# Challenges in the Early Diagnosis of Alzheimer's Disease

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3rd Early Alzheimer's Diagnostic and Treatment Workshop
Mount Sinai Medical Center
January 19, 2014

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## Disclosure of Interest

Research Support

1. NIA-ADNI, DIAN, A4
2. Alz Assoc-DIAN Clinical Trials
3. Fain Family Foundation, Champlin Foundation, White Family Foundation

Speakers Bureau
Athena

Clinical Trials
Janssen AI, Baxter, BMS, Pfizer, Genentech, Bayer, GE, Avid, Roche, Merck, Lilly, Functional Neuromodulation

Consultant
Janssen AI, Astra-Zeneca, Avid-Lilly, GE, Baxter, Pfizer, Athena, BMS, Biogen, and Merck

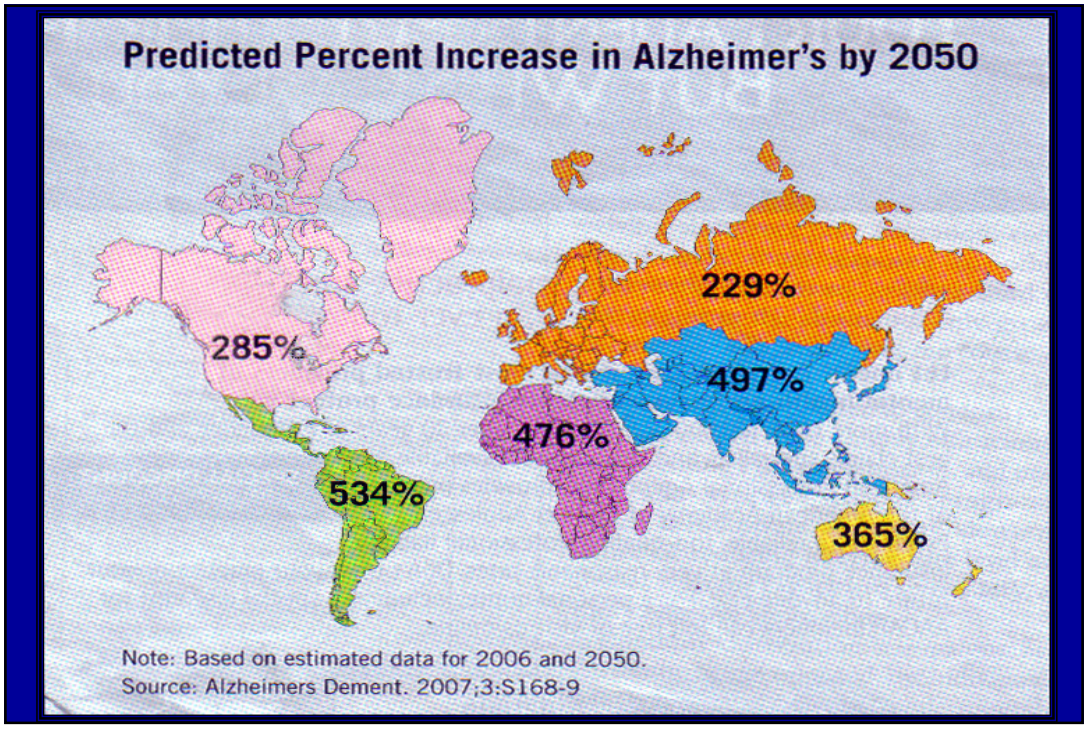
I own no stocks or equity in any pharmaceutical company and have no patents or royalties

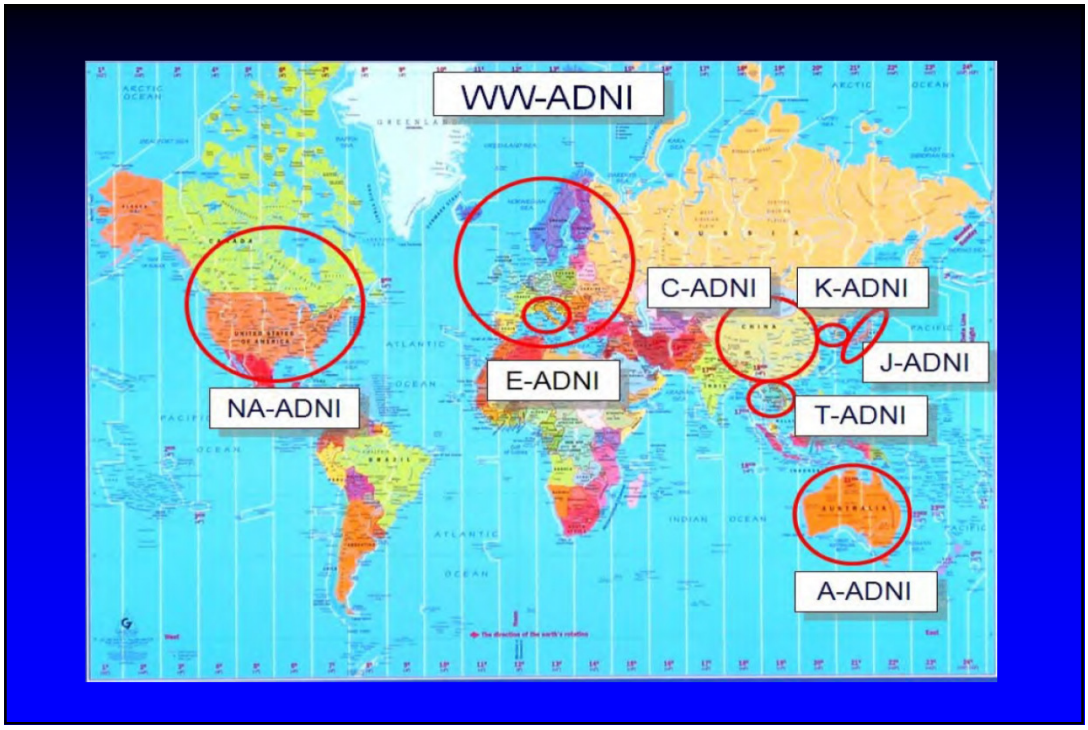
## Butler Hospital Memory and Aging Program

## Alarming Alzheimer's Statistics and Call to Action

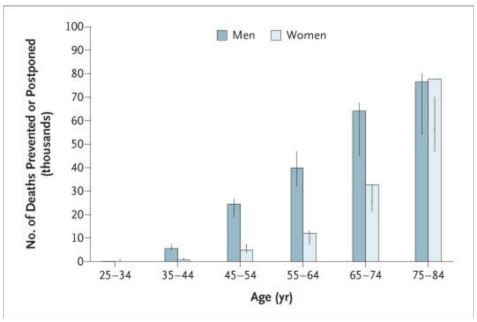
- Every 67 seconds someone develops AD in the US!
- The rate of AD doubles every 5 years after age 65 reaching 30-50% in those 85 and over
- 10,000 baby boomers will be turning 65 every day for the next 15 years (77 million)
- Delaying onset by 1-2 years can significantly reduce the number of cases, disease burden, and cost

