



Beta Amyloid Deposition in Very Healthy Adults: Risk Factors and Cognitive Consequences

Denise C. Park

**Distinguished University Professor
Regents Research Scholar
University of Texas at Dallas**

RESEARCH SUPPORTED BY

The National Institute on Aging

28 years of continuous support

The Alzheimer's Association

Avid Radiopharmaceuticals

Collaborators



**Dr. Kristen
Kennedy**



**Dr. Karen
Rodrigue**



**Dr. Mike
Devous**



Gerard Bischof



Jenny Rieck



Andy Hebrank

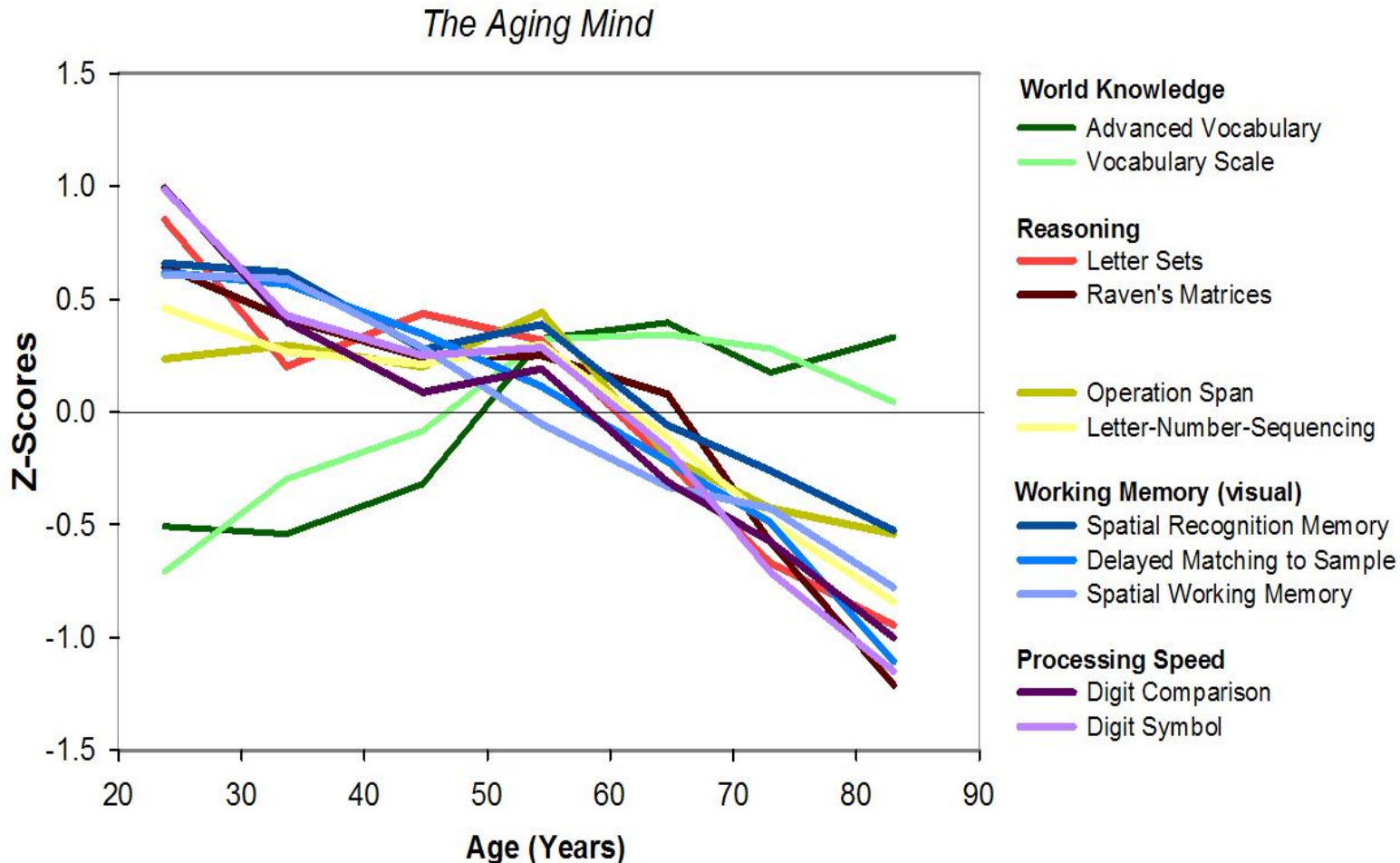
Approaching the Issue of MCI from a “Healthy Aging” Perspective

- What is “healthy” or “normal” aging?
- Assumptions typically associated with research on healthy participants

Individuals who are functioning at high levels have healthy brains..

Individuals with neurological disease are excluded from healthy aging studies

The Aging Mind in Healthy Adults: 2002



Neuroimaging and a Revised View of the Aging Mind

It is a false dichotomy to conceptualize a mind as healthy or unhealthy with age .

Few people by the age of 60 are without some type of subtle or frank neural pathology.

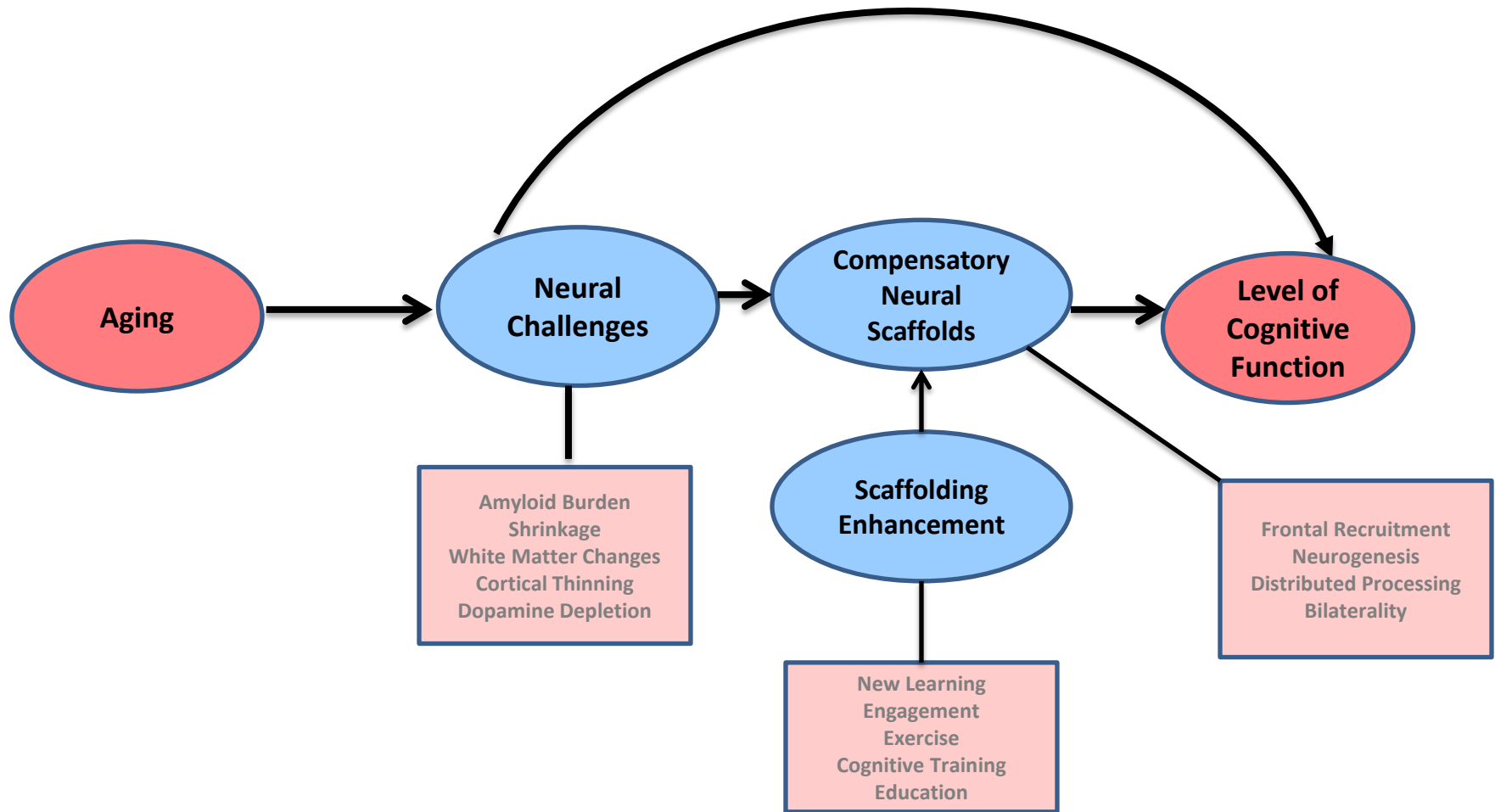
People can exhibit very high levels of cognitive function in the context of pronounced neuropathology.

