

## Challenges in the Early Diagnosis of Alzheimer's Disease



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2<sup>nd</sup> Annual Early Alzheimer's Educational Forum  
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

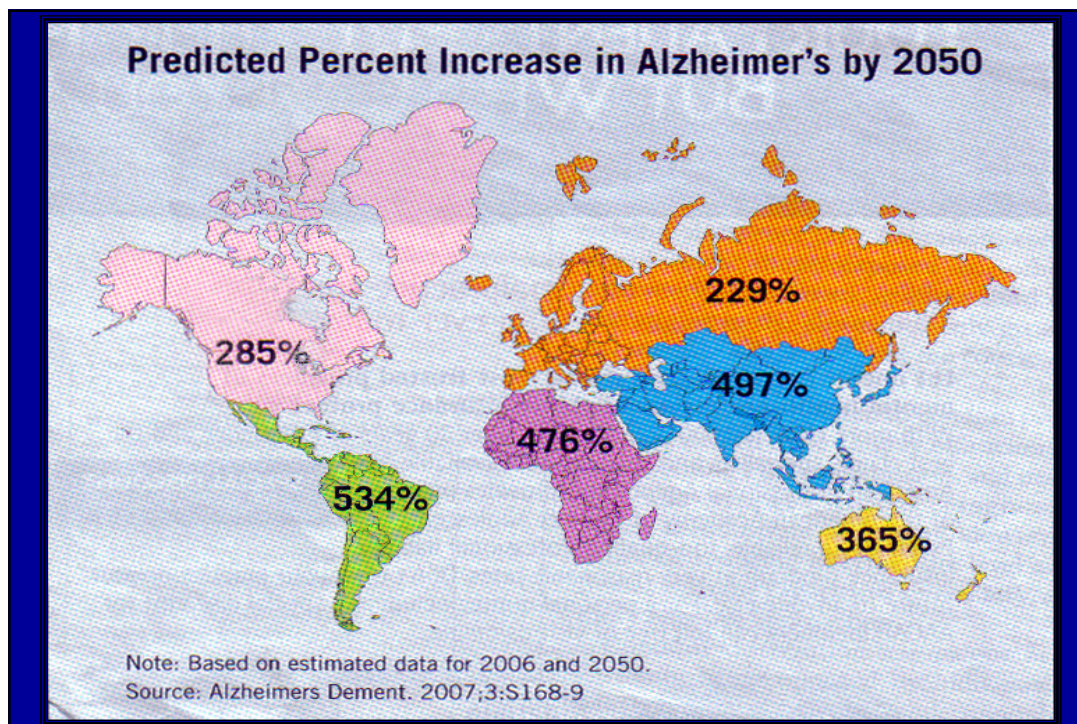


### Alarming Alzheimer's Statistics and Call to Action

- 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

