Research on Disease-Modifying Treatments

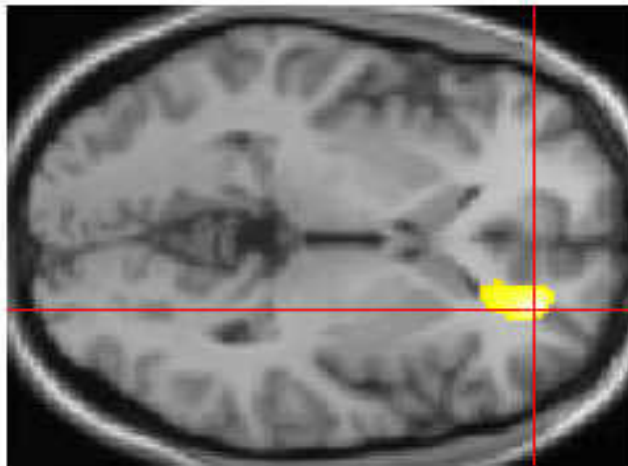


# Anti-Inflammatory Medicine Increased Cognition and Brain Function in Normal Aging

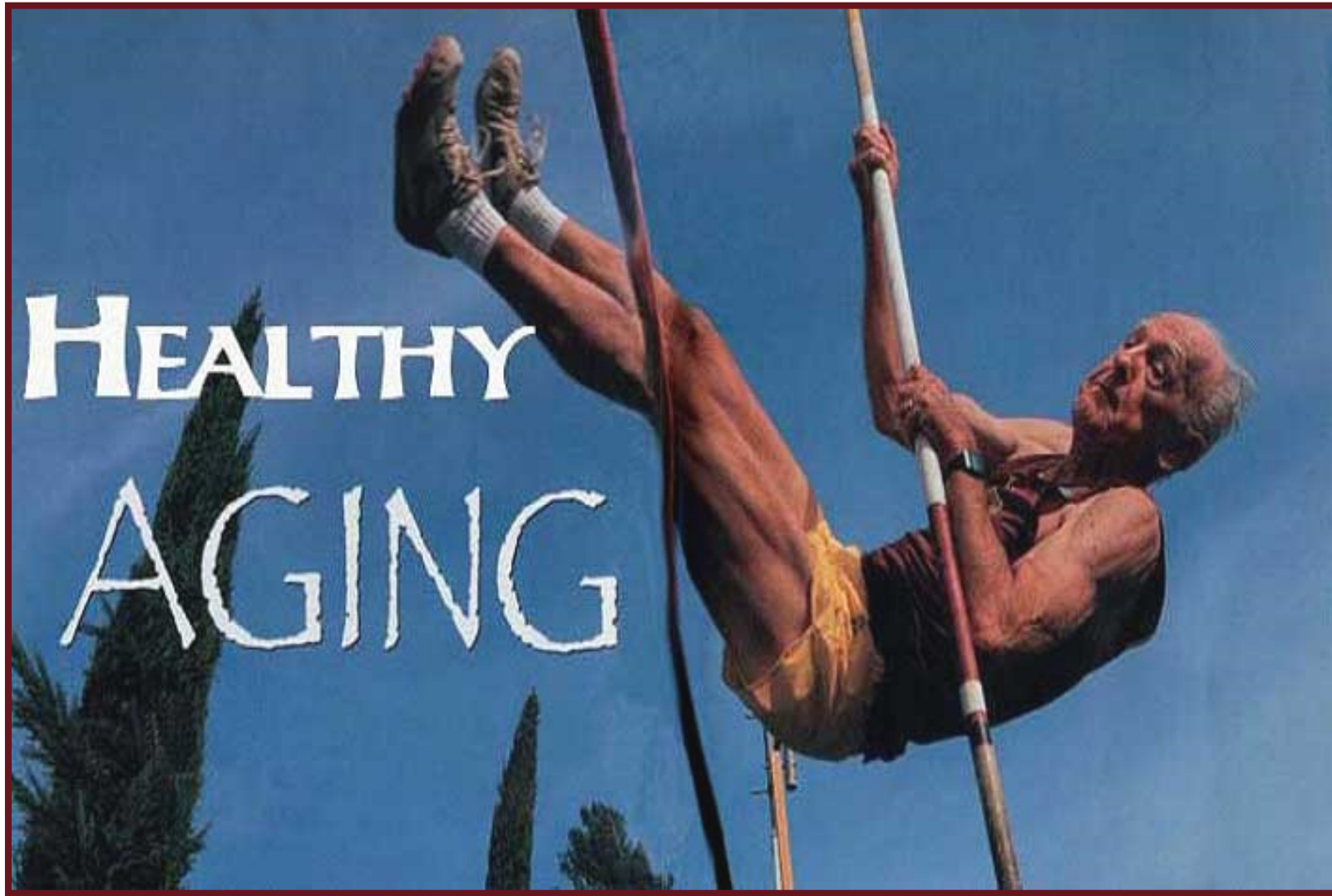
sagittal



transverse



- Mean age: 59 years
- 18-month placebo-controlled trial
- Cognition improved
  - Executive function ( $P=.03$ )
  - Semantic memory ( $P=.02$ )
- Brain function (PET scanning)
  - 6% increase in prefrontal cortex ( $P=.003$ )



# Brain Healthy Lifestyle Associated with Lower Dementia Risk

- Genetics account for only part of dementia risk
- Potential non-genetic factors
  - Physical conditioning
  - Mental stimulation/cognitive training
  - Stress management
  - Nutrition

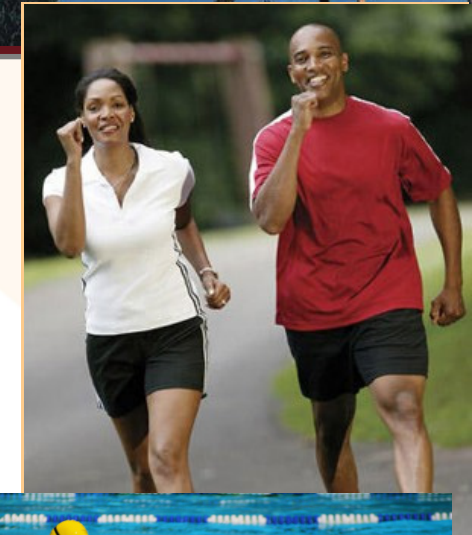
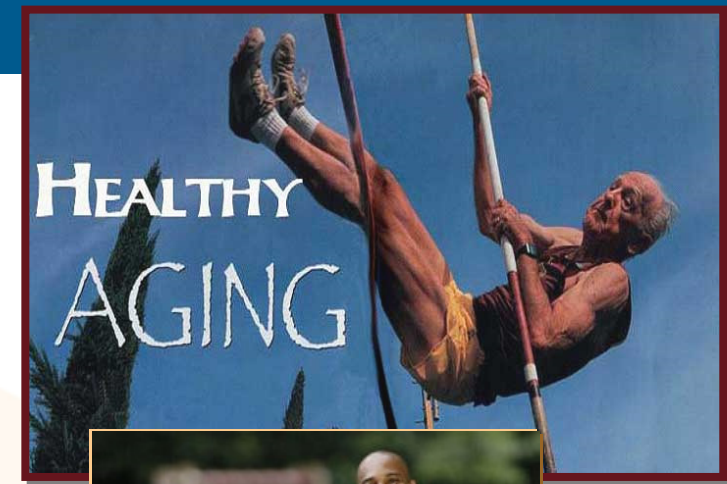
# Memory Complaints and Healthy Behaviors

- Gallup Poll interviews of 18,552 US adults, 18–99 years
- Memory complaints:
  - 14% of younger adults
  - 22% of middle-aged adults
  - 26% of older adults
- Healthy behavior more common in older adults
- More healthy behaviors reported...