The brain can adapt and remodel in response to pathology

People differ in their cognitive reserve and how much they are able to adapt.

The Scaffolding Theory of Aging and Cognition provides a view of the aging mind that integrates brain structure and function to predict cognitive function.

The Scaffolding Theory of Aging and Cognition



How early in the lifespan can we detect Alzheimer's disease and why does it matter?

- Consider the progress we have made on heart disease and many types of cancer.
- We are at the beginning of this era in the brain
 - Tremendously excited and hopeful about developing drugs and behavioral interventions to slow age-related decline.
 - Delaying aging process by five years would cut the rate of Alzheimer's disease in half.
 - Slowing the rate of aging of various aspects of the brain is a tremendously important goal.

Basic Research: The Dallas Lifespan Brain Study

- Conduct a very large study of the brain across the entire lifespan.
 - How do changes in the brain relate to cognition as we age?
 - Can the brain protect itself from some aspects of neural deterioration associated with aging? How?
 - Can we use this information to determine on whom and what age we need to intervene?
 - Use every available technique to fully characterize the brain as it ages.
 - Develop a neural footprint of healthy versus unhealthy aging.

Study Protocol

Screening

Cog Session 1

Cog Session 2

Psycho-Social

MRI Session

Genetics

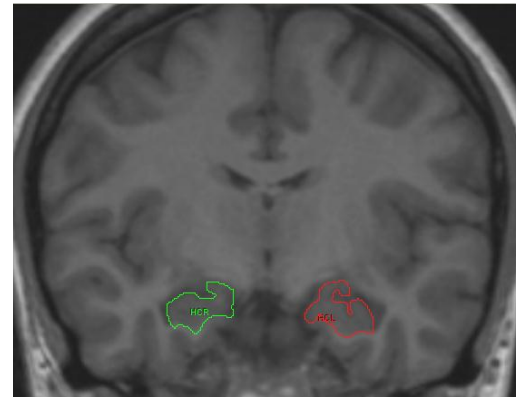
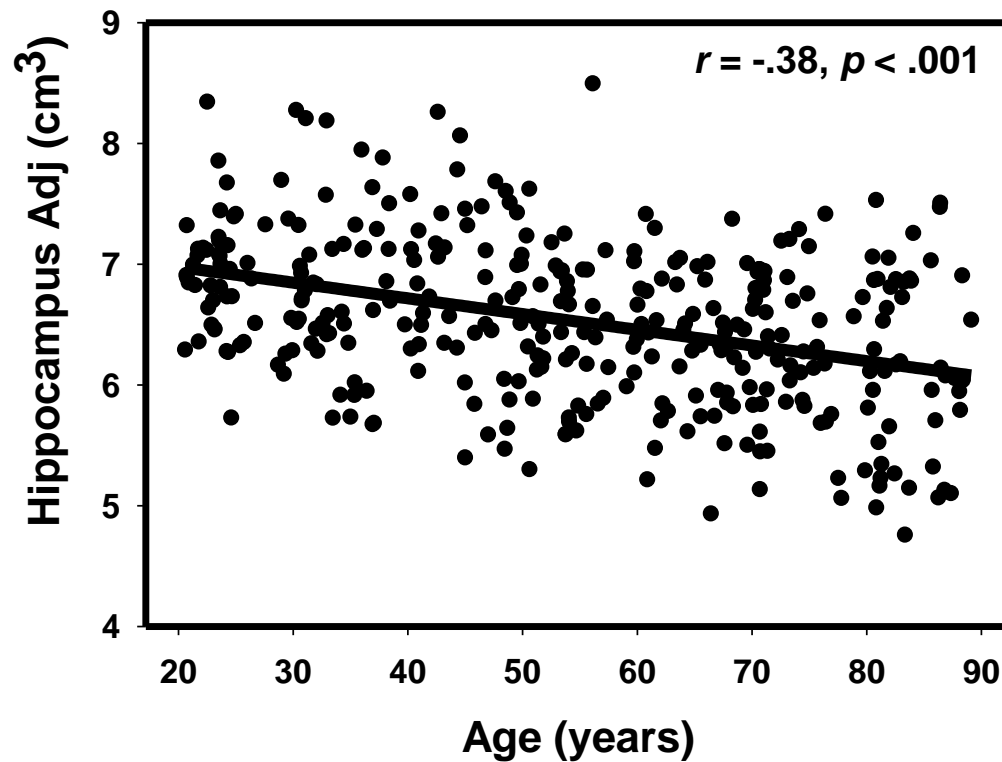
PET Session