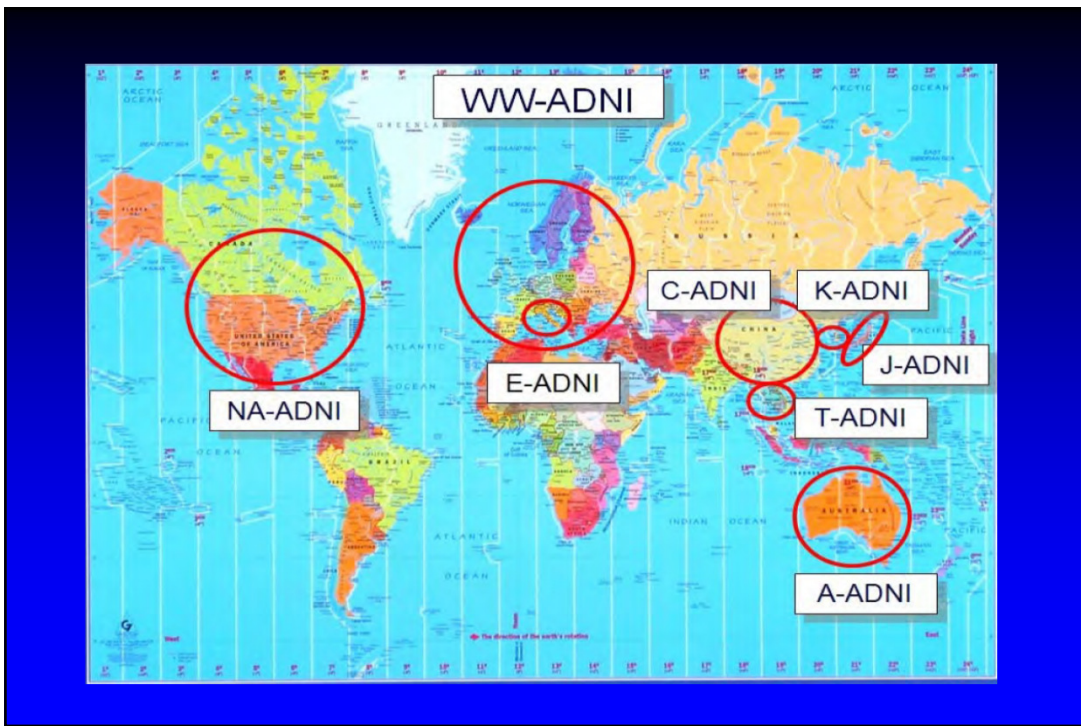




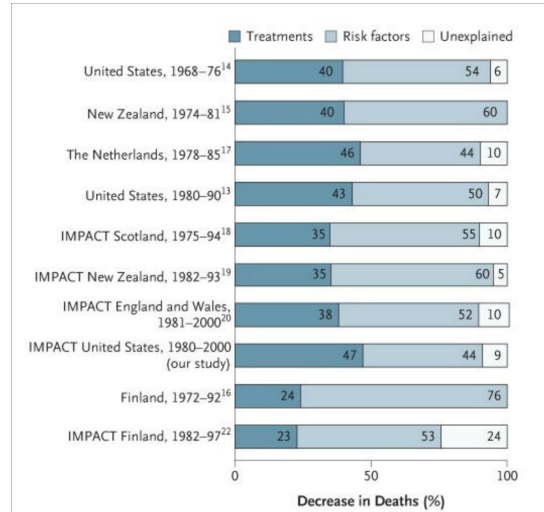
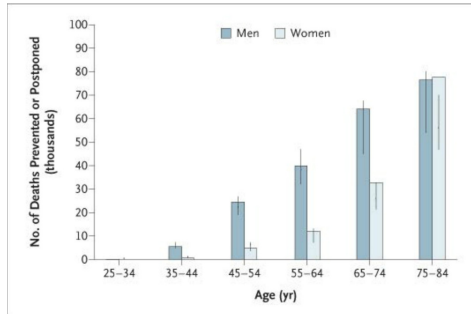
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Challenge 1: Develop broad public-private partnerships to build the research infrastructure to win the fight against AD