 fewer memory complaints

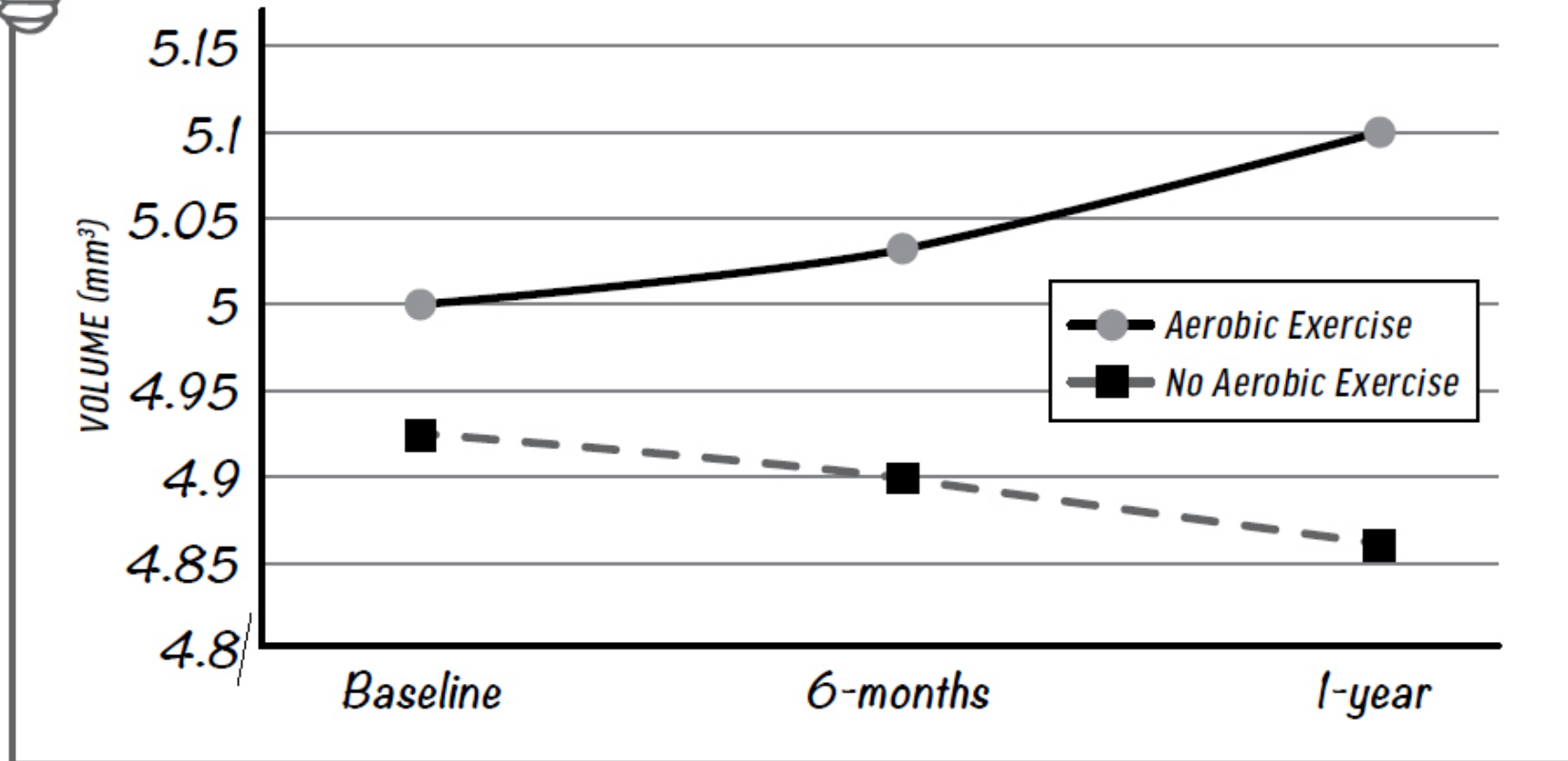
# Physical Exercise

- Active laboratory animals
  - larger brains
  - better memory
- Human studies
  - Cardiovascular conditioning
    - larger brain size
  - Physically active adults
    - lower Alzheimer's risk
  - Brisk walking
    - improves cognition (vs stretching/toning)





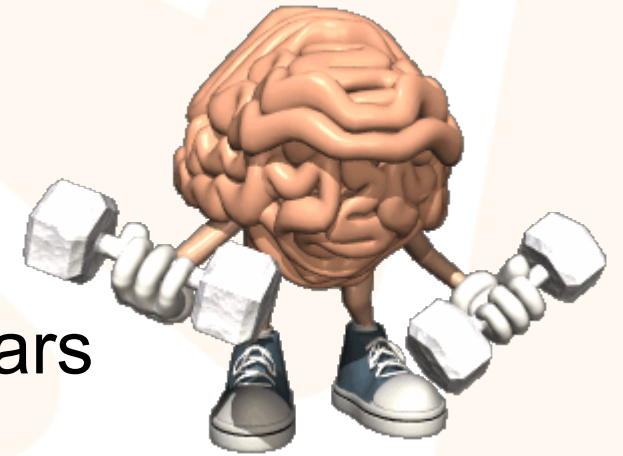
## Exercise Grows the Hippocampus



Middle-aged and older volunteers who walked briskly

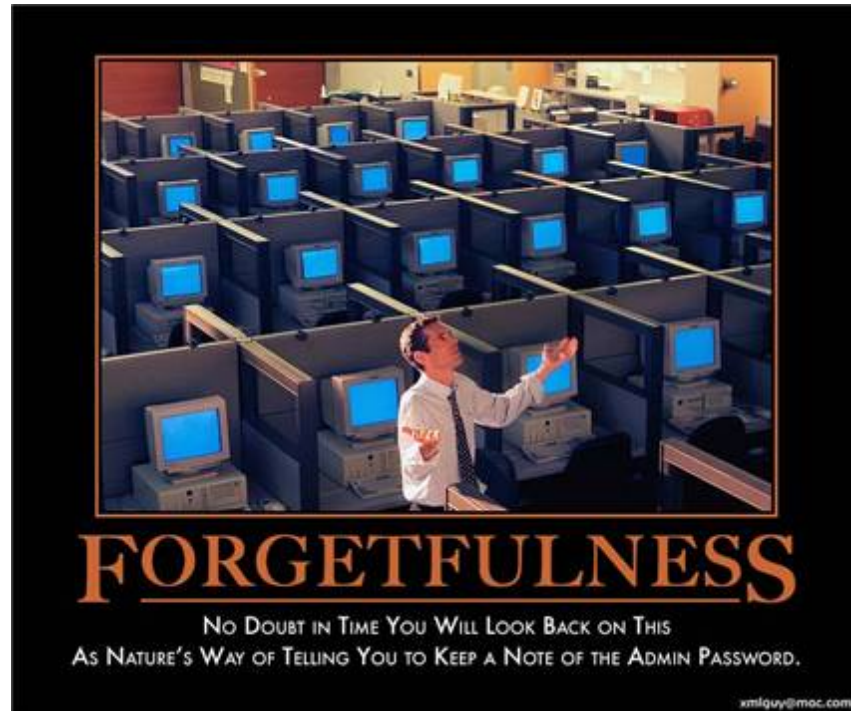
# Mental Exercise Builds Brain Muscle

- Mental stimulation
  - activates neural circuits
  - lowers Alzheimer's risk
- Education, bilingualism lowers dementia risk
- Memory training benefits maintained for  $\geq 5$  years



# Is Technology Weakening Your Memory Ability?

- ◆ Does relying on your computer shrink your hippocampus?



How many phone numbers do you know by heart?



# Digital Immigrants

- Learn technology late
- Older brains may be
  - Reaction time, memory
- Resistance to technology



RUPERT  
MURDOCH  
GOES TO WAR  
BY MARK BOWDEN

THE IDEAS ISSUE

# Atlantic

JULY/AUGUST 2008

WWW.THEATLANTIC.COM

IS  
Google  
MAKING  
US  
Stoopid?