The Complete Sample

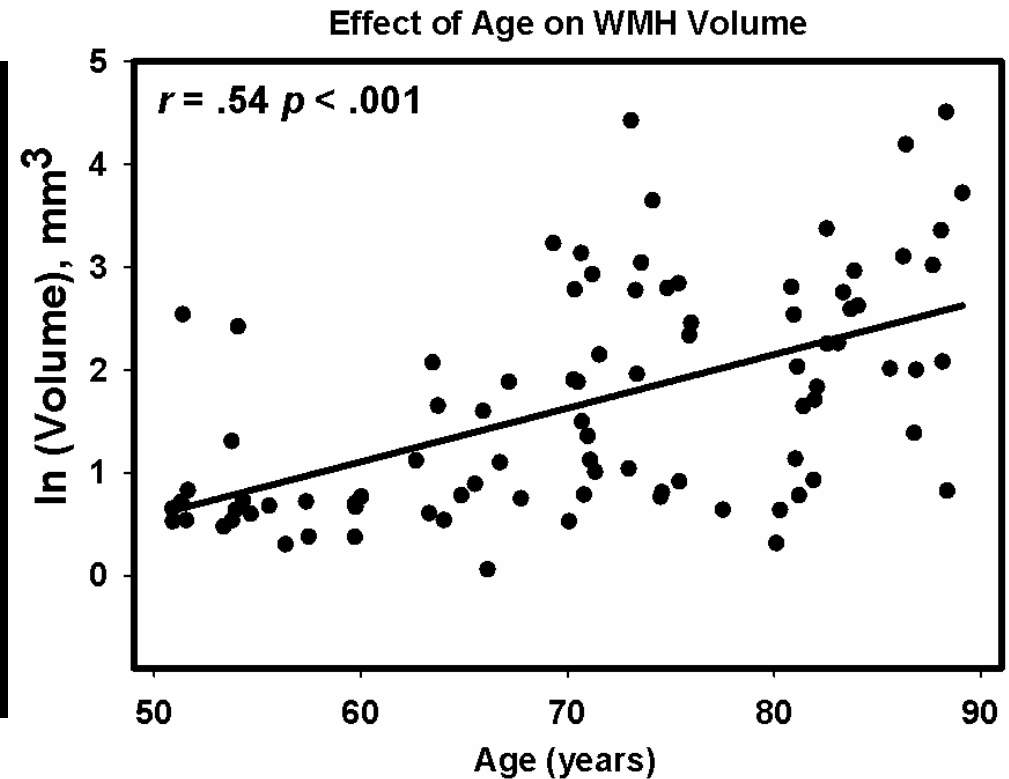
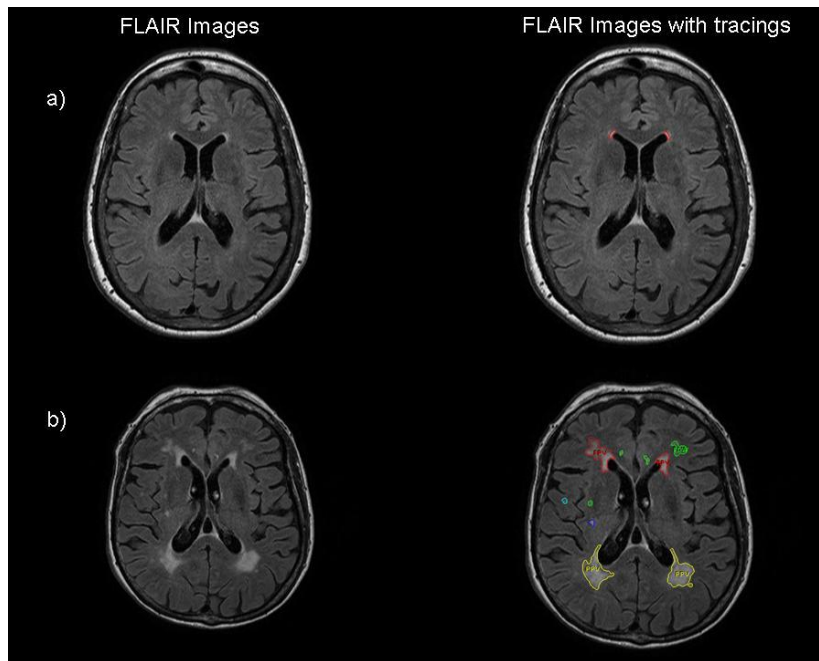
Decade	Total	Mean Yrs Education	MMSE	By Sex	
	N			Women/ N	Men N
20-29	50	16.3 (11 - 20)	29.00	32	18
30-39	49	17.5 (11 - 24)	28.49	31	18
40-49	50	16.1 (11 - 23)	28.47	32	18
50-59	51	17.4 (12 - 24)	28.65	34	17
60-69	50	16.9 (12 - 24)	28.10	32	18
70-79	51	15.9 (11 - 23)	27.78	32	19
80-89	49	15.2 (11 - 23)	27.28	32	17



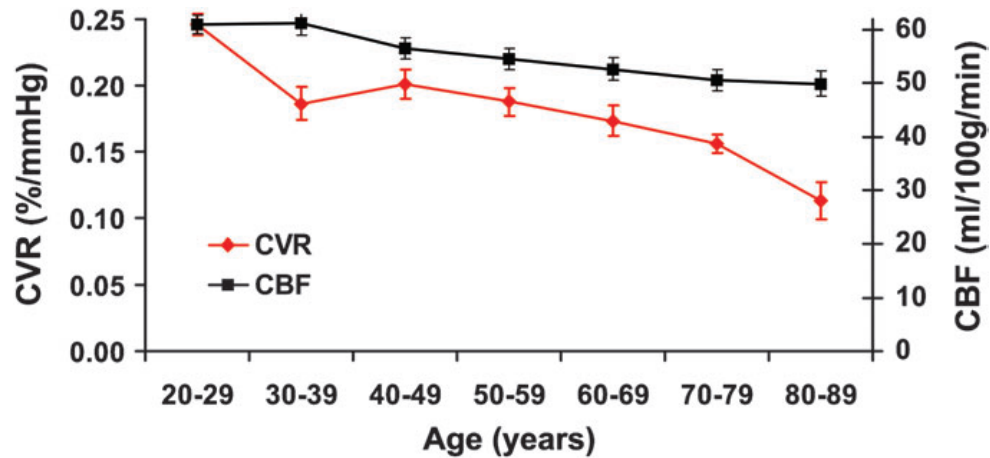
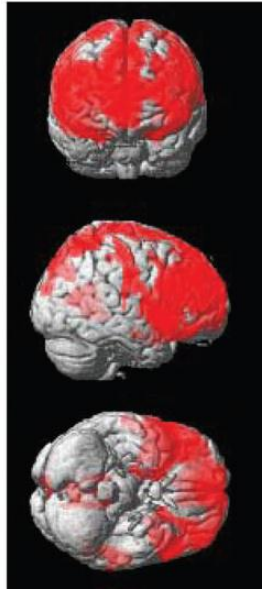
The Hippocampus, a part of the brain critical to memory, shrinks with age



Increases in White Matter Hyperintensities as a function of age



Functional Imaging - Measures of Neurovascular Health



Lu et al., (2010)
Cerebral Cortex

Responding to Neural Challenge: Imaging a Word Judgment Task

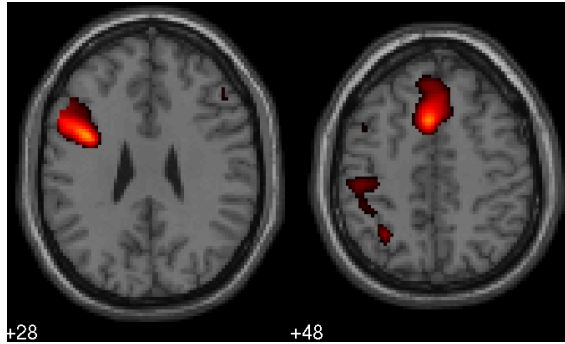
Is this word a living or nonliving thing?