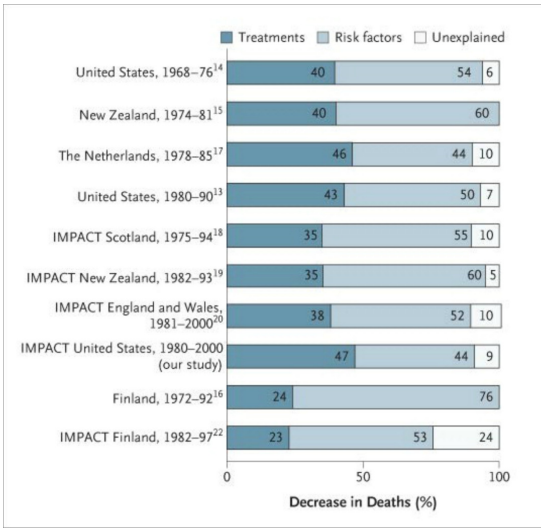
*** Alz Dementia 2007;3:186-191**


Predicted Percent Increase in Alzheimer's by 2050
285%
229%
497%
476%
534%
365%
Note: Based on estimated data for 2006 and 2050.
Source: Alzheimers Dement. 2007;3:S168-9


WW-ADNI
C-ADNI
K-ADNI
J-ADNI
E-ADNI
NA-ADNI
T-ADNI
A-ADNI

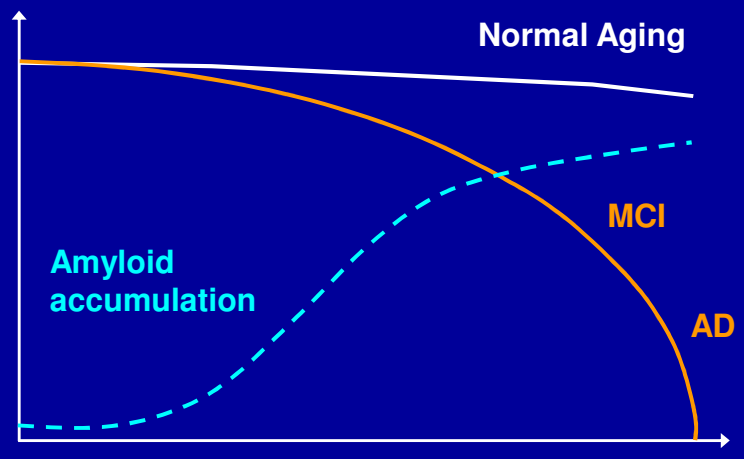
# Dramatic Decrease in Cardiac Deaths 1980-2000