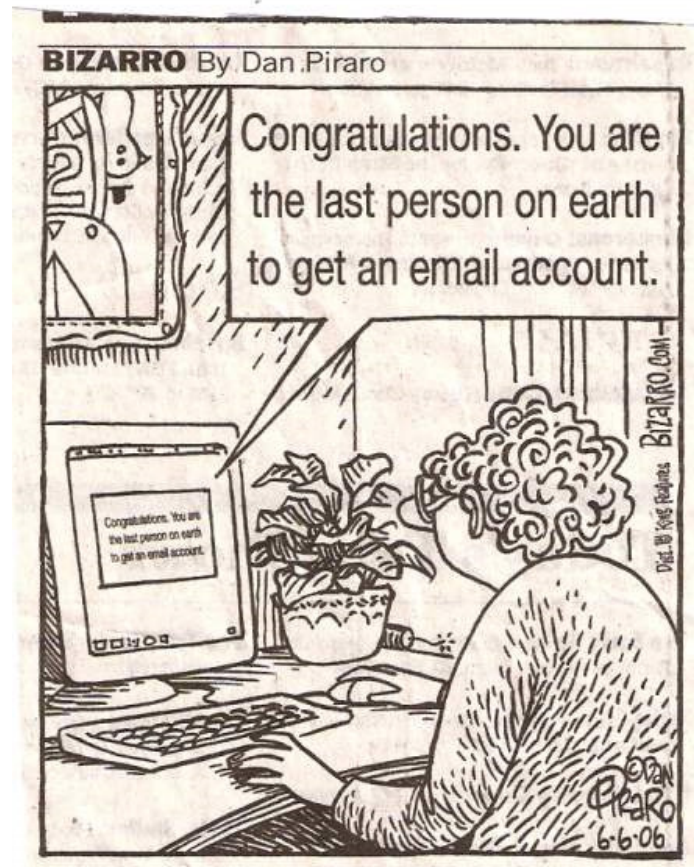
WHAT THE INTERNET IS DOING TO OUR BRAINS