- Book
- Dog
- House
- Ghost
- Virus
- Sponge

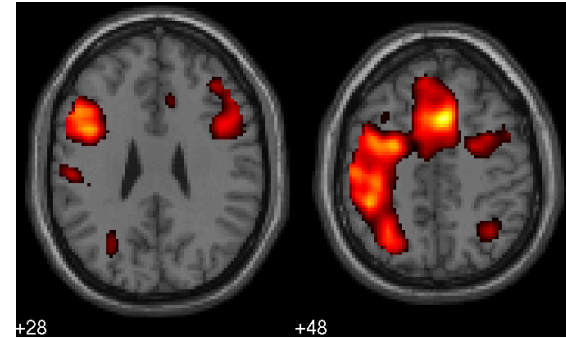


Age Differences in Brain Patterns When Judging a Word

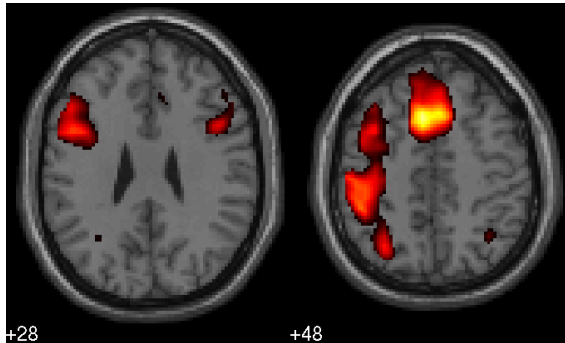
21-29



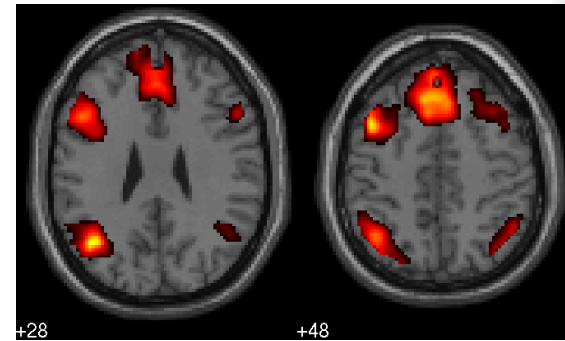
60-69



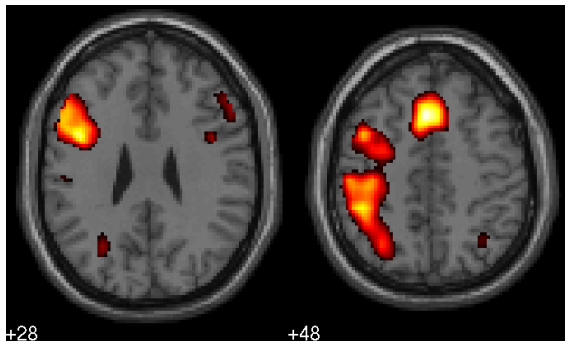
30-49



70-88



50-58



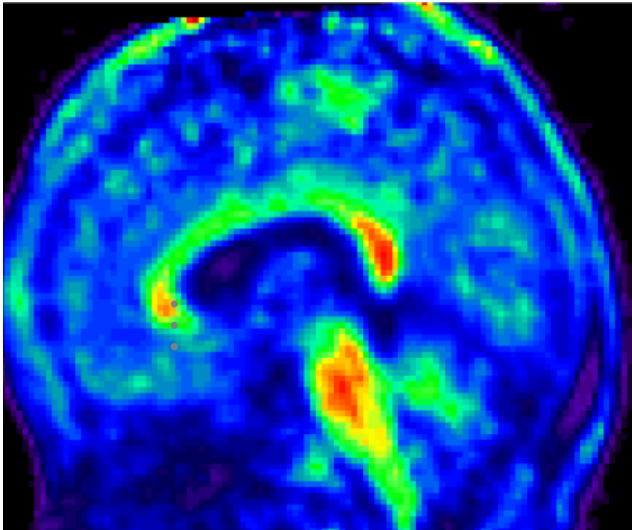
$p < .05$, FWE correction

Kennedy et al. In prep.

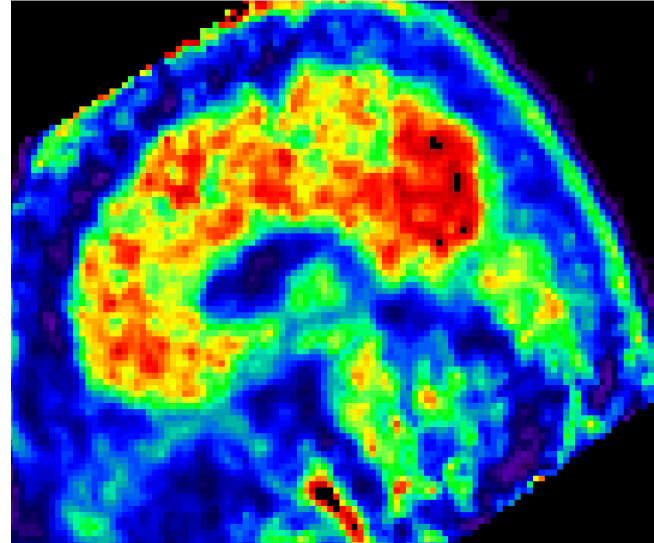
Amyloid and the Dallas Lifespan Brain Study

- We examined the implications of amyloid deposition on cognition in a large subsample from the DLBS.
- Interventions are ultimately likely to focus on healthier and younger adults than have previously been studied with amyloid imaging.
- Imaged 137 healthy adults age 30 to 90 using PET and Florbetapir (Avid Radiopharmaceuticals)

Healthy adults with different levels of amyloid measured by florbetapir



Low amyloid in 75 year old male



High amyloid burden in 62 year old male

Questions We Addressed

What is the prevalence of amyloid deposition in DLBS adults aged 30 to 90?

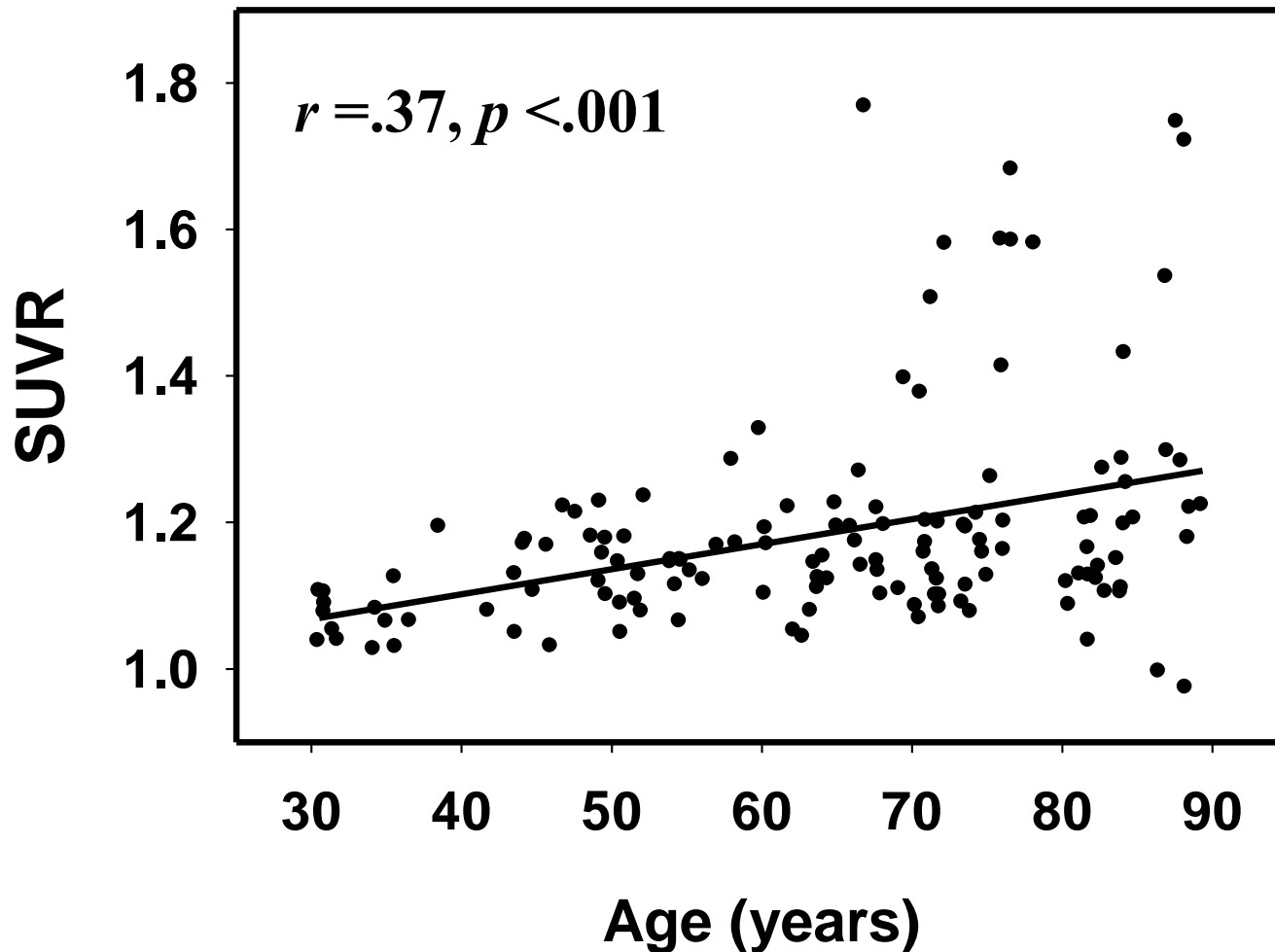
Do high amyloid individuals show lower performance on cognitive tasks?