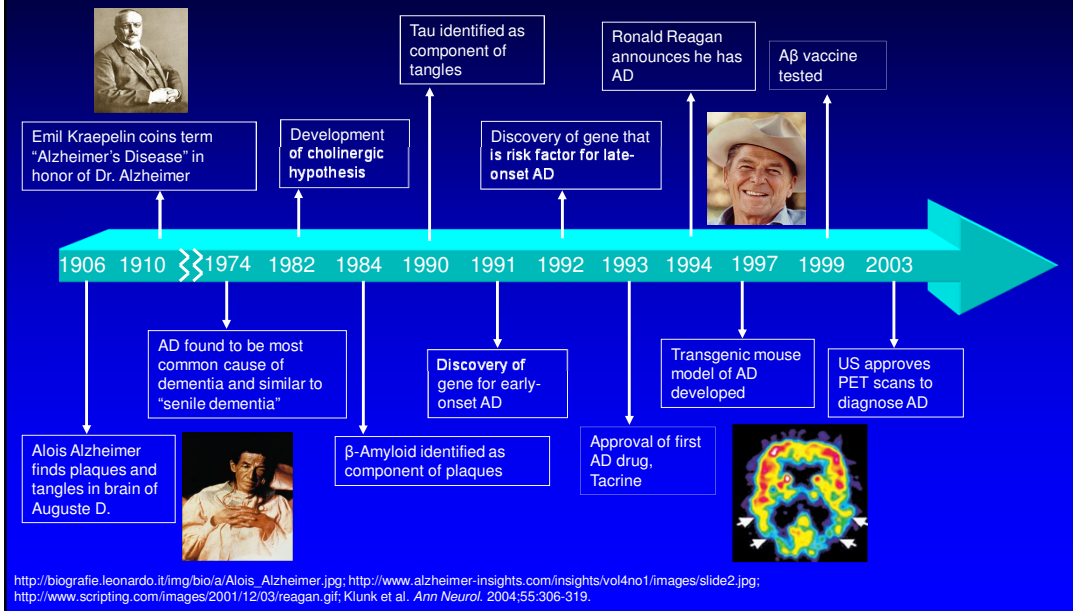


## Dramatic Decrease in Cardiac Deaths 1980-2000



Ford, NEJM, 2007

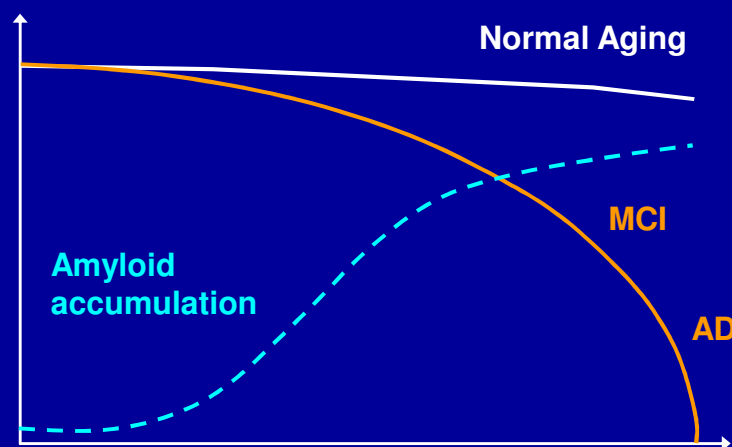
## Timeline of Alzheimer's Disease



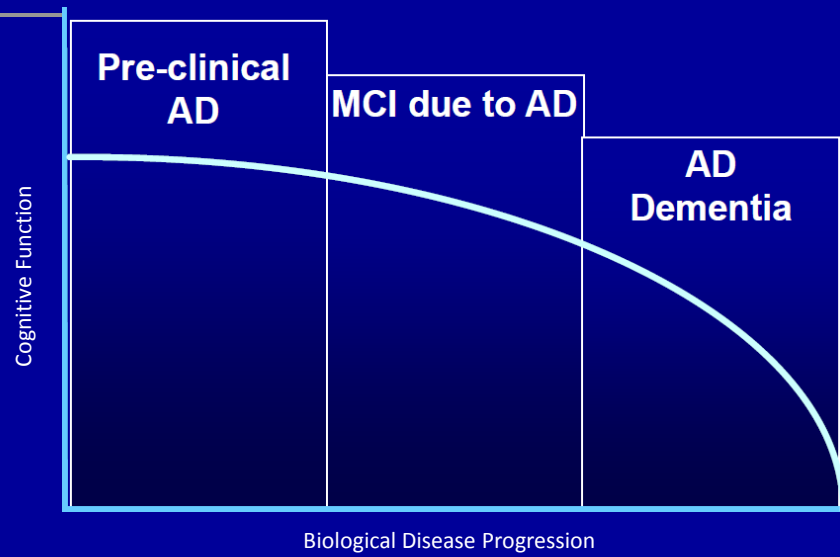
## Important New Developments

- Alzheimer's Disease Neuroimaging Initiative (ADNI) and Dominantly Inherited Alzheimer's Network (DIAN)
- FDA approval of first Amyloid PET imaging (Amyvid) for clinical use in 2012, flutemetamol and florbetaben under review
- First Tau PET tracers in clinical development
- Wide array of anti-amyloid agents in clinical trials
- New criteria for the diagnosis of preclinical and mildly symptomatic Alzheimer's disease
- Growing awareness of the public health impact of AD and development of a national plan
- Secondary prevention trials in people at risk beginning in 2013