# Your Brain on Google

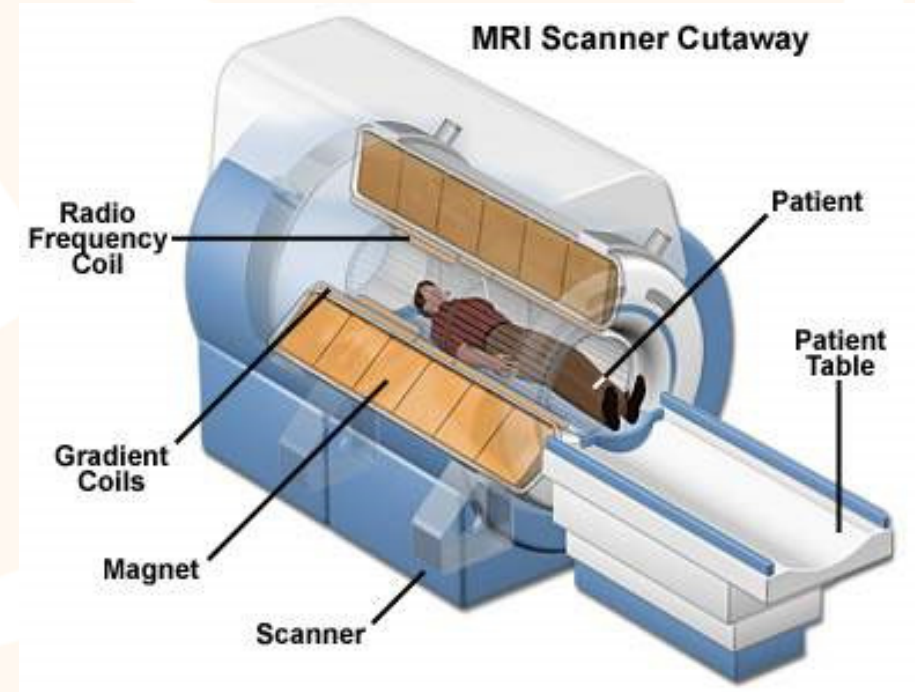


# Study Methods

Recruit middle-aged and older people with minimal Internet experience

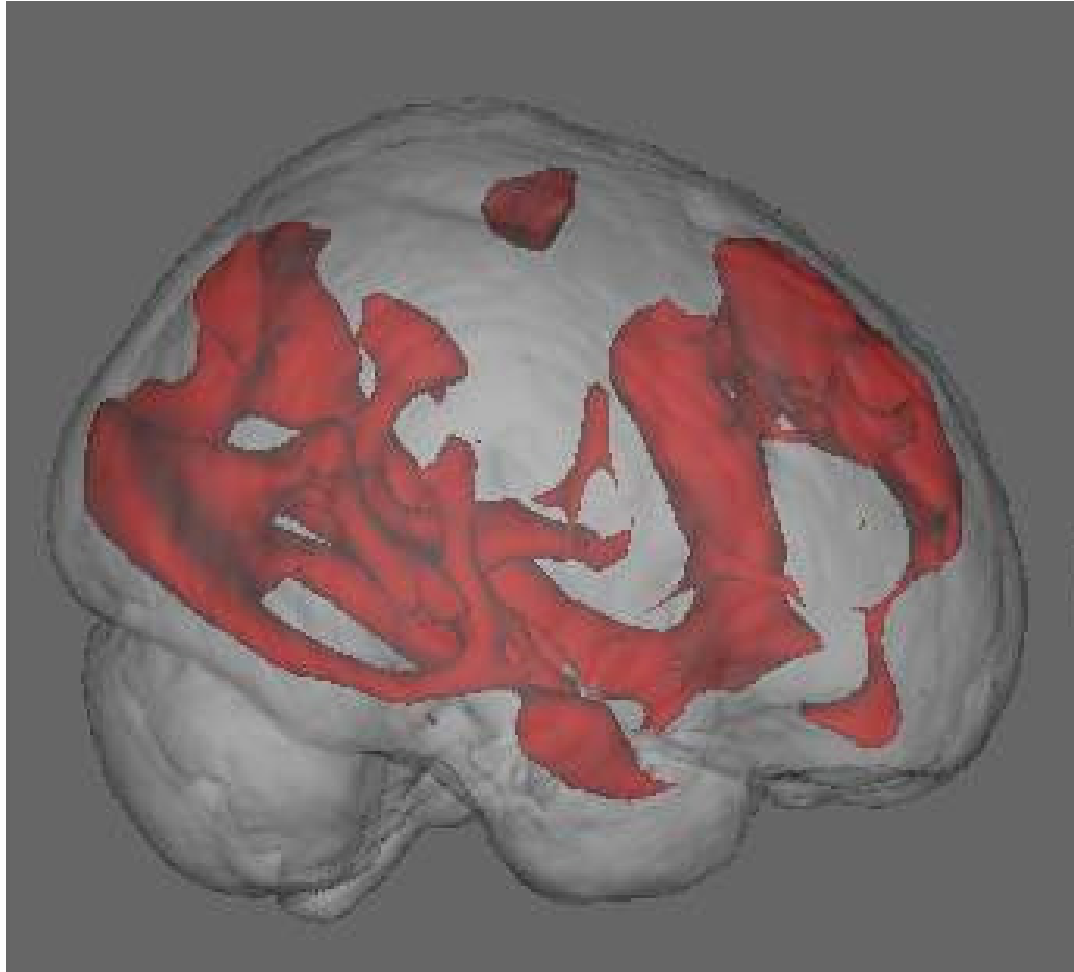


# Functional MRI

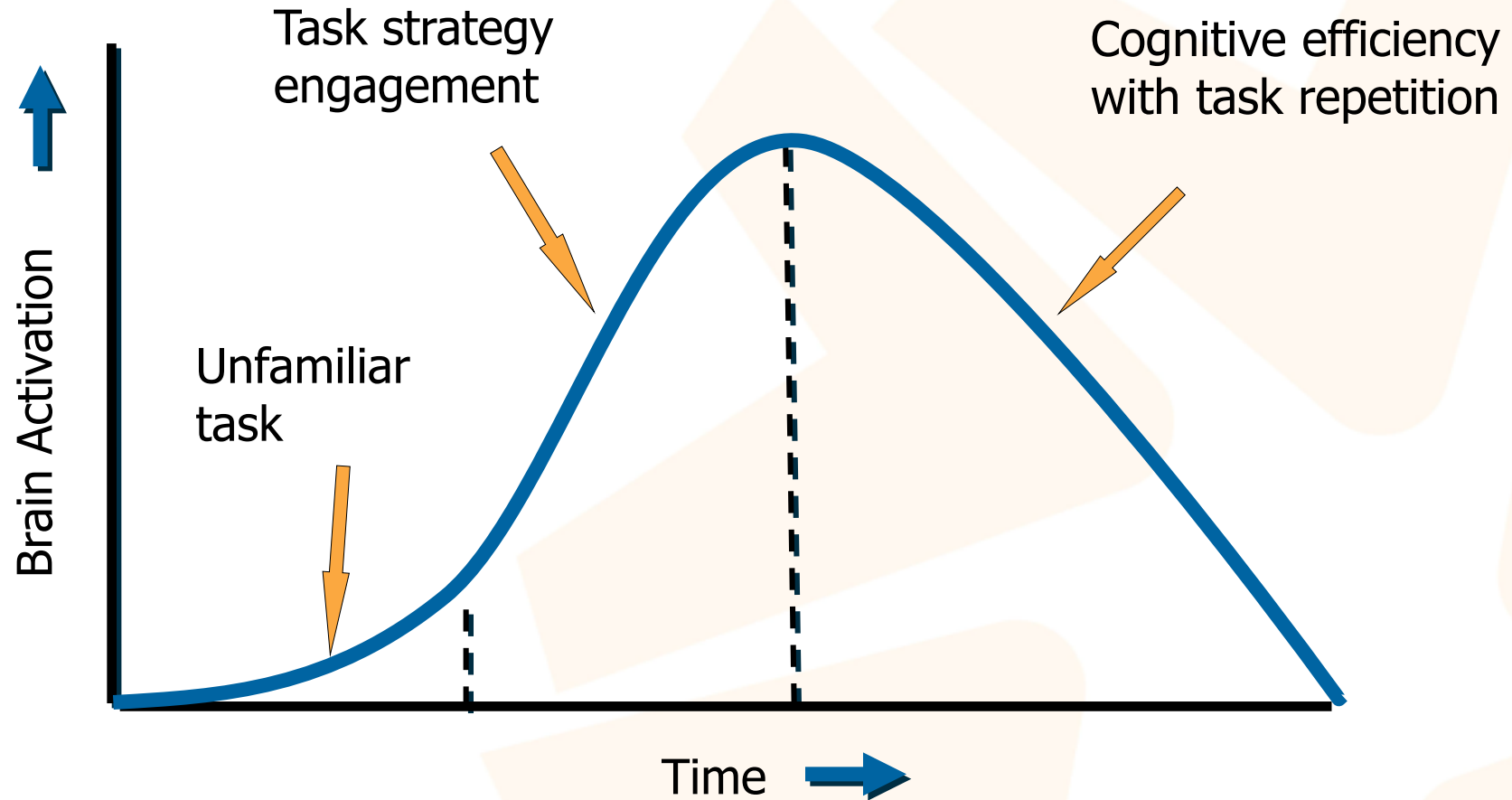


MRI = magnetic resonance imaging.

# Your Brain on Google

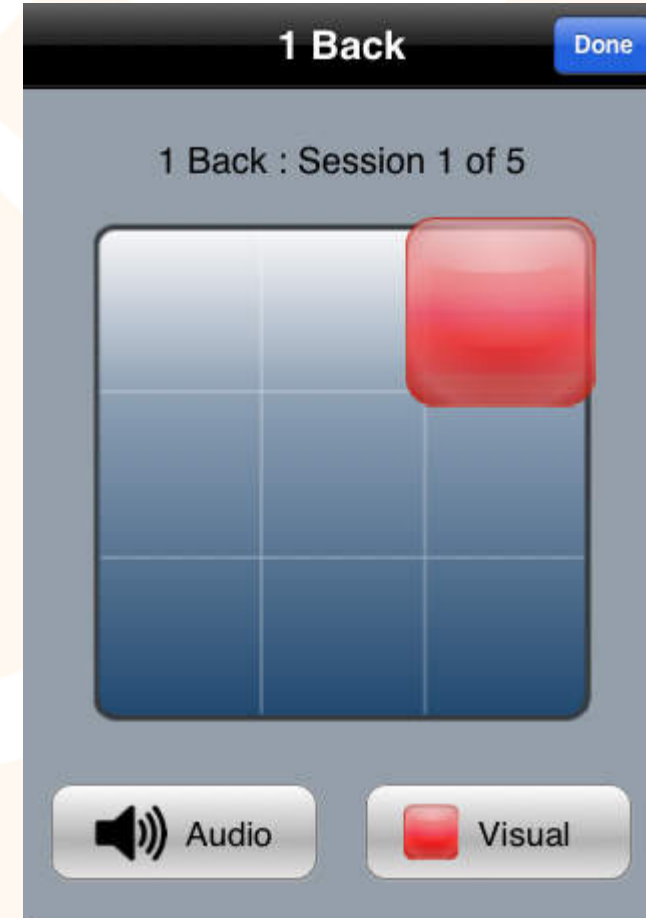


# Neural Network Responses to Mental Challenge



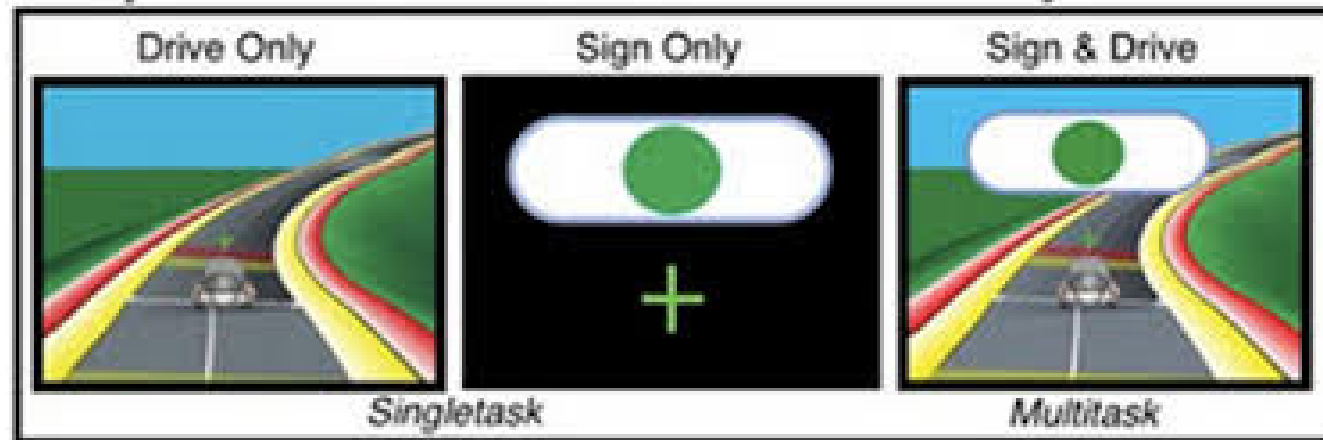
# Some Computer Games Boost Intelligence

- Training working memory increases fluid intelligence
- Benefits observed in younger and older adults



# Video Games That Improve Multitasking

- 70-year-old performs like an untrained 20-year-old after several weeks
- Brain benefits last 6 months



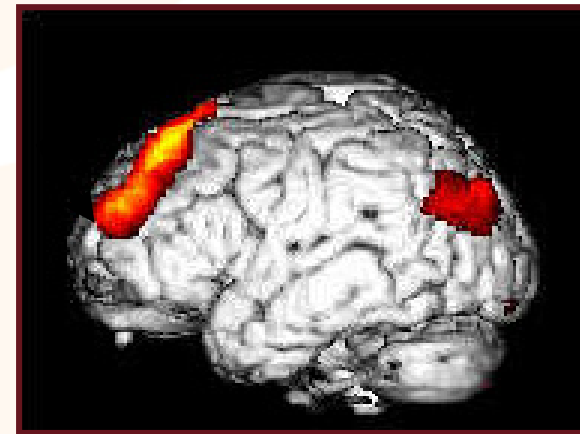
# Technology Can Train Our Brains

- Improved visual attention and reaction time
- Surgeons who play video games make fewer surgical errors



# Short-Term Benefits of Healthy Lifestyle

- 6-week memory fitness program
  - Independent living participants (Erickson Living)
  - Significant ( $P < .001$ ) memory improvements
- 2-week healthy lifestyle/memory training
  - Significant improvement in memory and brain efficiency (prefrontal cortex)