Do high amyloid individuals show different patterns of neural activity on functional MRI tasks?

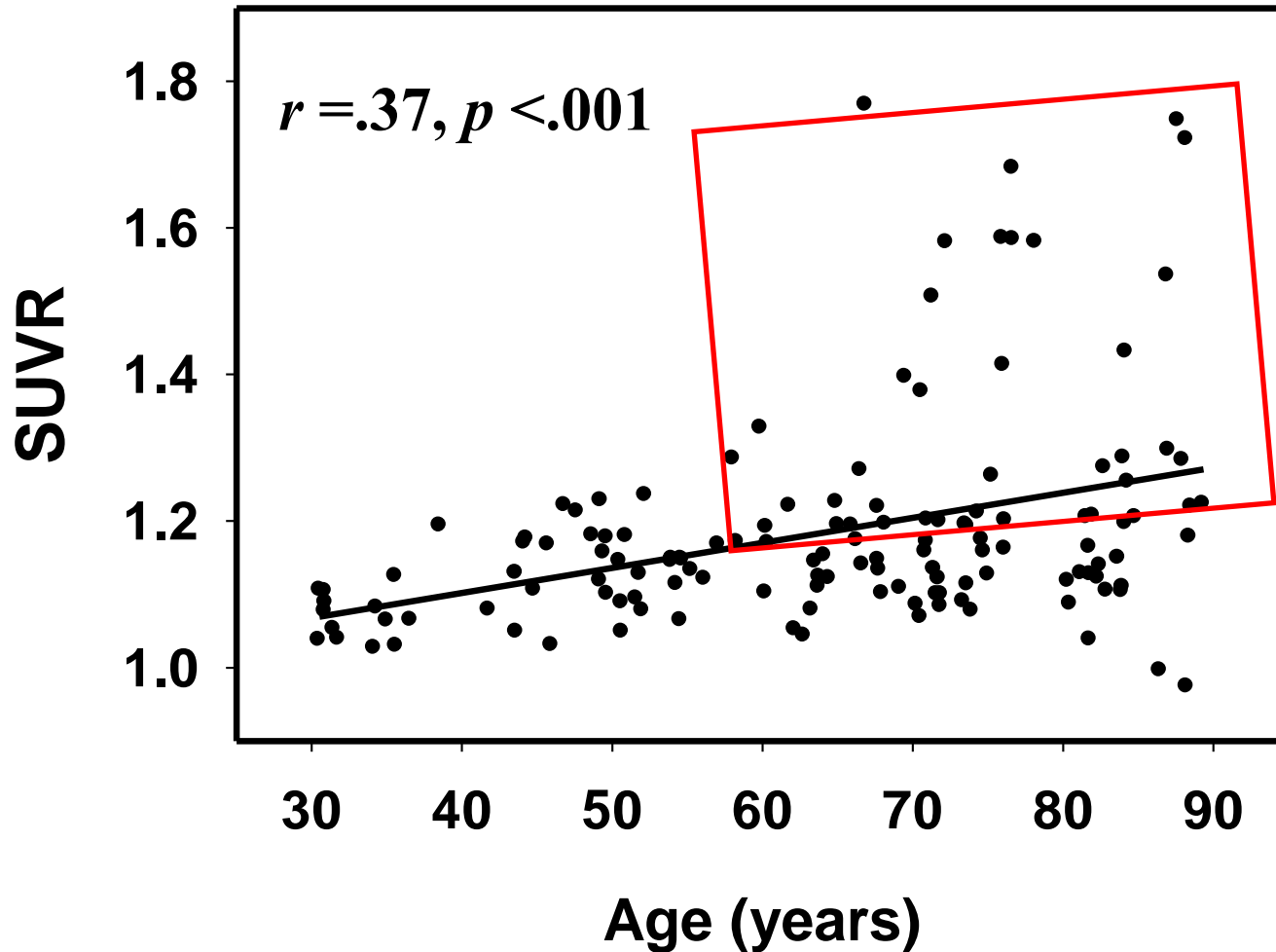
How much of cognitive decline attributed to “aging” in normal adults is due to the presence of amyloid?

What is the prevalence of amyloid deposition in healthy adults?