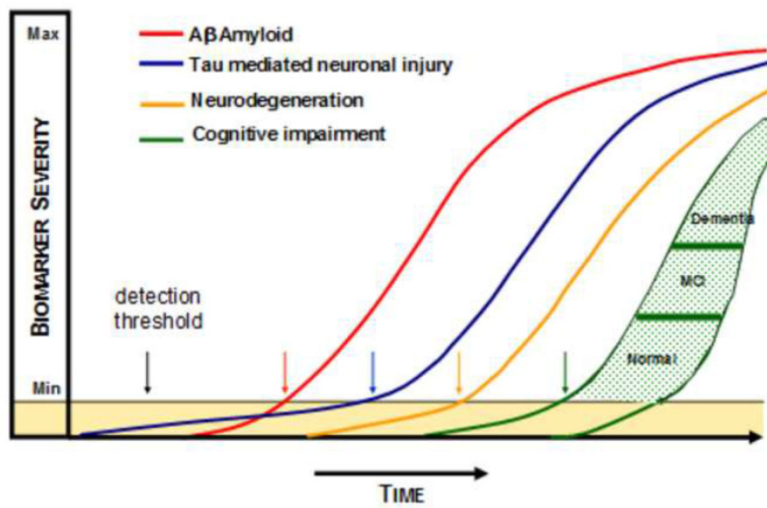
## Alzheimer's Disease Trajectory



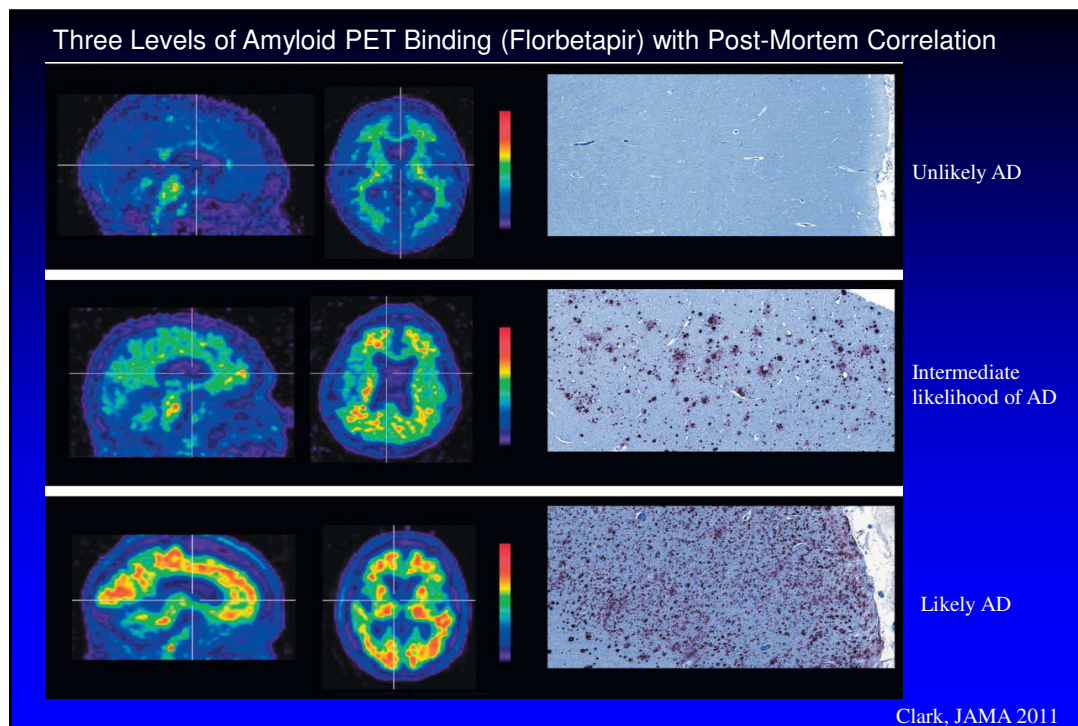
## Reconceptualizing Alzheimer's Disease



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



Jack Lancet Neurology 2013



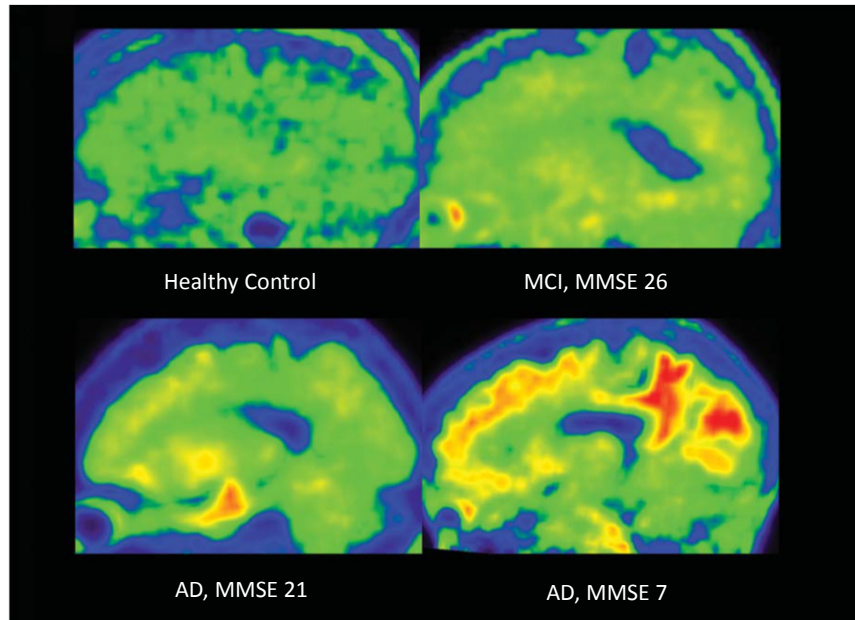
## DIAN amyloid PET

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Bateman, New England Journal of Medicine 2012