# LOOK, SNAP, CONNECT

## **LOOK**

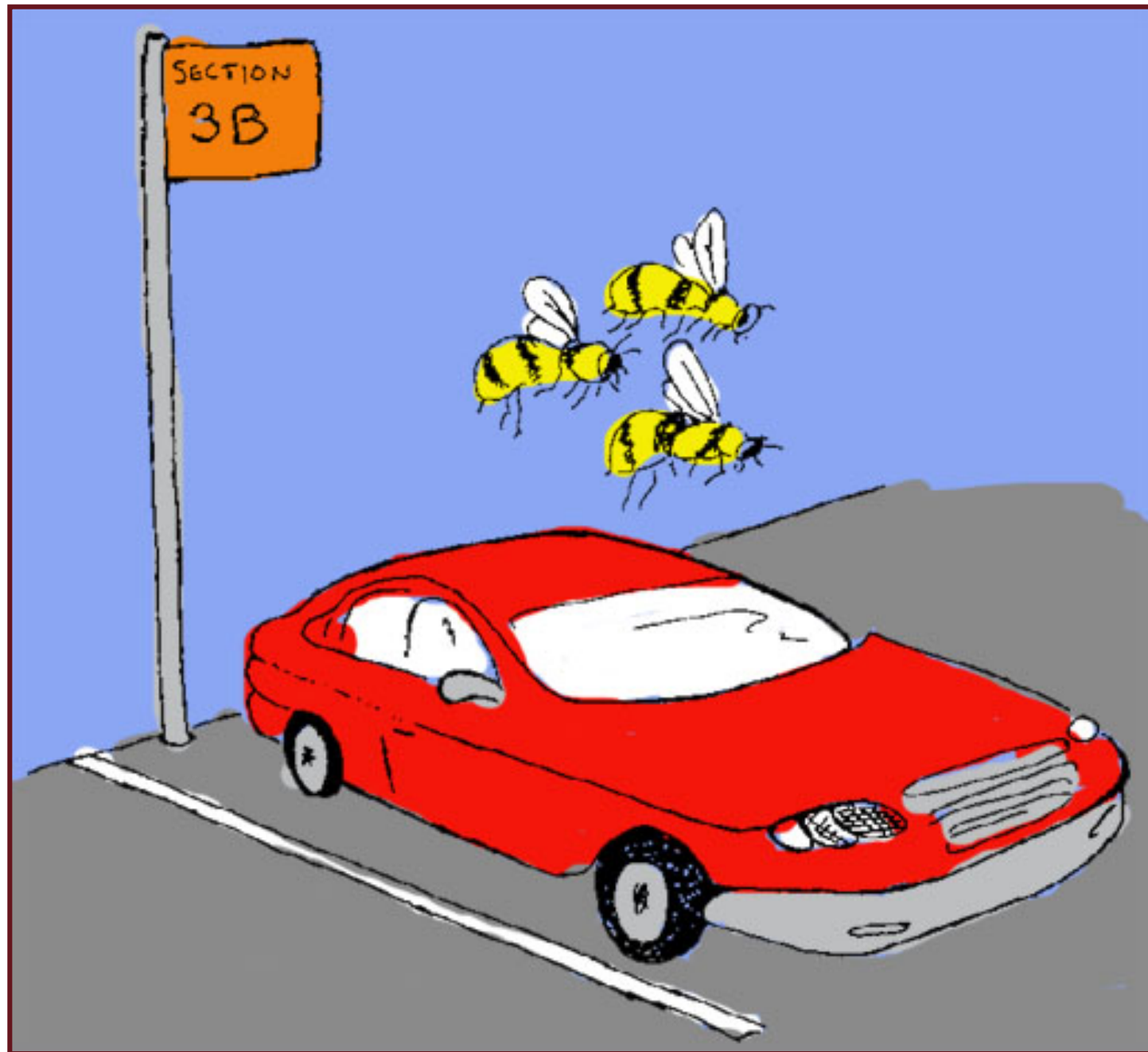
Actively observe what you want to learn

## **SNAP**

Create a vivid mental snapshot or memorable image

## **CONNECT**

Visualize a link to associate images







Harry



Lisa



**Sue Bangel**

# Word List

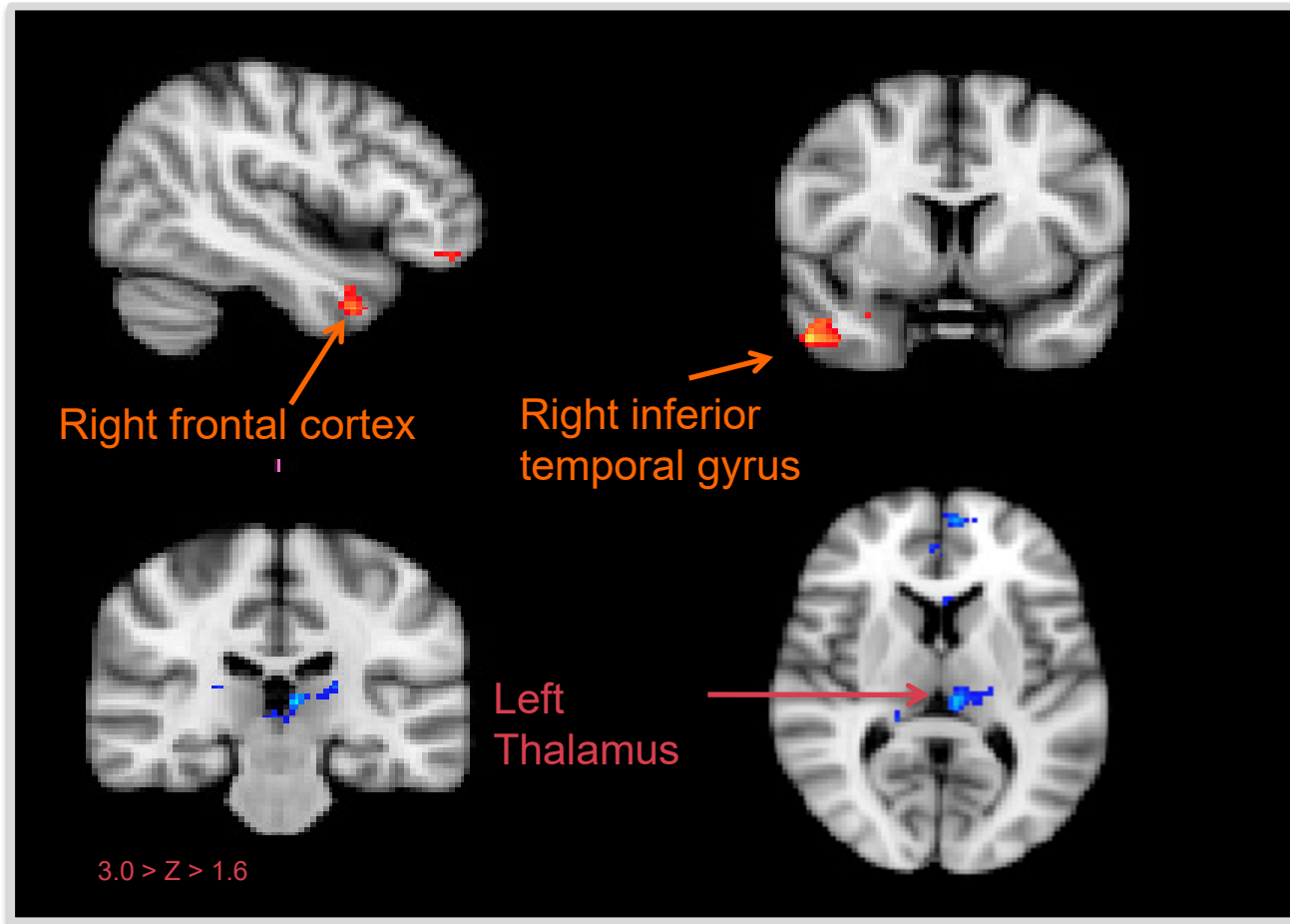
- Beach
- Professor
- Horse
- Teddy bear
- Cigar
- Nun
- Palm tree
- Pasta

# Stress and Alzheimer's Risk

- **Animal studies:**
  - Chronic stress
    - smaller brains
    - impaired memory
- **Human studies:**
  - People prone to stress
    - 2-fold greater Alzheimer's risk
  - Cortisol injections
    - Temporary memory impairment



# Stress Reduction Improves Brain Health



- Effect of meditation vs relaxation on brain activity:

Meditation > Relaxation

Relaxation > Meditation

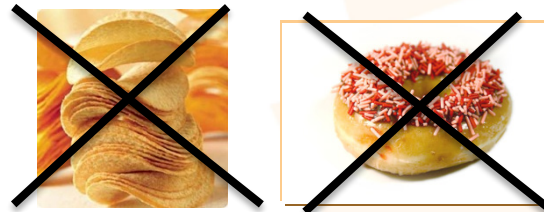
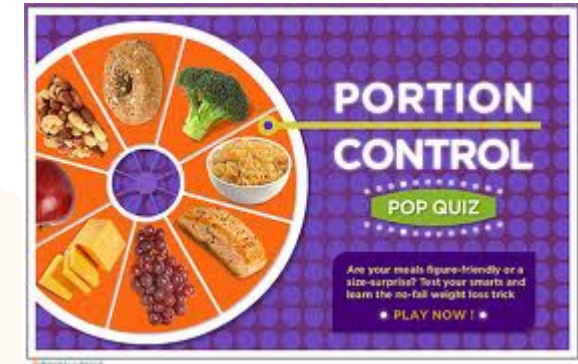
- 10 minutes of daily meditation alters brain neural activity

Managing stress →

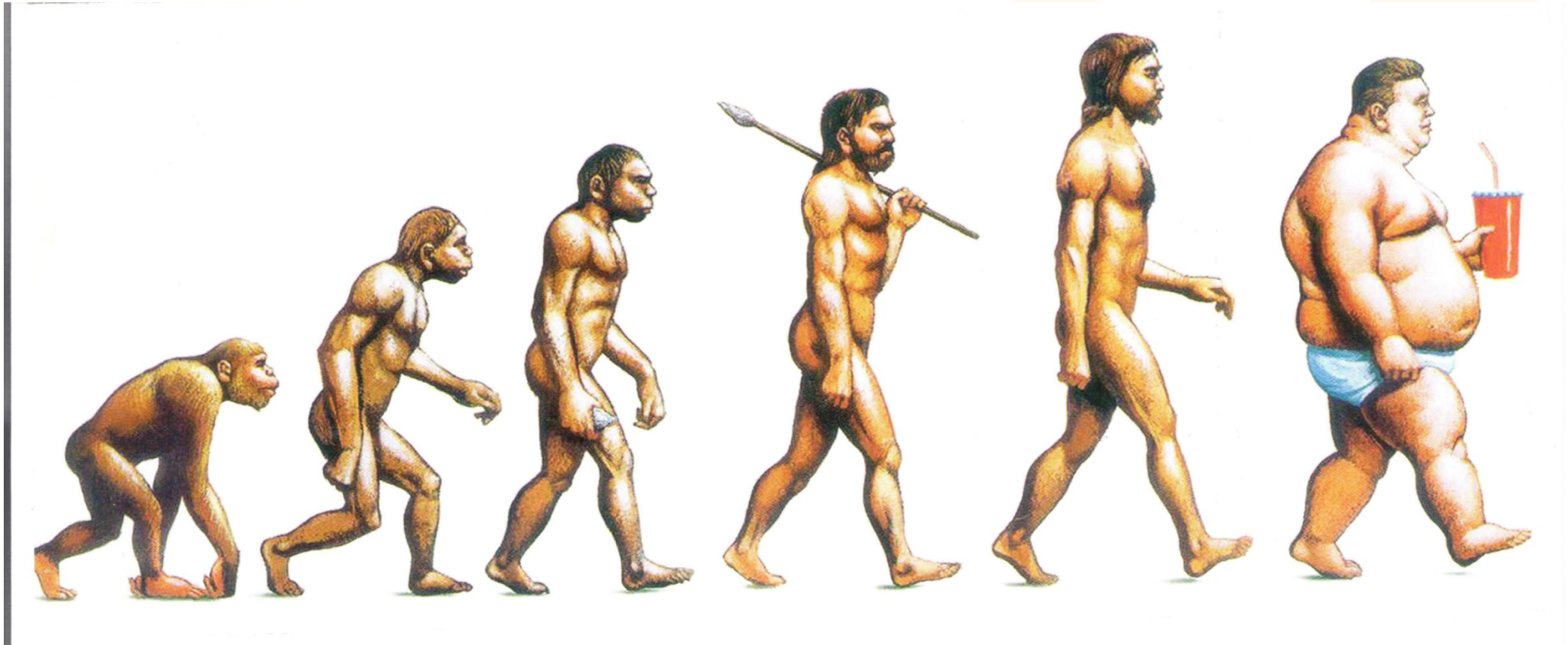


# Nutrition and Brain Health

- Weight management
- Omega-3 fats
  - Fish, nuts, flaxseed
- Antioxidant fruits and vegetables
- Avoid processed food, refined sugars



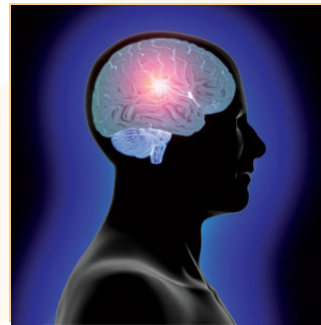
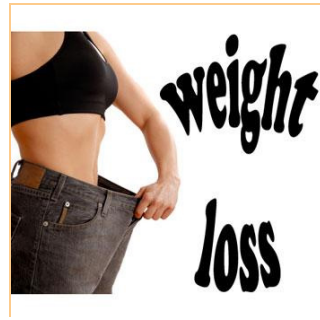
# Evolution and Body Weight



# Obesity Worsens Memory

## *Weight Loss Improves Memory*

- Obese people have a 4-fold increased risk for dementia
- Obese patients underwent weight-loss surgery →
  - Significant memory improvements compared with controls after:
    - 12 weeks
    - 2 years



- Overweight/obesity worsens memory
- Weight loss restores memory function

# Brain Protective Beverages

- Red wine (resveratrol)
  - Antioxidant, “anti-aging”
- Any alcohol in *moderation*
- Caffeine
  - Associated with lower risk for Alzheimer’s and Parkinson’s disease