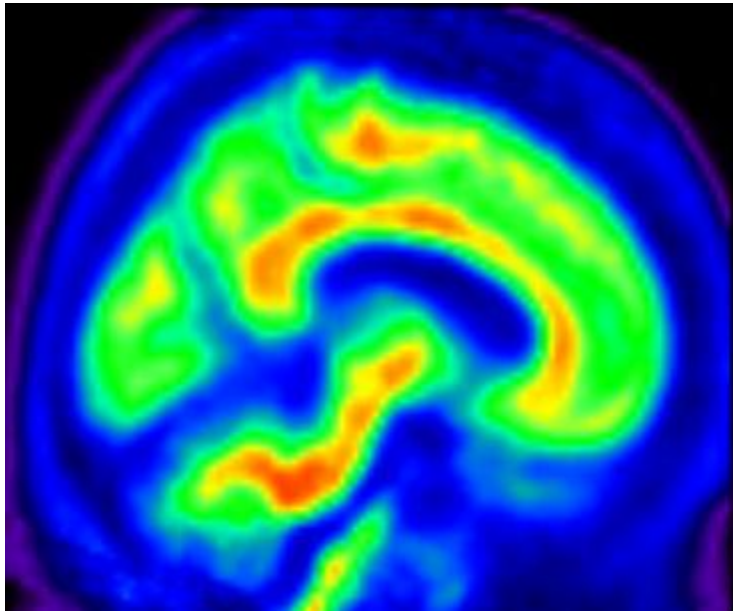
Effect of Age on Mean Cortical Uptake



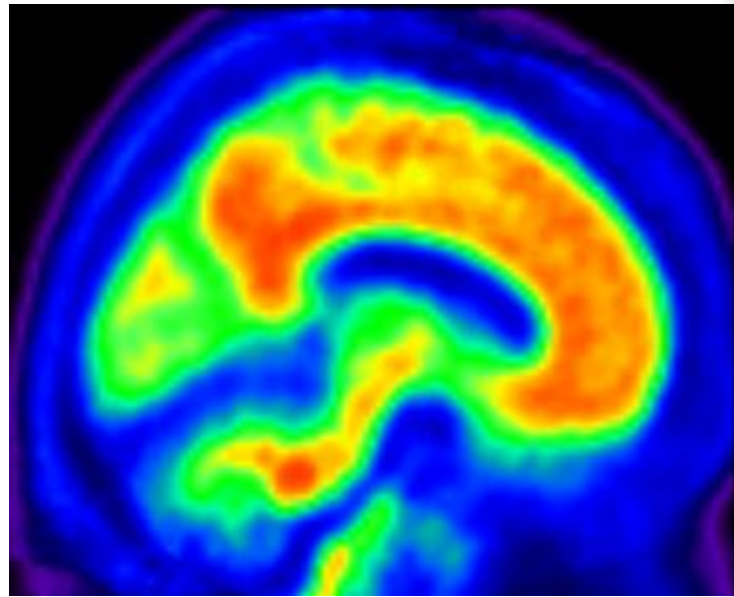
Effect of Age on Mean Cortical Uptake



Mean amyloid uptake in Age and Gender-Matched High and Low Amyloid Subjects



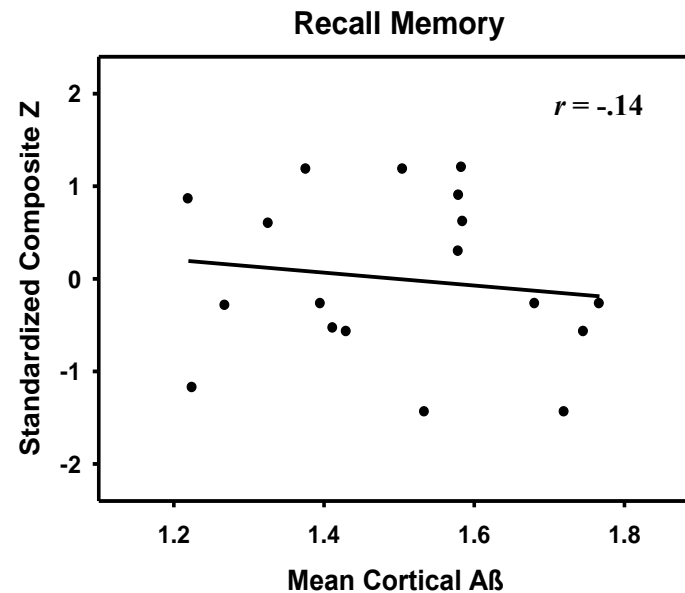
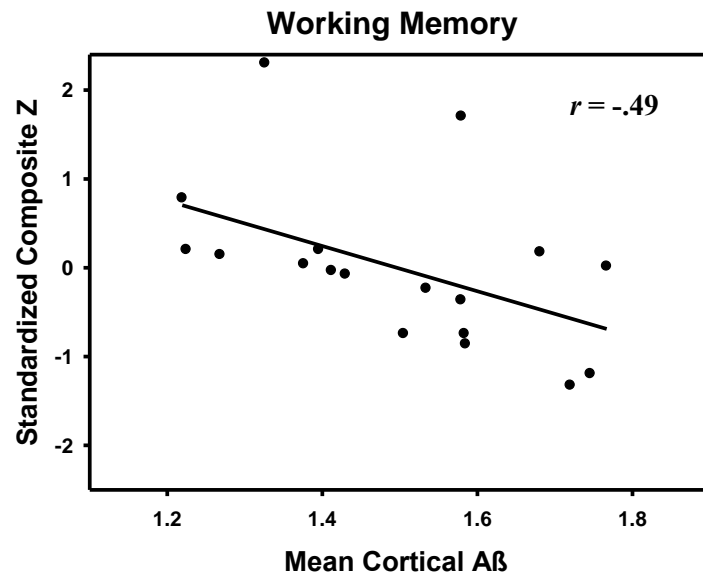
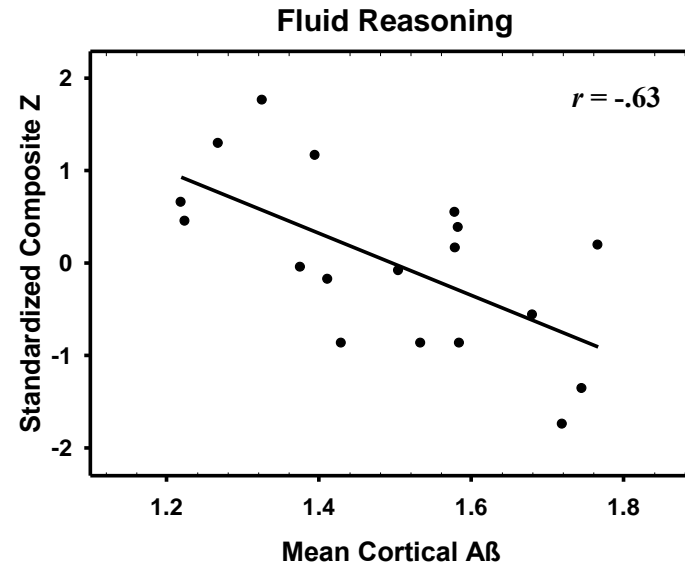
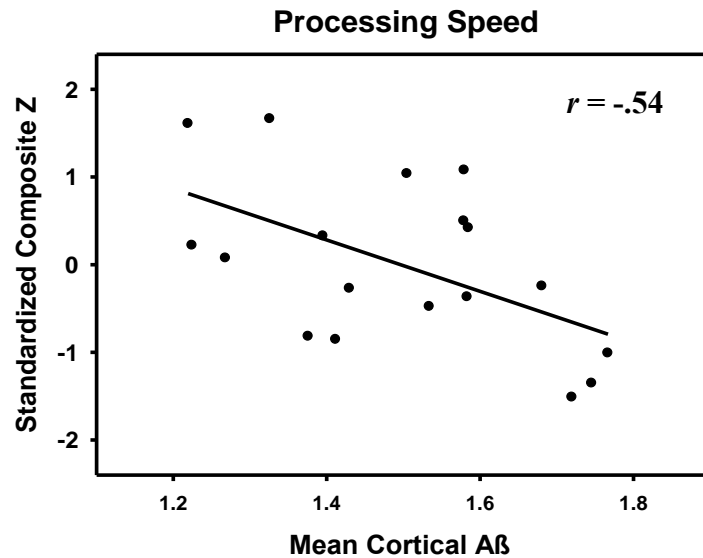
Low Amyloid: n = 18



High Amyloid (N=18)

Images are on same scale; red is highest uptake

In the 18 high amyloid adults, cognitive performance decreased with more amyloid.