## Clinical Development of Tau PET



## Value of Concerns about Testing

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## 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

## Challenge 2: Promoting Healthy (Brain) Aging

- Determine and promote the factors that promote longevity and healthy brain aging
- Staying mentally and physically active
- Staying socially engaged
- Controlling CV risk factors-weight, BP, chol, blood sugar, stop smoking
- Eating a balanced diet, vitamins, nutrients, anti-oxidants, red wine-resveratrol



Challenge 3: 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

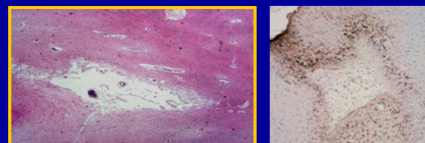
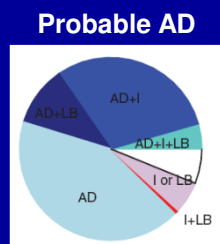
- Symptoms are occurring frequently and interfering with ADLs
- Being repetitive
- Not coming up with the names or words later
- Not recalling that conversations or events ever took place
- Not realizing that there is a memory problem

## Challenge 4: 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



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

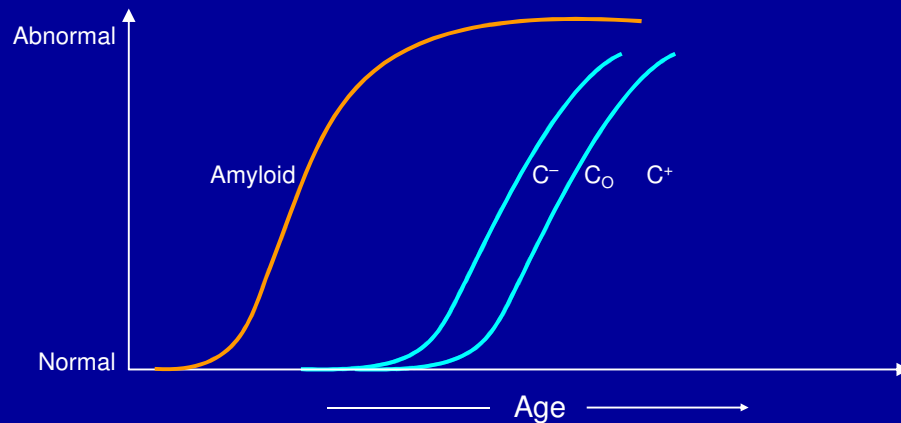


## Modulators of Biomarker Temporal Relationships

$C^-$  = 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

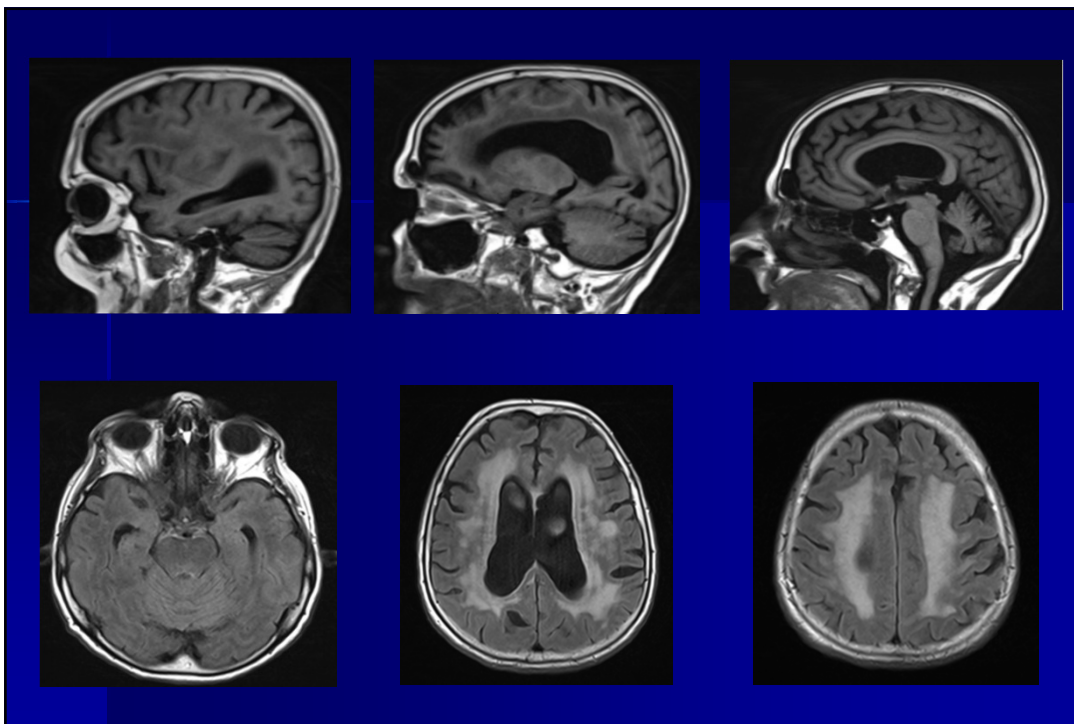
$C_0$  = cognition in subjects without co-morbidity or enhanced cognitive reserve