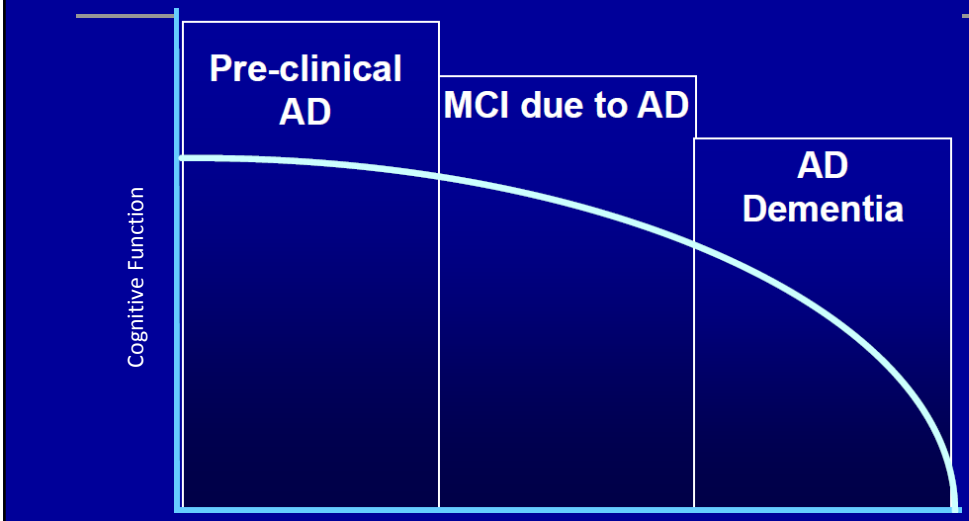




Ford, NEJM, 2007

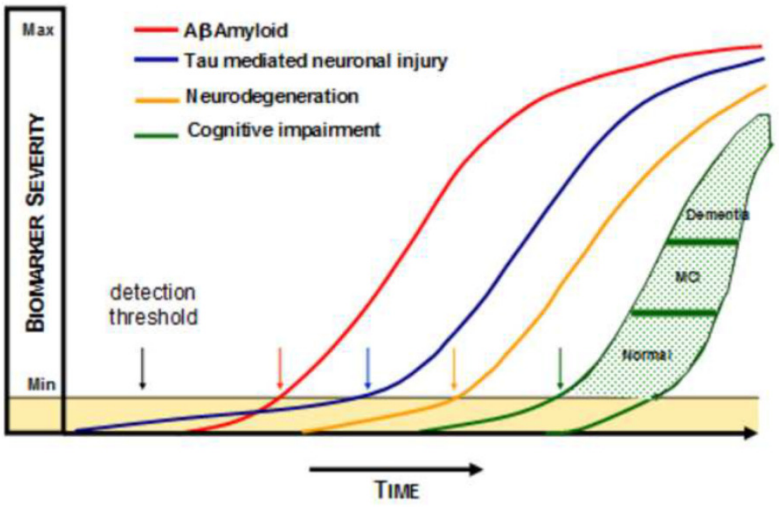
# Alzheimer's Disease Trajectory



## Reconceptualizing Alzheimer's Disease

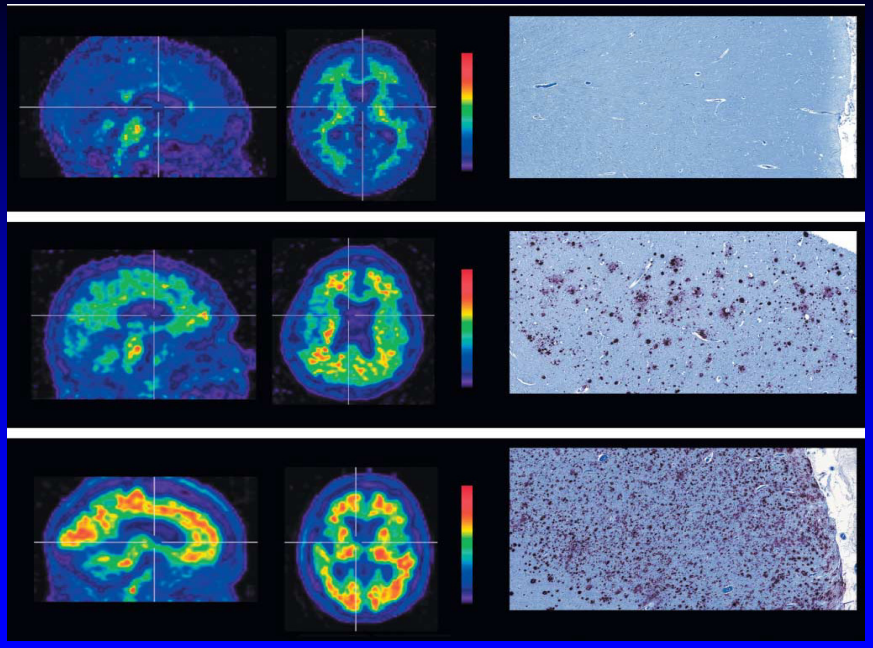



McKhann et al, Albert et al, & Sperling et al, *Alzheimers Dement* 2011




Jack Lancet Neurology 2013

Three Levels of Amyloid PET Binding (Florbetapir) with Post-Mortem Correlation



Unlikely AD

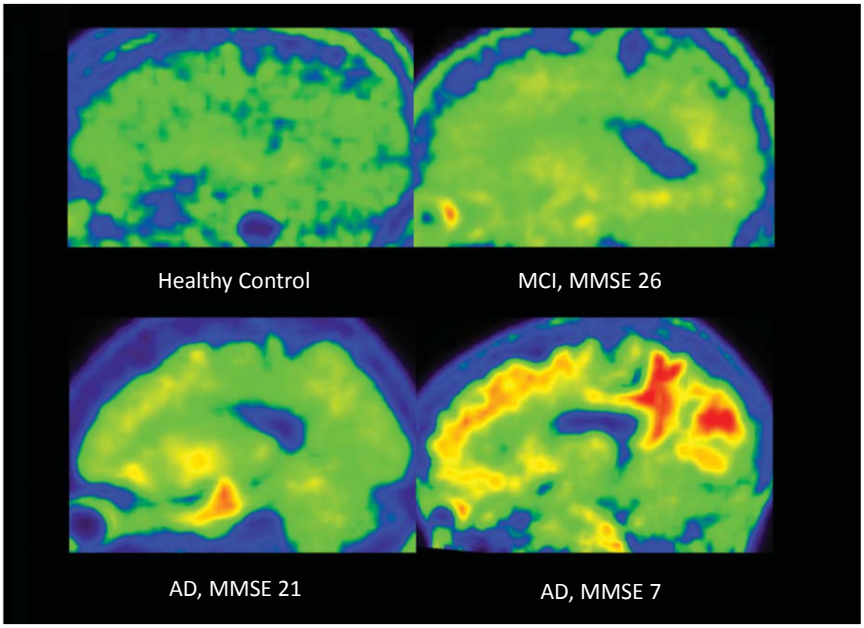
Intermediate likelihood of AD

Likely AD

Clark, JAMA 2011

# DIAN amyloid PET

## Clinical Development of Tau PET




## Preventing or Delaying AD in People at Risk

- DIAN-TU-2 year trial testing two anti-amyloid monoclonal antibodies in individuals with an autosomal dominant mutation
- API-5 year trial testing an anti-amyloid monoclonal antibody in patients with a PS1 mutation in Colombia
- A4-3 year trial testing an anti-amyloid monoclonal antibody in individuals 65-85 with normal cognition and a positive amyloid PET scan, will also study the impact of disclosure of amyloid PET results
- API-Under development, trial treating ApoE4 carriers (homozygotes) before expected age of onset

## Challenges in Early Diagnosis

- Screening methods to detect early cognitive decline
- Biomarkers to increase diagnostic certainty
- Proximity markers to predict rate of decline
- Careful clinical interpretation of amyloid PET scans
- Non-amnestic and atypical presentations
- Assess contribution of co-morbid conditions and genetic modifiers
- Develop new biomarkers for primary prevention
- Ensure broad access and training

Challenge 1: Develop screening methods to detect early cognitive decline

### Cognitive Decline in Aging (after age 70)

- Verbal abilities, e.g. proper word finding
- Memorizing / new learning
- Abstraction
- Reaction time
- Central processing

## Age-Related Cognitive Changes

- Age-related cognitive change does not substantially progress or significantly impair daily functioning.
- Older people may learn new information and recall previously learned information, but may do so less rapidly and efficiently.

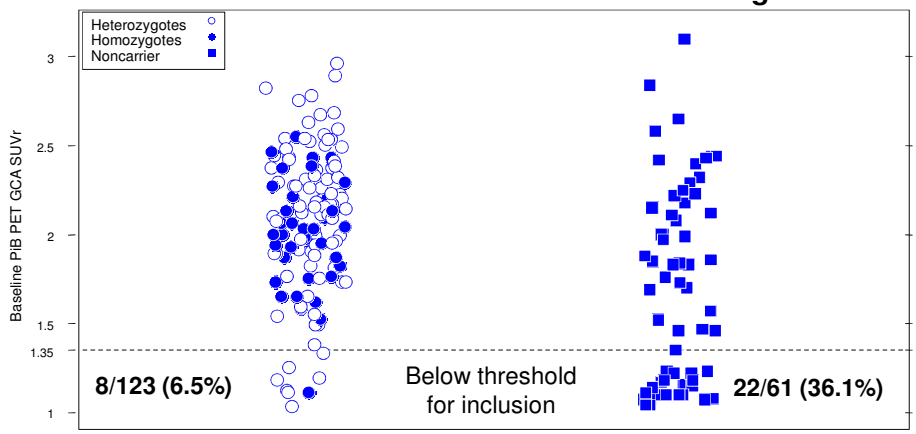
## Differentiating Cognitive Aging From the Beginning of a Cognitive Disorder

Troublesome signs

- Symptoms are occurring frequently and interfering with ADLs
- Being repetitive
- Not coming up with the names or words later
- Not recalling that conversations or events ever took place
- Not realizing that there is a memory problem

Challenge 2: Biomarkers to increase diagnostic certainty

**Distribution of PIB PET Global Cortical Average SUVr**




APOE ε4 carriers
302 Study N=123

Non-carriers
301 Study N=61

| | Carrier GCA SUVr | Non-Carrier GCA SUVr | P-value |
|---|---|---|---|
| All PiB PET analysis population | 2.07 | 1.72 | p<0.0001 |
| PiB PET analysis population | 2.14 | 2.05 | p=0.18 |

Salloway and Sperling, NEJM 2014

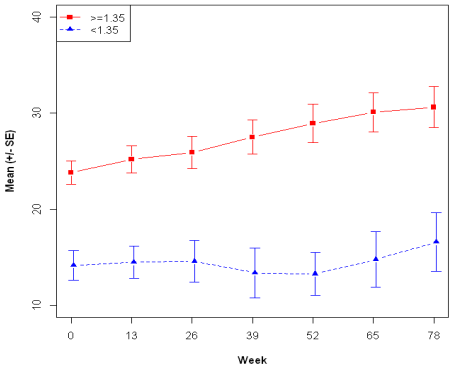
## Clinical Outcomes in Amyloid Negative Subjects in Bapineuzumab and Solanezumab Phase 3 Mild-Mod AD

- Amyloid negative (amy-) in placebo-completers defined as PIB SUVr < 1.35 (Bapi) and FBP SUVr < 1.1 (Sola)
- > 20% of subjects were amy-
  - Lower proportion of amy- in ApoE4 carriers than non-carriers (11.1% vs 45.5% for bapi and 8.2% vs 41.7% for sola)
- Amy+ subjects were more impaired at baseline and the rate of decline in amy- subjects was less than expected for mild-moderate AD
- The underlying diagnosis in the amy- cases is unclear