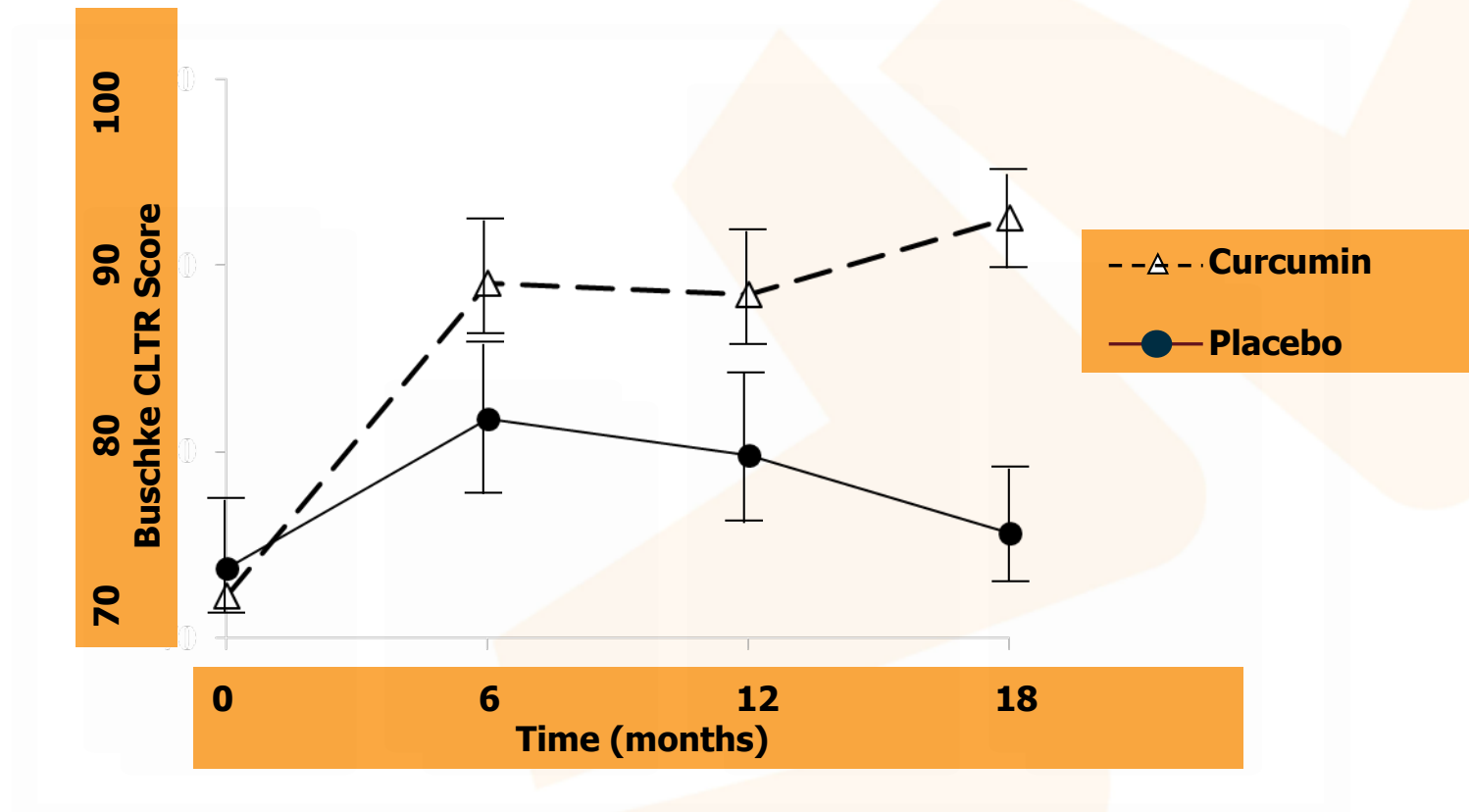


# New Research on Nutrition

- Double-blind placebo-controlled studies in people at risk for dementia
  - Curcumin: antioxidant, anti-inflammatory, anti-amyloid properties (Small GW, et al. *Am J Geriatr Psychiatry*. 2018;26(3):266-277.)
    - 18-month study
    - Outcomes: memory tests/scans of plaques and tangles
  - Pomegranate extract (ClinicalTrials.gov Identifier: NCT01571193)
    - Antioxidant polyphenols
    - 12-month study
    - Outcomes: memory tests

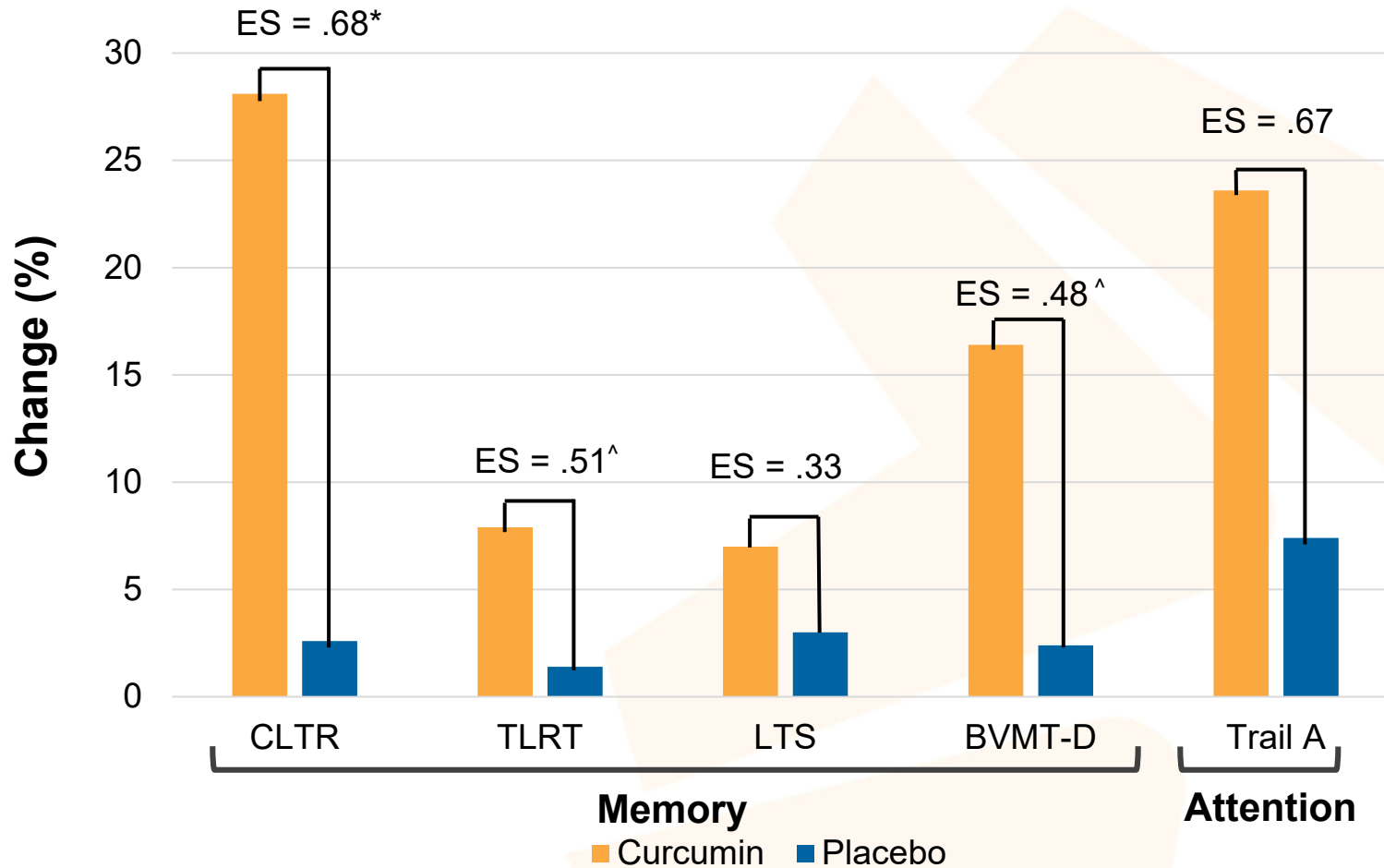


# Changes in Memory Scores in Curcumin and Placebo Groups



Mean ( $\pm$  SEM) change from baseline in Buschke Consistent Long-Term Retrieval (CLTR) score for 90 mg (twice daily) curcumin- and placebo-treated non-demented participants.

# Cognitive Changes at 18 Months



CLTR = Buschke Consistent Long-Term Retrieval; TLRT = Buschke Total Long-Term Retrieval; LTS = Buschke Long-Term Storage; BVMT-D = Brief Visual Memory Test-Revised - Delay Recall; Trail A = Trail Making Test, Part A; ES = between group effect size.