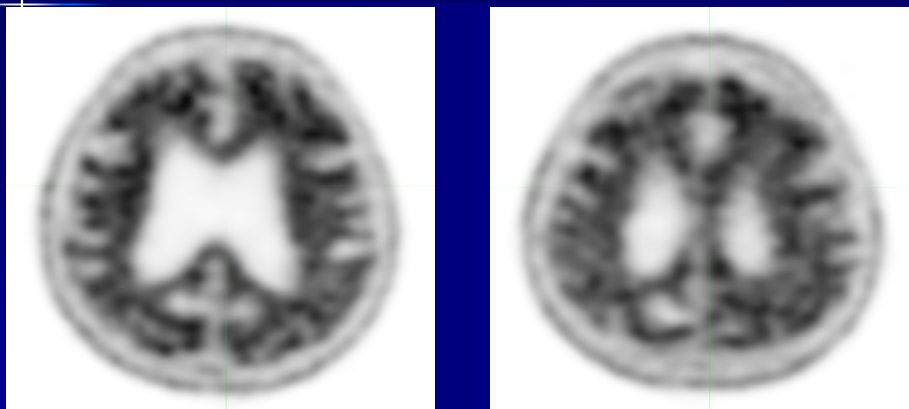
Jack et al: Lancet Neurol 9:119, 2010

## 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



Florbetapir PET, SUVr

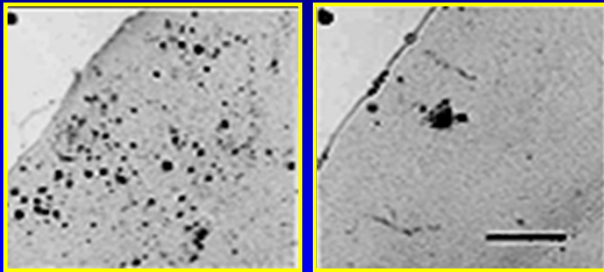


## Anti-amyloid Immunotherapy: Amyloid “Vaccine” Reduced Plaque Burden and Memory Loss in Transgenic Mouse Model of AD

### Amyloid Stain (Mouse Brain)

Unvaccinated

Vaccinated



### Immunization with amyloid- $\beta$ attenuates Alzheimer- disease-like pathology in the PDAPP mouse

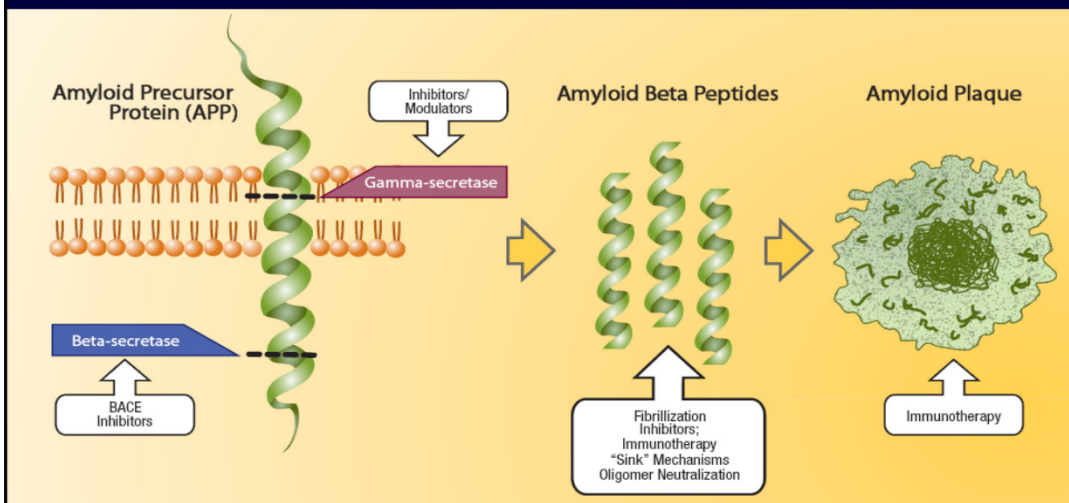
Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon,  
Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang,  
Kelly Johnson-Wood, Karen Khan, Dora Kholodenko,  
Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter,  
Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez,  
Christopher Vandeventer, Shannan Walker, Mark Wogulis,  
Ted Yednock, Dora Games & Peter Seubert