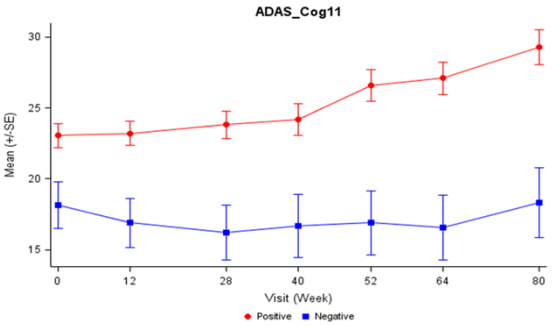
Salloway, Sperling AAIC 2013, NEJM 2014

## ADAS-cog/11 over time: observed data

Bapineuzumab



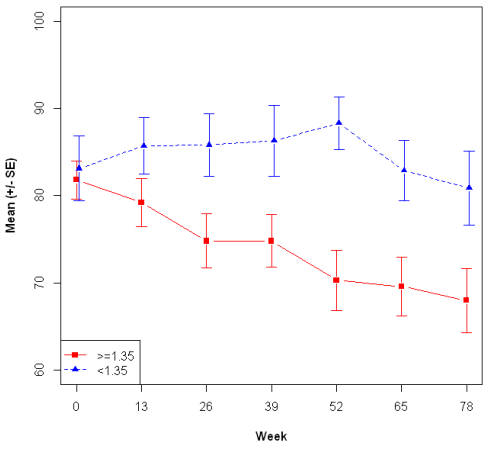

Solanezumab



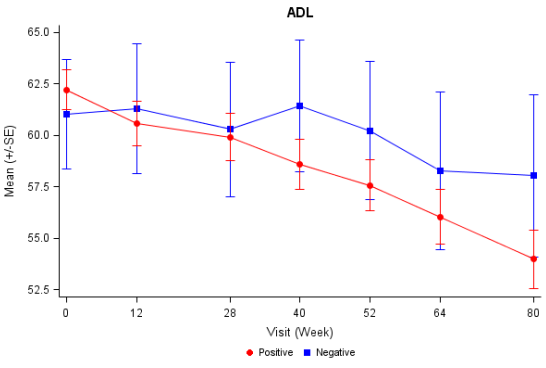

Salloway, Sperling AAIC 2013



Bapineuzumab DAD

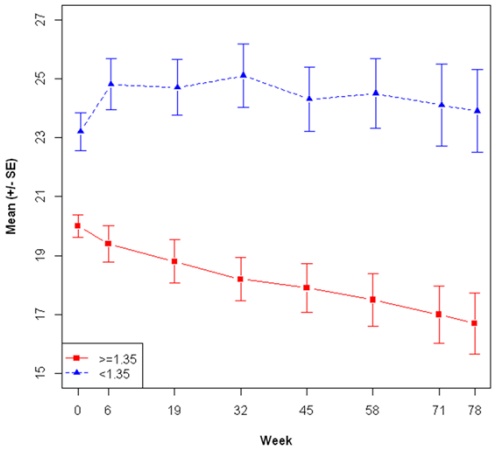



Solanezumab ADCS-ADL

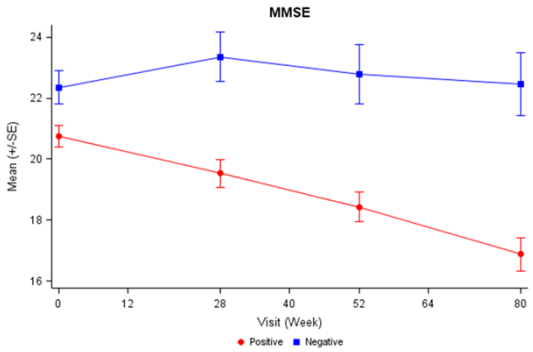


# Change on the MMSE

Bapineuzumab




Solanezumab

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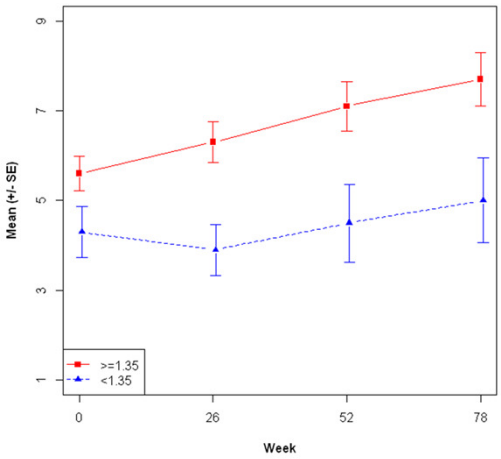
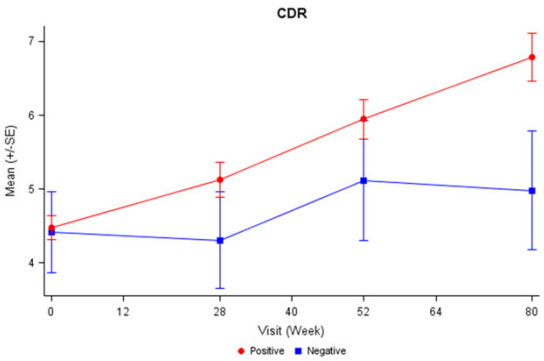
# Change on the CDR-SB

Bapineuzumab




Solanezumab

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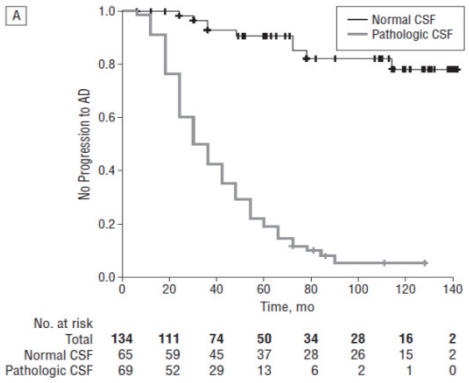
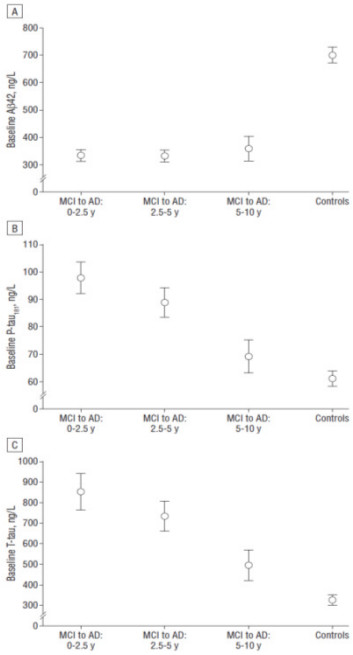
Challenge 3: proximity markers to predict rate of cognitive decline

CSF Predictors of Progression from Amnestic MCI to Dementia




A (Aβ42)/P-tau < 6.16




Buchave Arch Gen Psych 2012

Challenge 4: careful clinical interpretation of amyloid biomarkers

## Amyloid PET is chemically specific

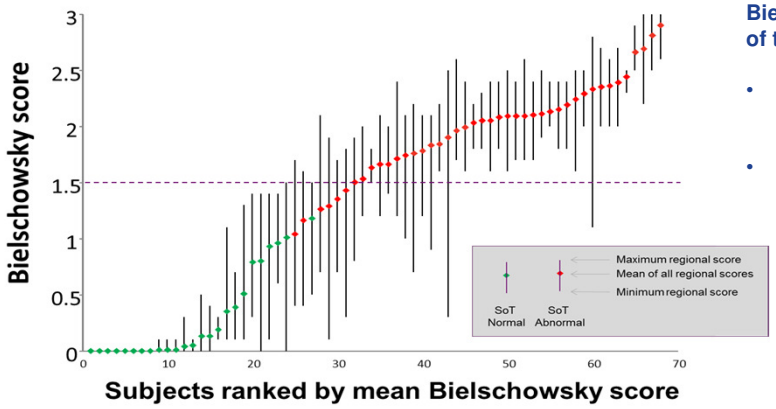
- Tracer binds amyloid plaque fibrils
  100% specific