Amyloid Burden by Risk Group

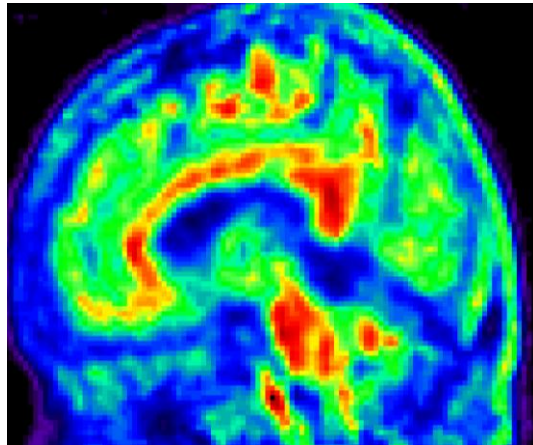
Genetic Risk

Vascular Risk

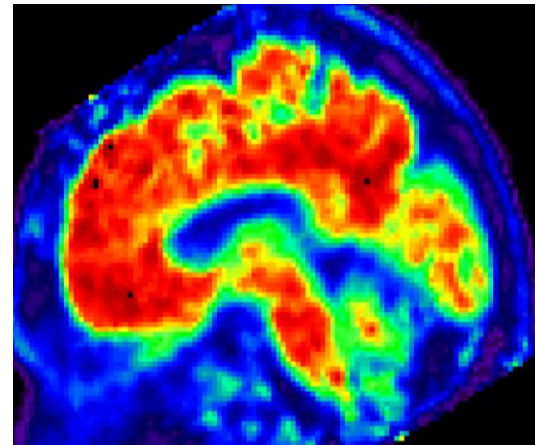
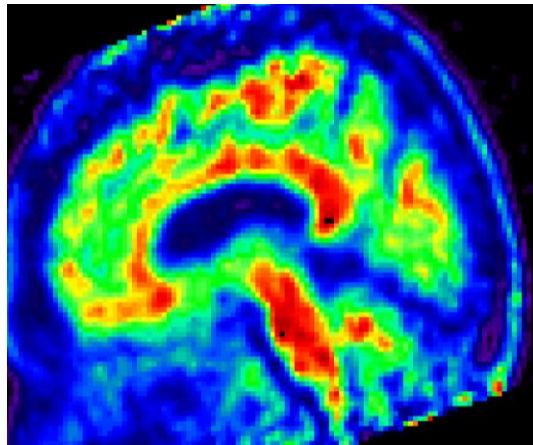
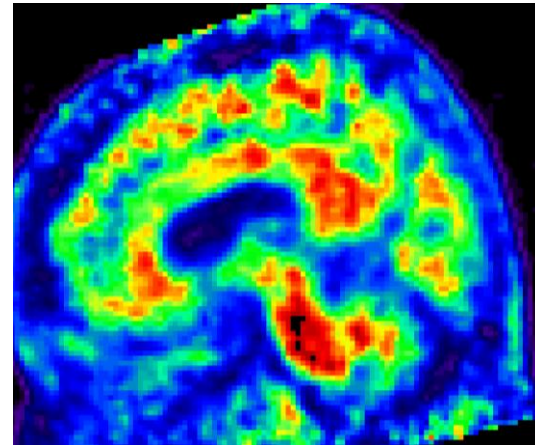
Normotensive

Hypertensive

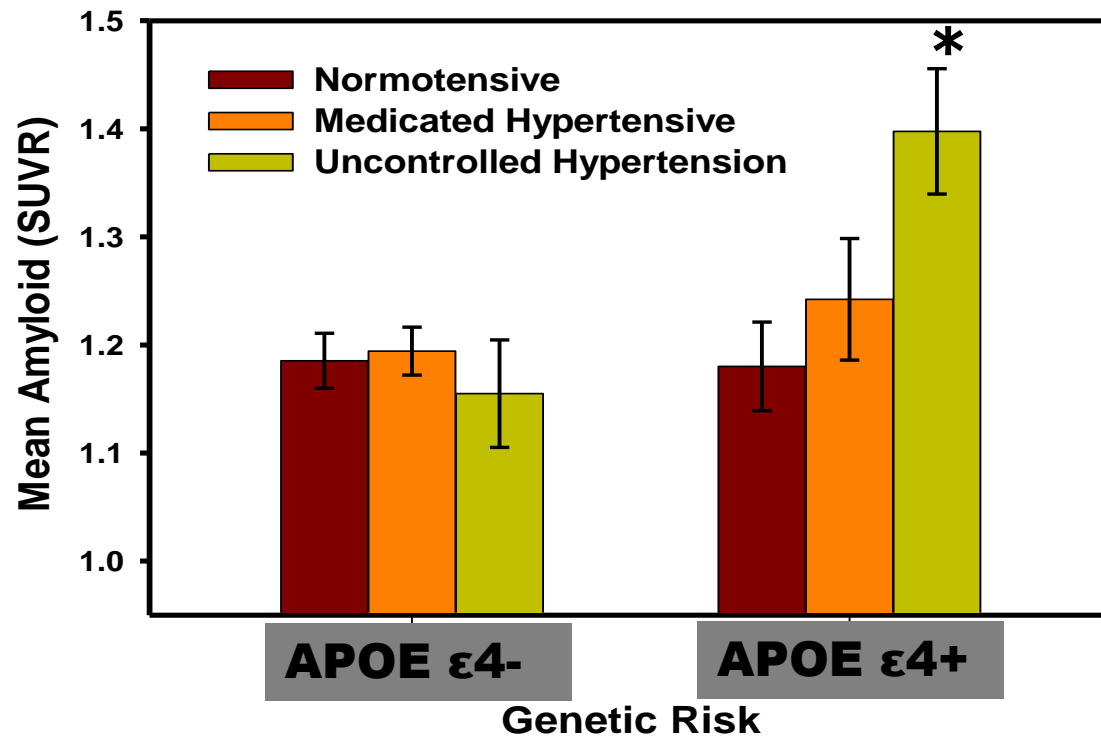
APOE $\epsilon 4$ -



APOE $\epsilon 4$ +



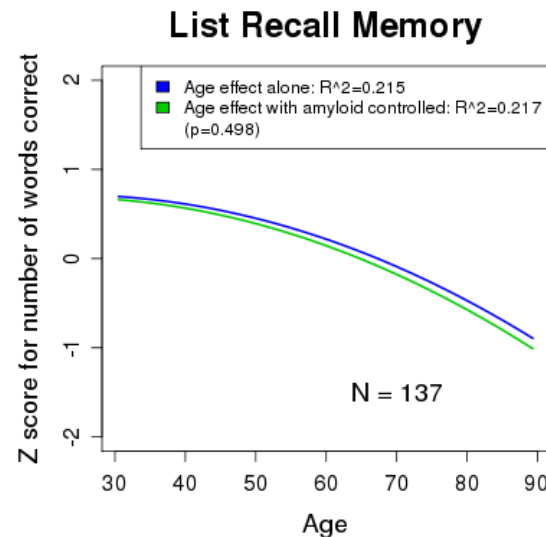
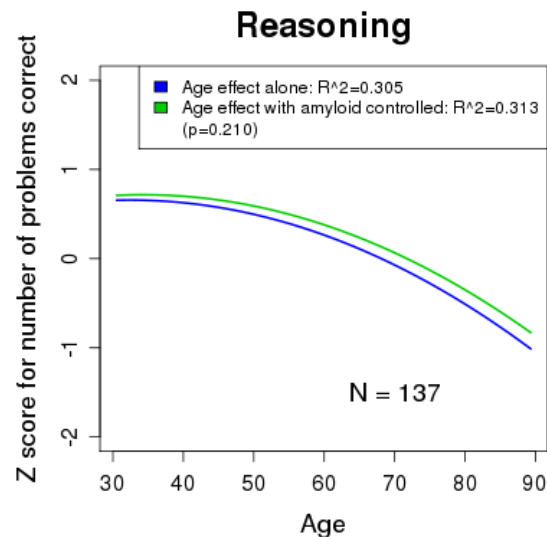
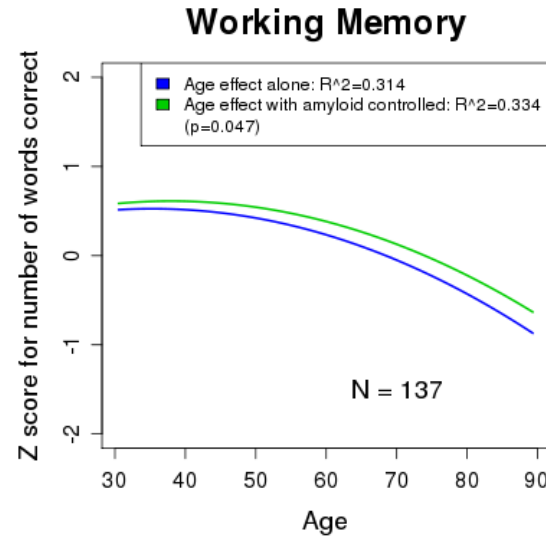
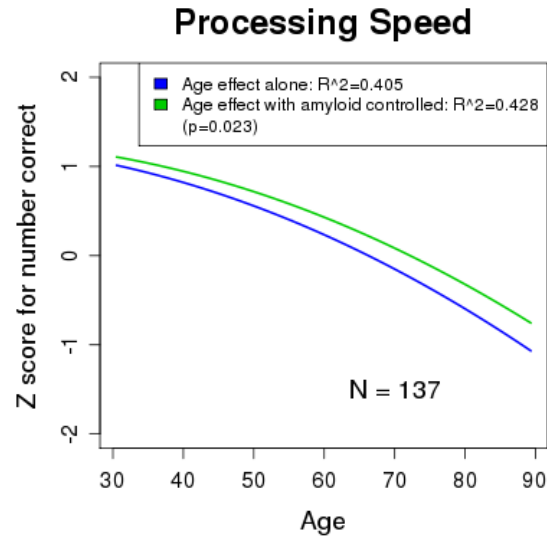
Adults with a genetic risk factor for Alzheimer's and uncontrolled hypertension had the most amyloid



Age-adjusted means plotted

*Hypertension Group × APOE: $F(1, 113) = 9.52, p = .003$

Age effects are still large when amyloid is controlled



What have we learned and what we will learn from the DLBS?