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California 94080, USA

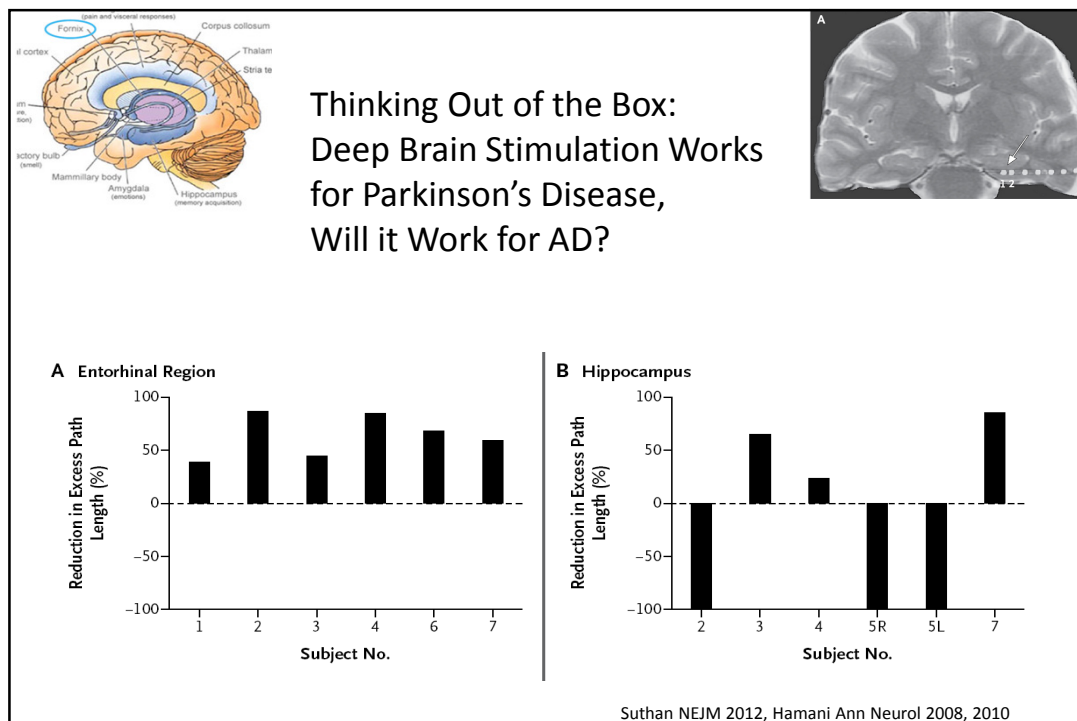
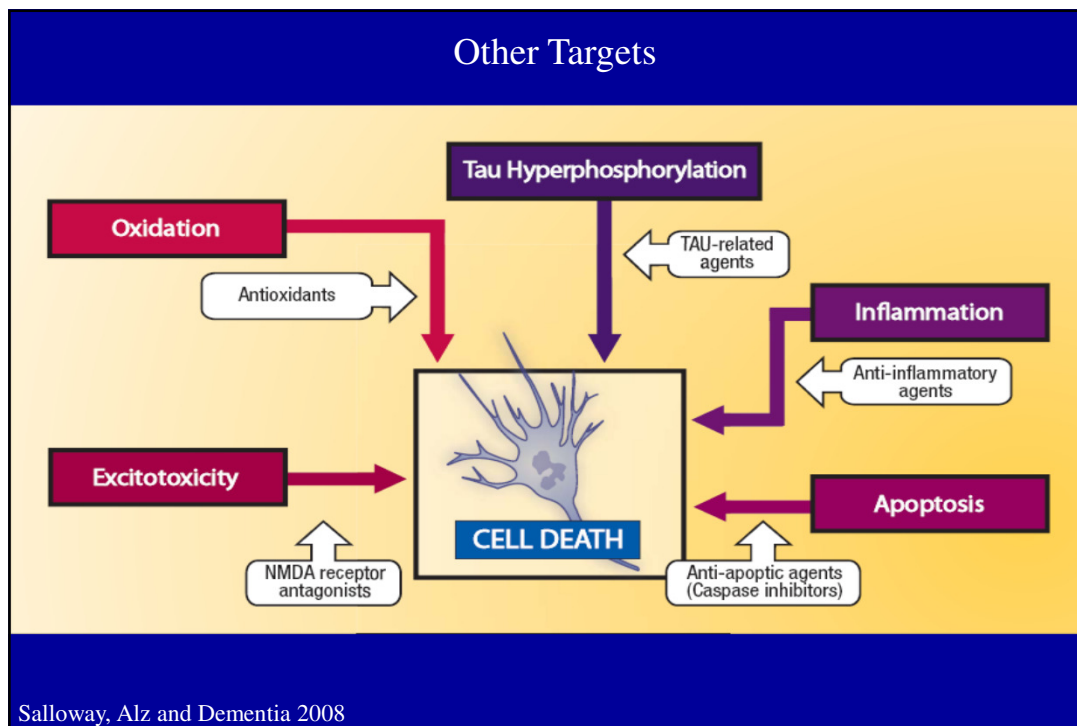
NATURE | VOL 400 | 8 JULY 1999