***However***

- Amyloid PET detects amyloidosis,
  not AD dementia
- not specific for clinical syndromes:
  - Normal aging
  - Lewy body dementia
  - Cerebral amyloid angiopathy
- Amyloid PET scans must be interpreted with care

Courtesy Keith Johnson

# Brain Autopsy Study Results: Broad, Spectrum of Amyloid Pathology




**Bielschowsky – Standard of truth (SOT)**

- Any region mean BSS score >1.5 = Abnormal
- All region means BSS scores ≤1.5 = Normal

imagination at work

Salloway, AD/PD 2013, under review



Challenge 5: Non-amnestic and atypical presentations

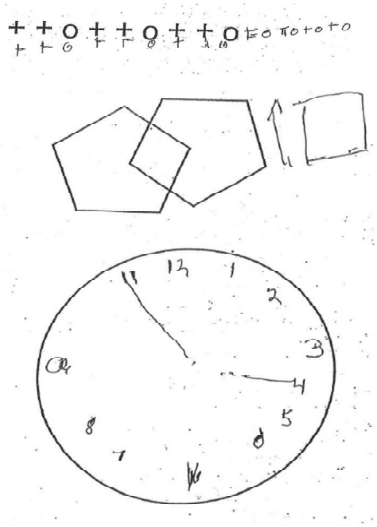
# AD Phenotypes

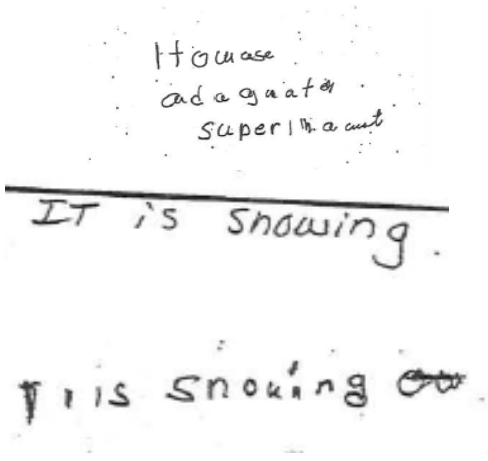
- Limbic and Cortical AD-78%
- Limbic predominant-11%
- Frontal variant
- Hippocampal sparing-11%
  - Progressive aphasia
  - Corticobasal syndrome
  - Posterior cortical atrophy

Murray, Lancet Neurology, 2011

- Video

MMSE 26
2/27/2013





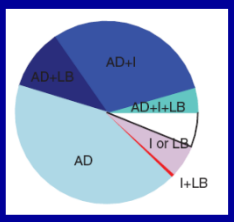
## Challenge 6: Assess the contribution of other medical conditions

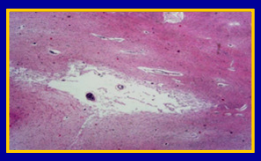
### Mixed dementia is the most common form of dementia

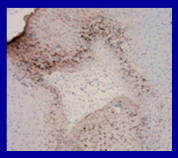
Cerebrovascular Disease and the Expression of Dementia in AD

- Among the AD-path cases
  - without infarcts: 57% demented
  - with infarcts: 93% demented
    - large infarct: OR 6.7 (0.9-48.3)
    - small infarct: OR 20.7 (1.5-288.0)
- The new criteria do not do a good job of integrating important co-morbid conditions

**Probable AD**



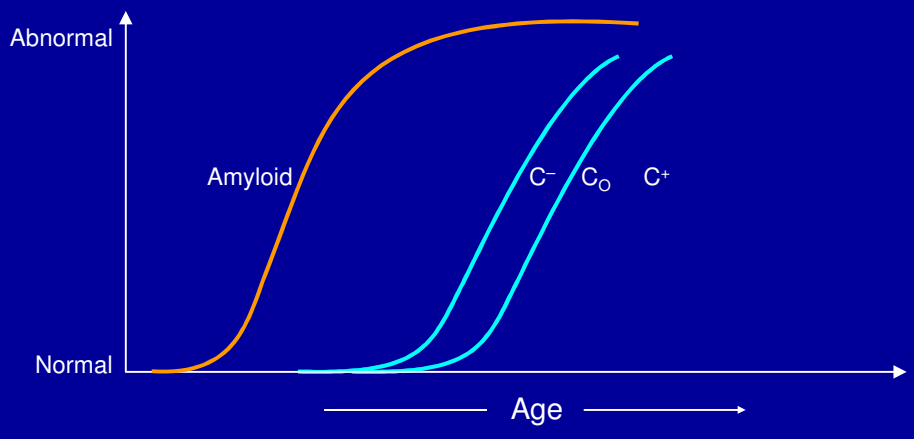





Snowdon et al. The Nun Study. JAMA 1997; 277: 813-817, Schneider Ann Neurol 2009

## Modulators of Biomarker Temporal Relationships

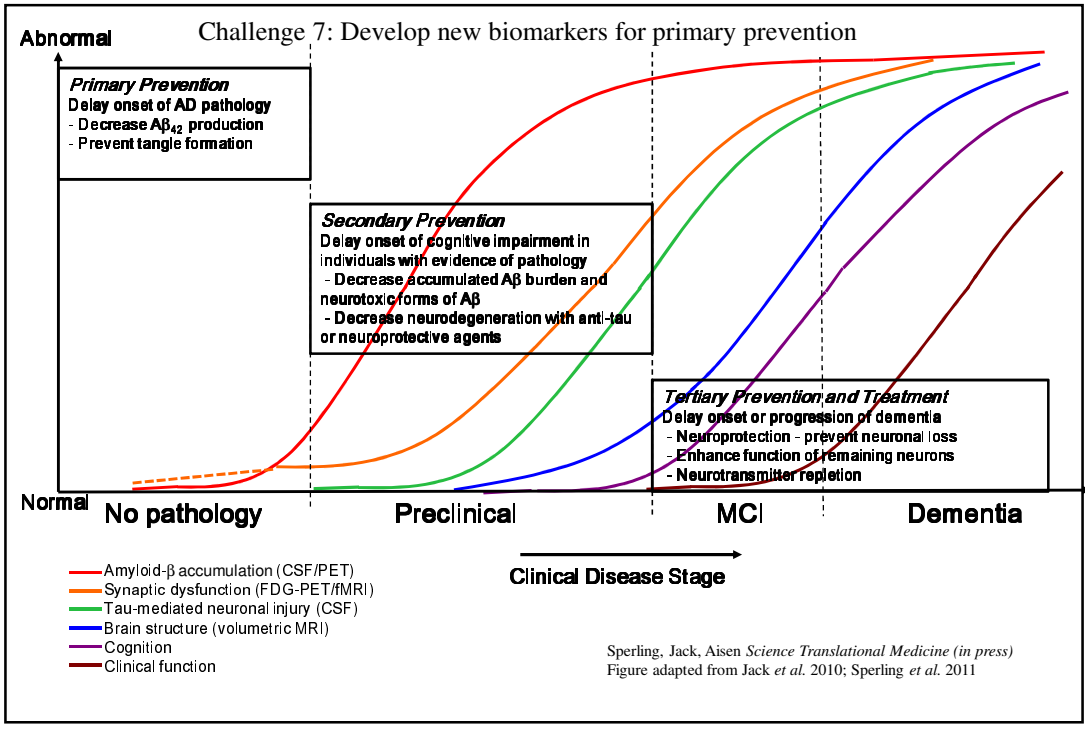
**$C^-$ = cognition in the presence of co-morbid pathologies (eg, Lewy bodies or vascular disease) or risk amplification genes**
**$C^+$ = cognition in subjects with enhanced cognitive reserve or protective genes**
**$C_O$ = cognition in subjects without co-morbidity or enhanced cognitive reserve**