- The structure of your brain matters for cognition, particularly white matter lesions.
 - How does this interact with amyloid to move people closer to Alzheimer's?
- Your brain works harder to perform cognitive tasks as you age and this begins in the 30's and continues through the 70's.
 - We think that this extra activity in middle age will predict poor cognitive aging.
- It looks like neural effort tops out by age 80 and does not increase and probably even decreases.
- Almost nothing is known about the neural life of oldest adults.

What have we learned and what we will learn from the DLBS?

- About 20% of very healthy adults have high levels of amyloid, but 80% have low levels\
 - How long can a person with a high amyloid load remain functionally normal?
 - Does high amyloid ALWAYS convert to Alzheimer's?
 - What about middle-aged with above-average loads for their age group?
- Uncontrolled hypertension and genetic risk together are accompanied by a high level of amyloid - But what is causal?? Does hypertension cause amyloid or does amyloid cause hypertension?
- Does a high level of education protect you?
 - We are adding a sample of less-educated and less healthy individuals.

TIME WILL TELL....

The importance of longitudinal research.

THE SYNAPSE PROJECT: A TRANSLATIONAL APPROACH

The Intervention Groups

QUILT

- Participants spent at least 15 hours per week in *Synapse*

- 5 hours were spent on formal instruction

- 10 hours were spent completing assignments

PHOTO

- Classes were held 2 times per week

COMBO

- Classes were made up of 6 participants in same intervention.

The Intervention Groups

QUILT

- A professional quilting instructor taught weekly classes
- Training started with learning basic machine skills
- Progressed to more difficult skills, used in a final project
 - Binding
 - Machine quilting
 - Hand quilting

PHOTO

COMBO



The Intervention Groups

QUILT

PHOTO

COMBO

- A professional digital photography instructor taught weekly classes
- Training started with learning basic camera and computer operations
- Progressed to more difficult skills, used in a final project
 - Photo editing
 - Photo journaling
 - Using Photoshop



The Intervention Groups

QUILT

- Participants took part in both digital photography and quilting classes
 - The first half was spent in one and the second half was spent in the other
 - The ordering was counterbalanced across participants

PHOTO

COMBO



The Intervention Groups

QUILT



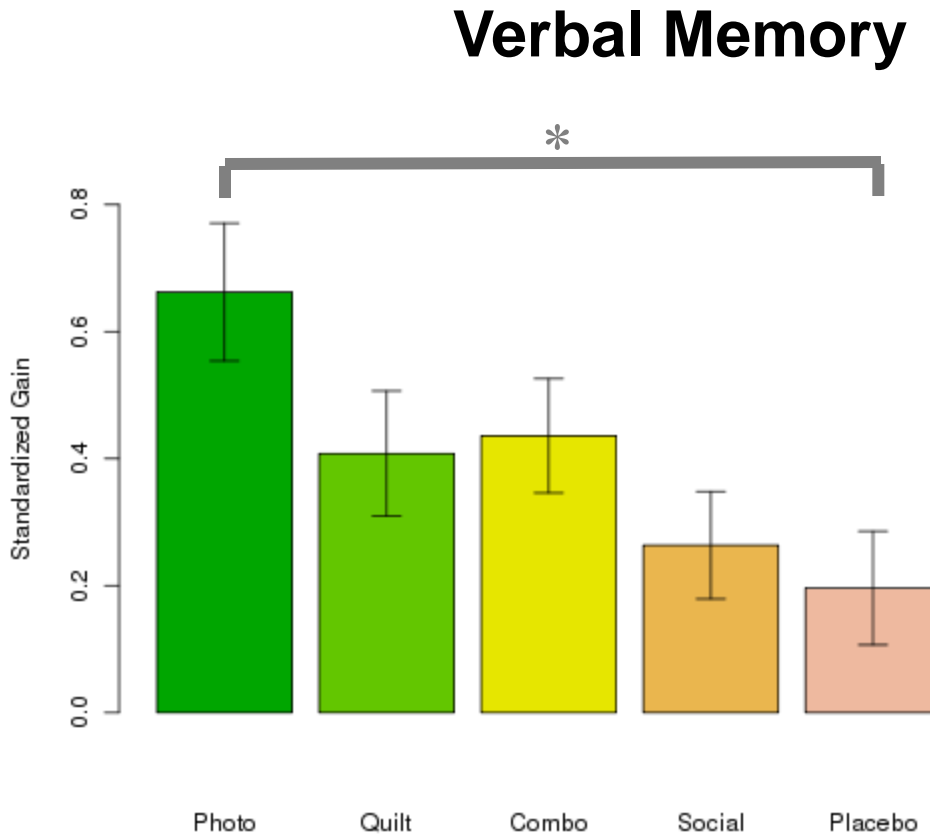
PHOTO



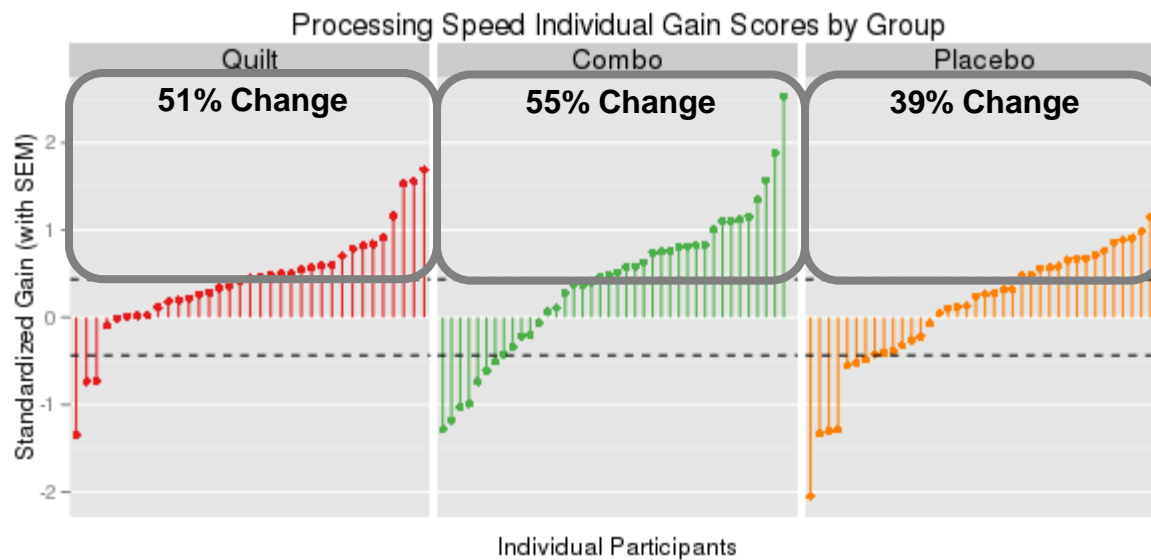
COMBO



Verbal Memory Gains for Each Group



Let's look at memory improvement for each subject



Let's look at memory improvement for each subject