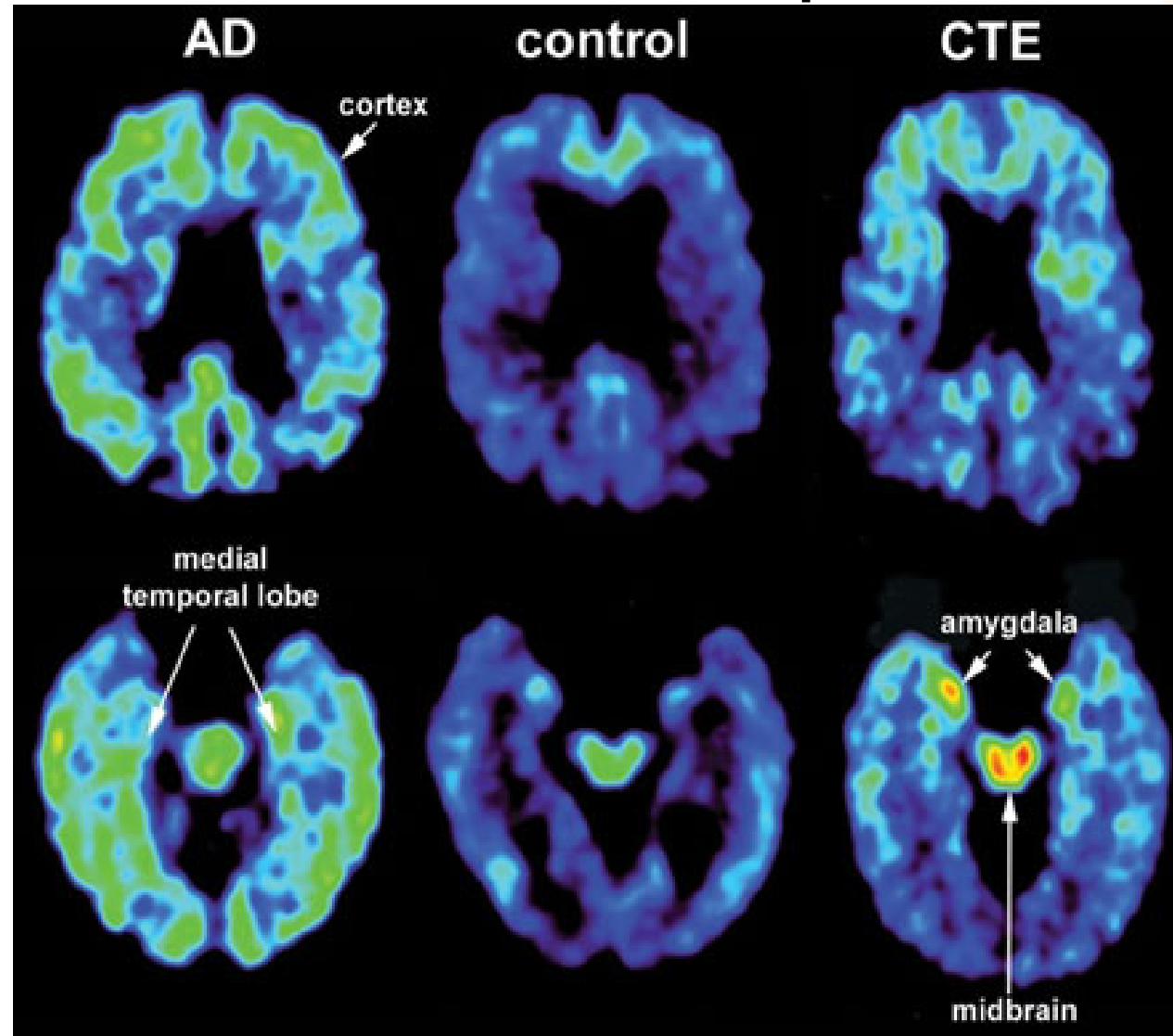
Between group significance: \*P=.05; ^P=.08

# Other Lifestyle Strategies Associated with Lowering Risk for Alzheimer's Disease

- Avoid head trauma
- If you smoke, stop
- Keep a positive outlook
- Treat hypertension and high cholesterol



# FDDNP-PET Scans Differentiate Alzheimer's Disease from Suspected CTE



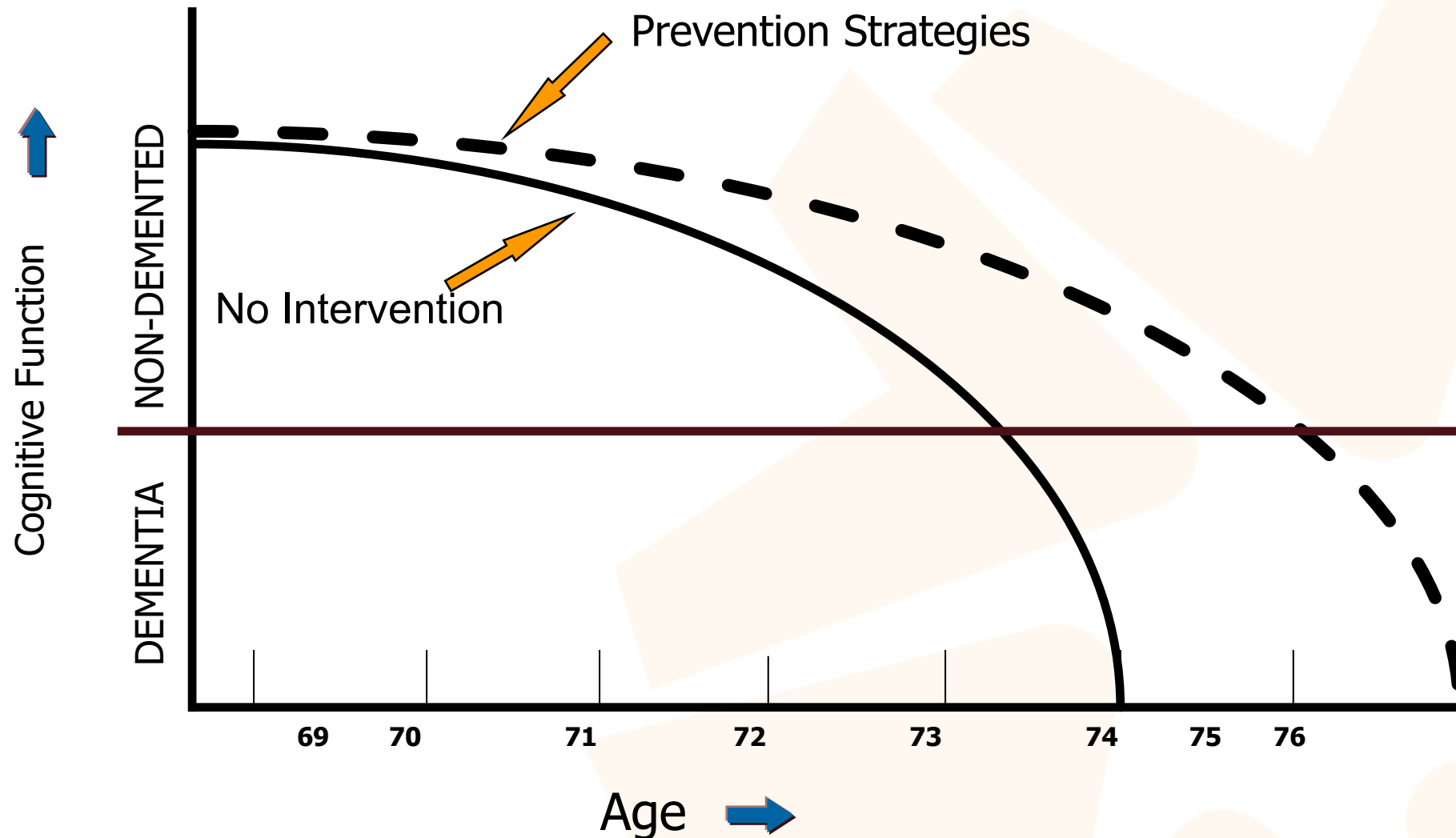
CTE = chronic traumatic encephalopathy.

Barrio JR, et al. *Proc Natl Acad Sci U S A*. 2015;112(16):E2039-E2047.

# Can We Prevent Alzheimer's Disease?

- If “prevent” means “cure,” then the answer is no
- Although true prevention is an ideal goal, intermediary targets are feasible:
  - delaying onset
  - slowing progression

# Prevention Goal: Delay Symptom Onset



# Preventing Alzheimer's Disease

- To definitely prove effectiveness of prevention:
  - Double-blind studies on thousands of people followed for years
- Compelling epidemiological and short-term clinical trials:
  - Already indicate what we can do now to delay symptom onset
- Physical exercise and healthy diet can prevent or delay the onset of diabetes
  - Having diabetes doubles probability of developing Alzheimer's
  - Prevention strategies lower risk for diabetes and Alzheimer's

# How Can We Help People to Change

- Educate
  - connection between lifestyle and disease prevention
- Fun and easy program
- See quick results
  - motivates to continue healthy behaviors so they become habits



# Modifiable Risks for Dementia

## 7 Major Risks

- Depression/stress
- Obesity
- Hypertension
- Diabetes
- Physical inactivity
- Smoking
- Low education/cognitive inactivity

## Impact

- Up to half of Alzheimer's cases worldwide are potentially attributable to these factors



Harry



Lisa



**Sue Bangel**



Do You Remember Your Story  
for the Word List?

# Word List

- Beach
- Professor
- Horse
- Teddy bear
- Cigar
- Nun
- Palm tree
- Pasta

# Conclusions

- Drug development is key to future of Alzheimer's disease prevention treatments
- Brain healthy habits can:
  - improve quality of life today
  - possibly stave off Alzheimer's disease symptoms in the future
- For more information:
  - [Longevity.UCLA.edu](http://Longevity.UCLA.edu)
  - [DrGarySmall.com](http://DrGarySmall.com)
  - Twitter: [@DrGarySmall](https://twitter.com/DrGarySmall)