**Jack et al: Lancet Neurol 9:119, 2010**

## Case 2: Mild Dementia with Co-Morbidity

- 85 yo woman with decline in short-term memory over 12 months
- Lives alone, drives, and plays cards daily at a senior center. Her daughter started paying her bills, after the gas was turned off
- Decline in her balance with falling and some shuffling, over 12 months, walking with a quad cane
- Some sx of depression and anxiety for 20 years




Sperling, Jack, Aisen *Science Translational Medicine (in press)*
Figure adapted from Jack *et al.* 2010; Sperling *et al.* 2011

Challenge 8: Ensure broad access and training

## Appropriate Use Criteria:

Patient characteristics

Amyloid imaging is appropriate in the situations listed below for individuals with all of the following characteristics:

1. A cognitive complaint with objectively confirmed impairment;
2. Alzheimer's disease as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and
3. When knowledge of the presence or absence of amyloid-beta pathology is expected to increase diagnostic certainty and alter management.

*Johnson et al., AA / SNMMI Amyloid Imaging Taskforce Report. Alzheimer's and Dementia, 2013*

## Appropriate Use Criteria:

Patient scenarios

Amyloid imaging is appropriate in the situations listed below

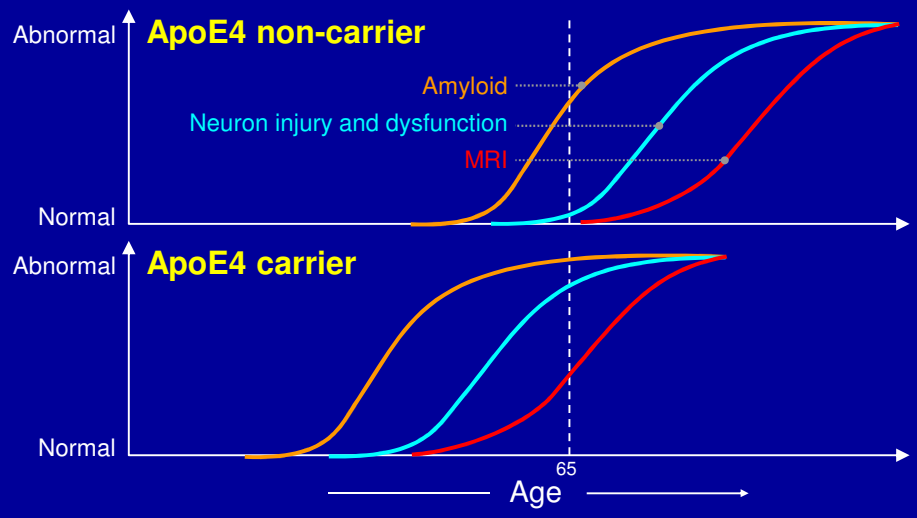
1. Patients with persistent or progressive unexplained mild cognitive impairment
2. Patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation, either atypical clinical course or etiologically mixed presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

*Johnson et al., AA / SNMMI Amyloid Imaging Taskforce Report. Alzheimer's and Dementia, 2013*

## Summary

## Back-up Slides

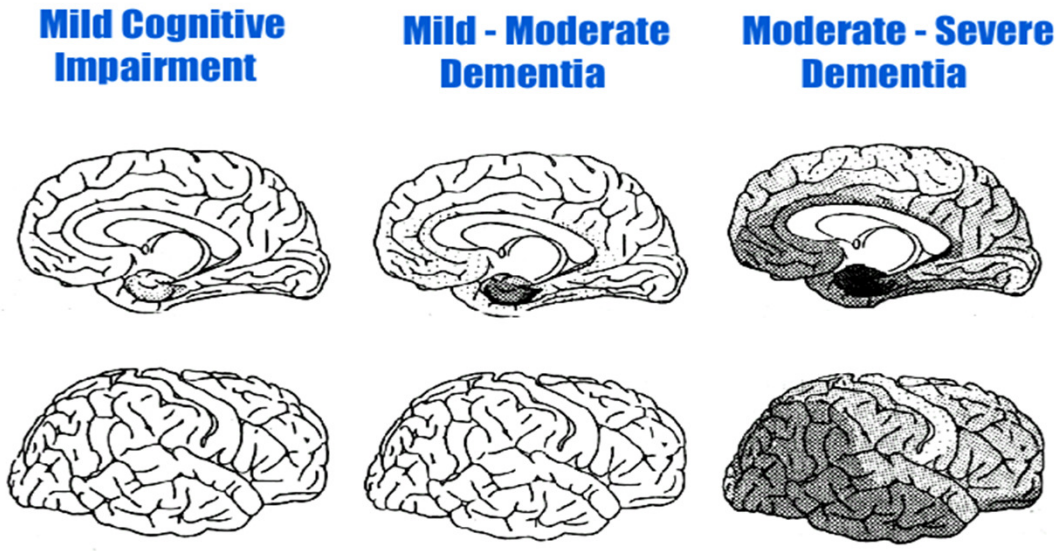
## Modulators of Biomarker Temporal Relationships