Morgan et al. *Nature*. 2000;408:982-985.

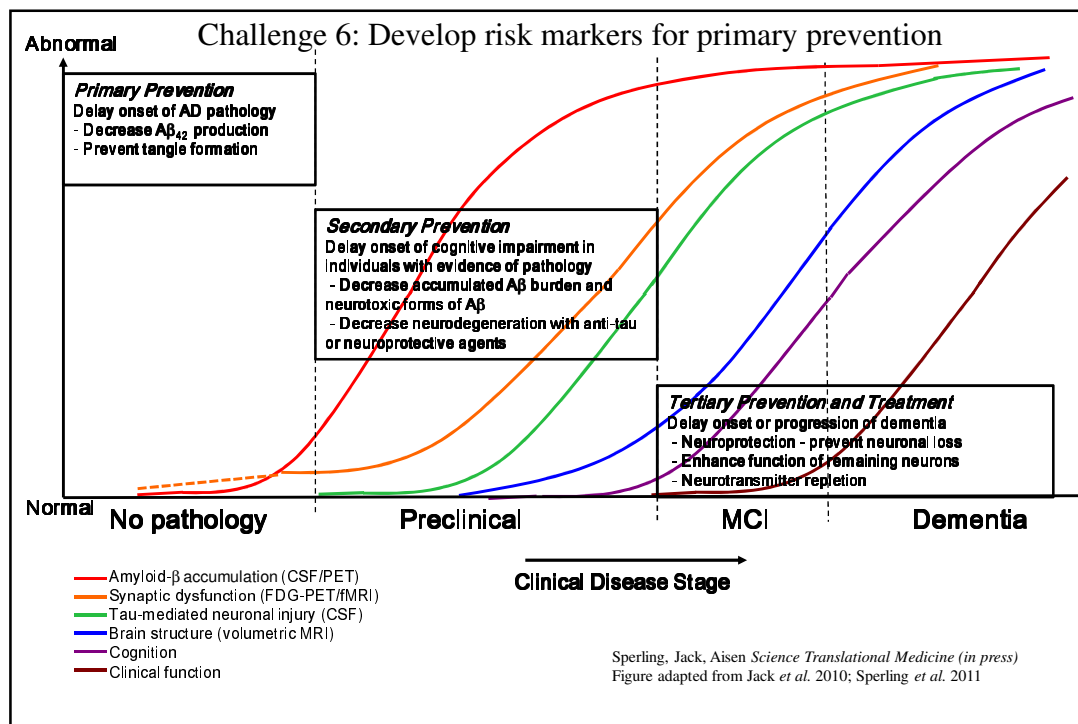
## Challenge 5: Develop new treatment targets and strategies for combining treatment



Salloway, *Alz and Dementia* 2008







**Challenge 7: Provide broad access and training in early diagnosis**



Juntos podemos hacerlo

Together we can do it



## Pathology of AD