Jack et al: Lancet Neurol 9:119, 2010

Torii Hunter Diving for Big Papi ALCS Grand Slam 10/13/13

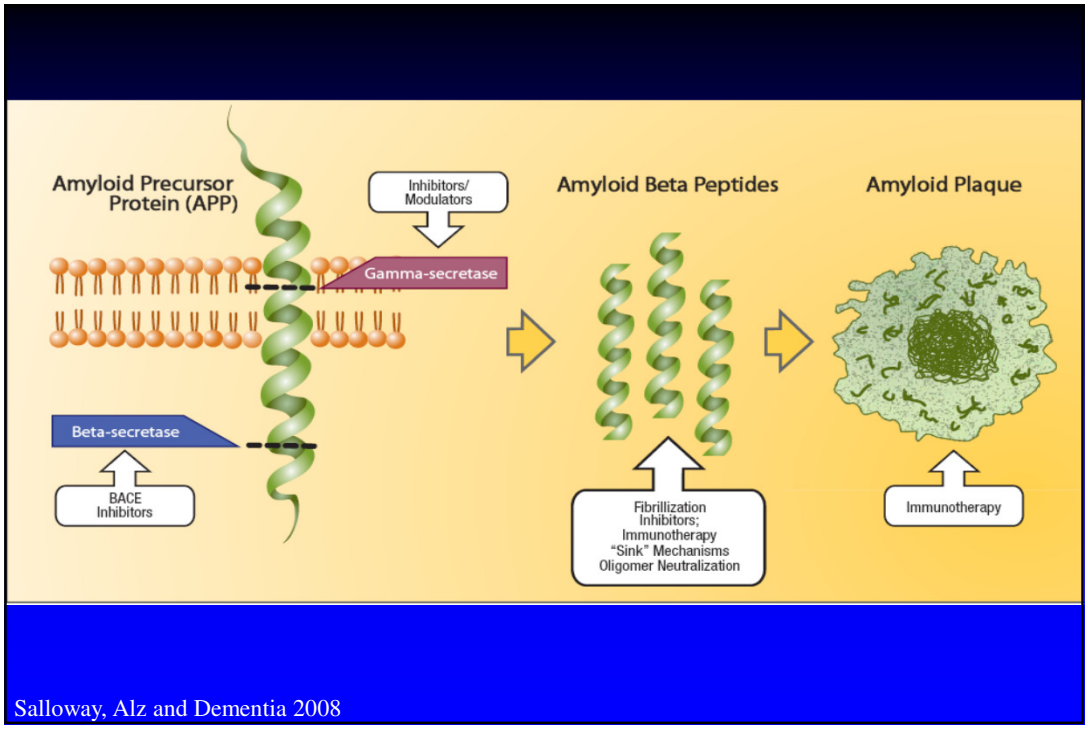
## Stages of Alzheimer's Disease



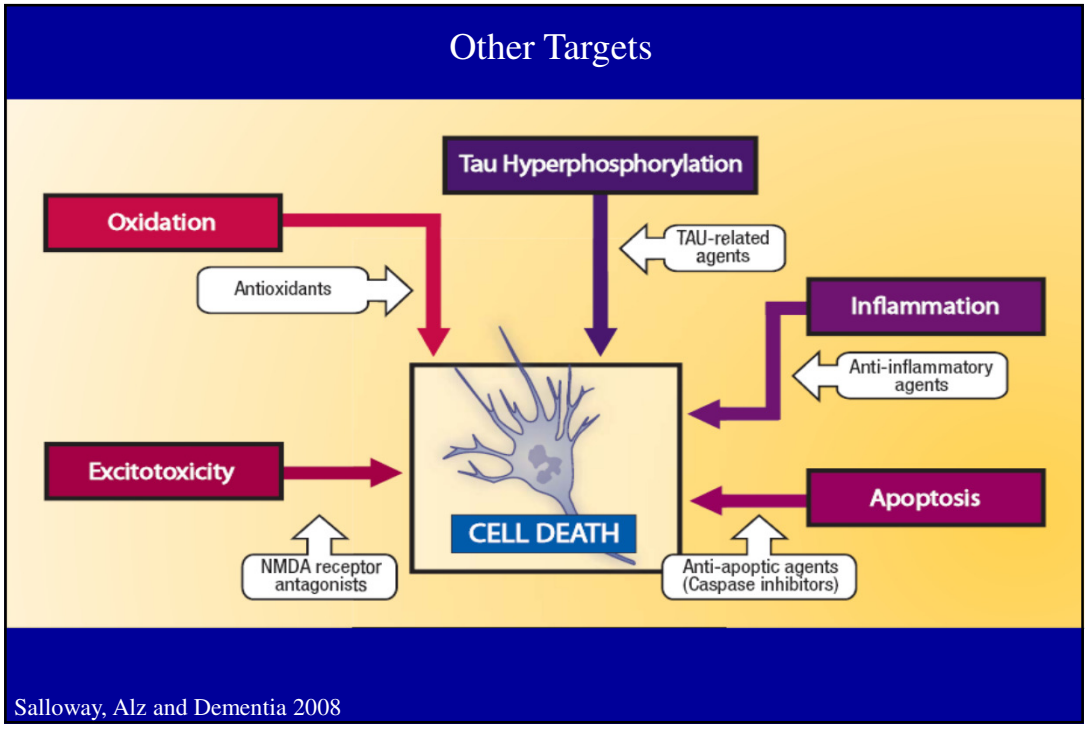

Based on Braak and Braak, 1994

## Urgent Need to Move Forward

- Growing wave of people at risk for AD
- Right drug(s), right time
- Combination treatments
- Forge public-private partnerships akin to a long-term Manhattan project to meet these goals
- Be persistent, innovative, and creative to identify novel targets and approaches

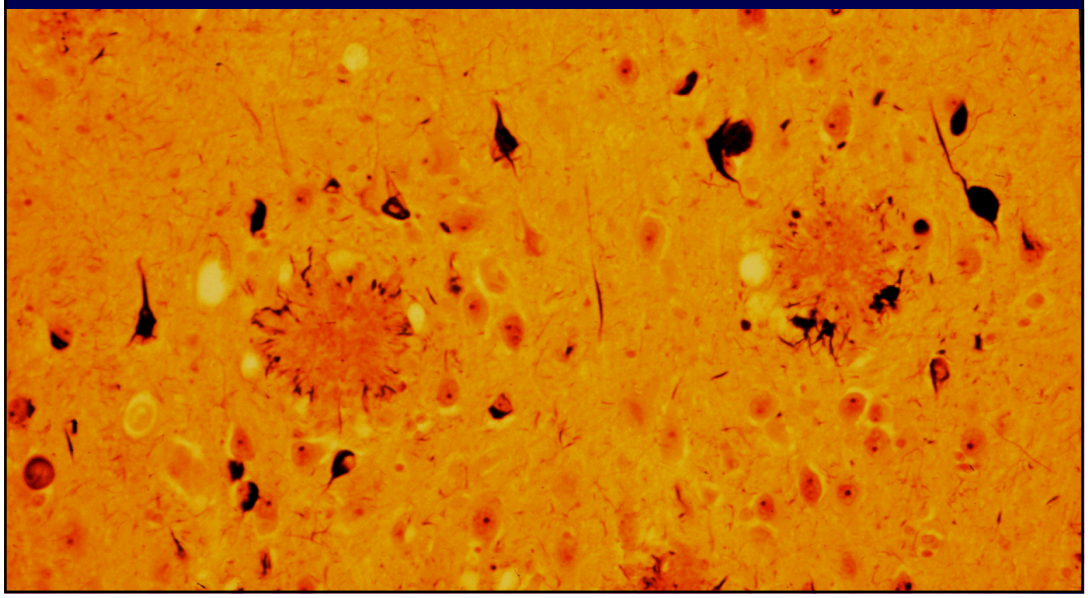



Salloway, Alz and Dementia 2008

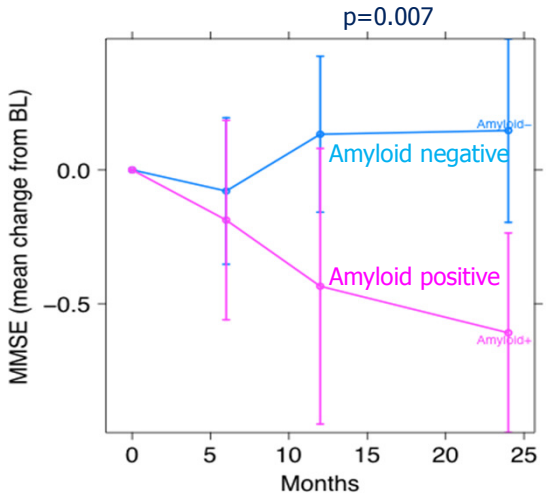



Salloway, Alz and Dementia 2008

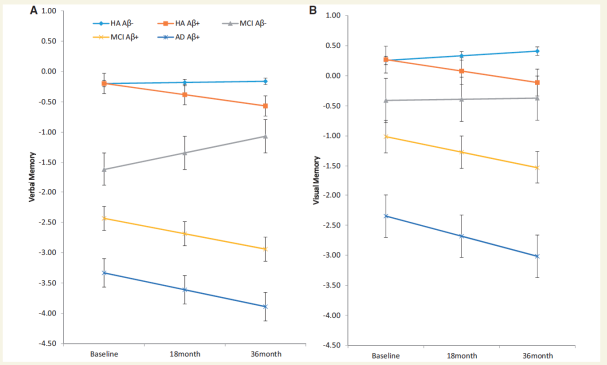
# Pathology of AD



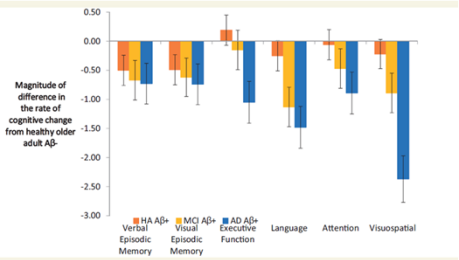
# MMSE change in normals is linked to amyloid



Change in Episodic Memory in AIBL*



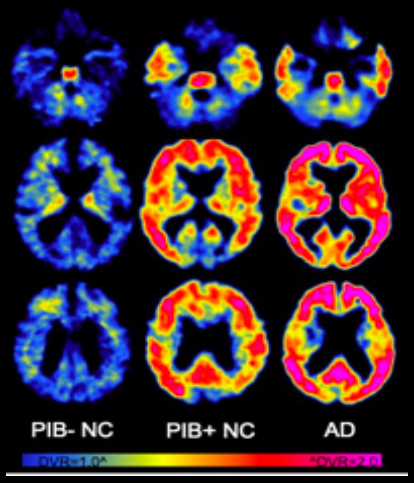

Change in Memory and other Cognitive Domains

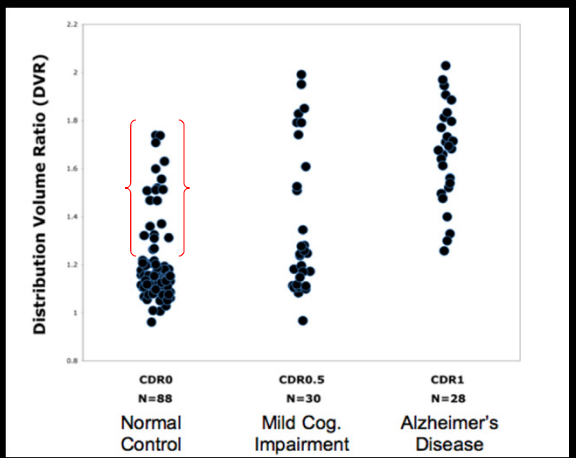



*Australian Imaging, Biomarkers and Lifestyle Study

Lim, Brain 2013

# Harvard Aging Brain Study
# PiB-PET Amyloid Imaging



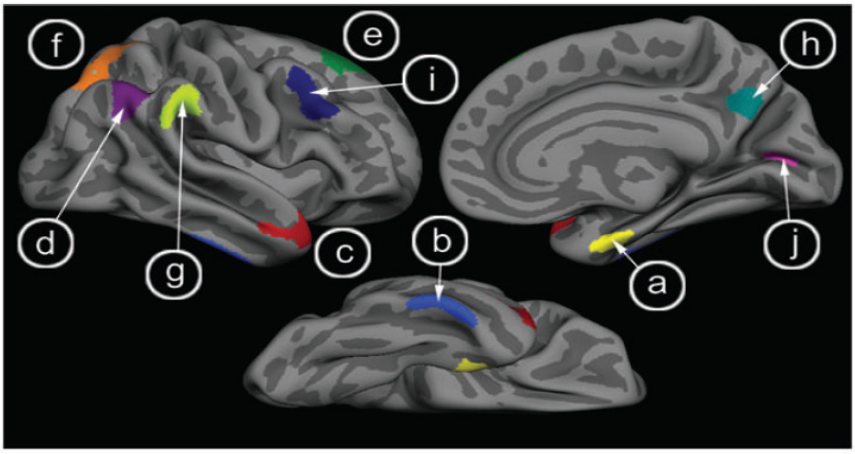




Amyloid + rate in normal elderly by age

| 60-64 | 65-69 | 70-74 | 75-79 | 80-84 | 85-89 |
|---|---|---|---|---|---|
| 6% | 13% | 22% | 25% | 47% | 37% |

Sperling R et al *NeuroMolecular Medicine* 2010

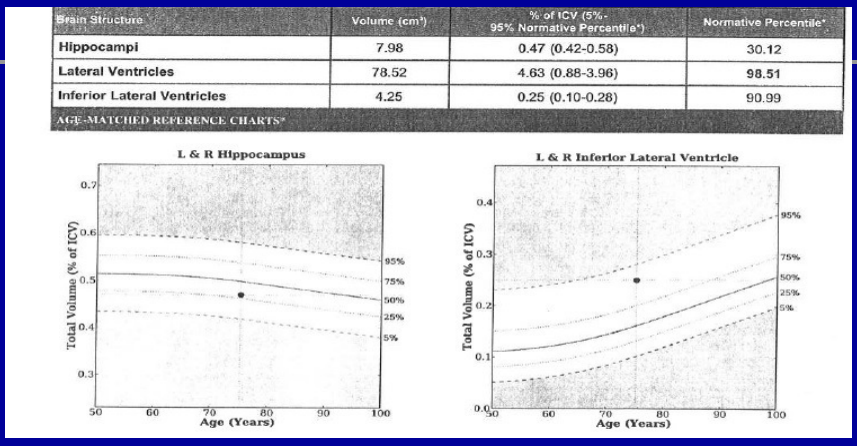
## Early Changes in Cortical Thickness Predict Cognitive Decline in ADNI Normal Controls




Dickerson Neurology 2012

## NeuroQuant 2010

| Brain Structure | Volume (cm³) | % of ICV (5%-95% Normative Percentile*) | Normative Percentile* |
|---|---|---|---|
| Hippocampi | 7.98 | 0.47 (0.42-0.58) | 30.12 |
| Lateral Ventricles | 78.52 | 4.63 (0.88-3.96) | 98.51 |
| Inferior Lateral Ventricles | 4.25 | 0.25 (0.10-0.28) | 90.99 |
| AGE-MATCHED REFERENCE CHARTS* | | | |




Hippocampal volume is 7.98 cc, 30th percentile for age. Temporal horn volume slightly enlarged-4.25 cc, 91st percentile. Lateral ventrical enlargement (LV percentile- 98.5). Left side has considerably more ventricular dilation and the anatomical distortion has led to some overestimation of the size of the left hippocampus. Visual inspection reveals qualitative entorhinal thinning.