# Brain Changes in Asymptomatic Individuals with Autosomal-dominant Alzheimer's Disease

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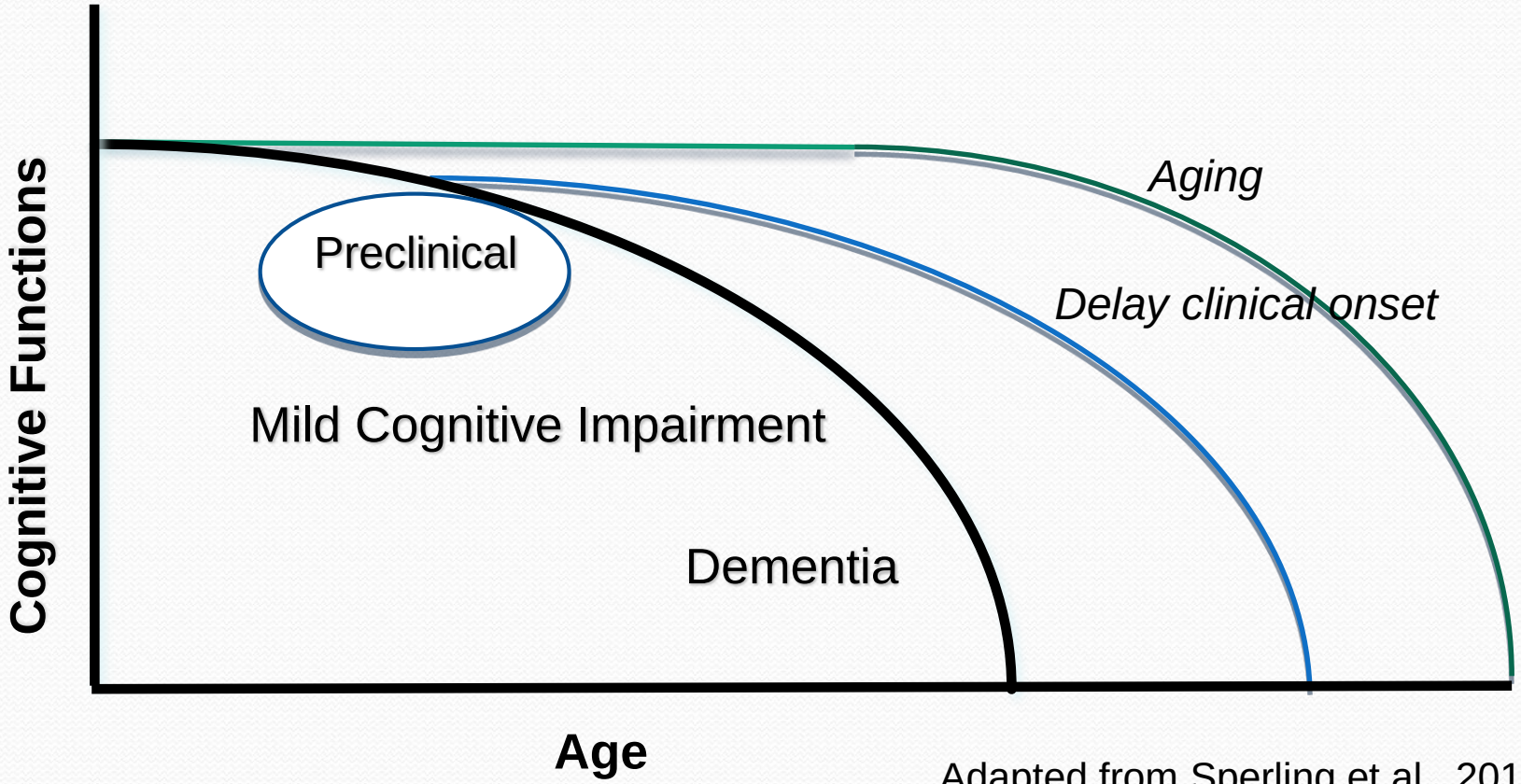
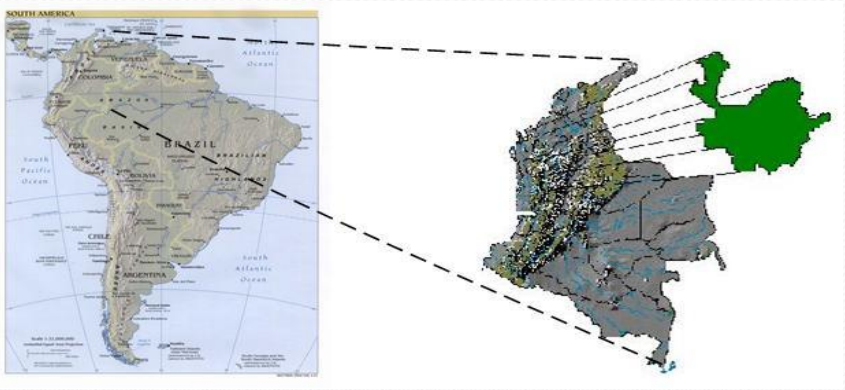
# Continuum of Alzheimer's disease




Adapted from Sperling et al., 2011

# A large extended family with early-onset AD in Antioquia, Colombia



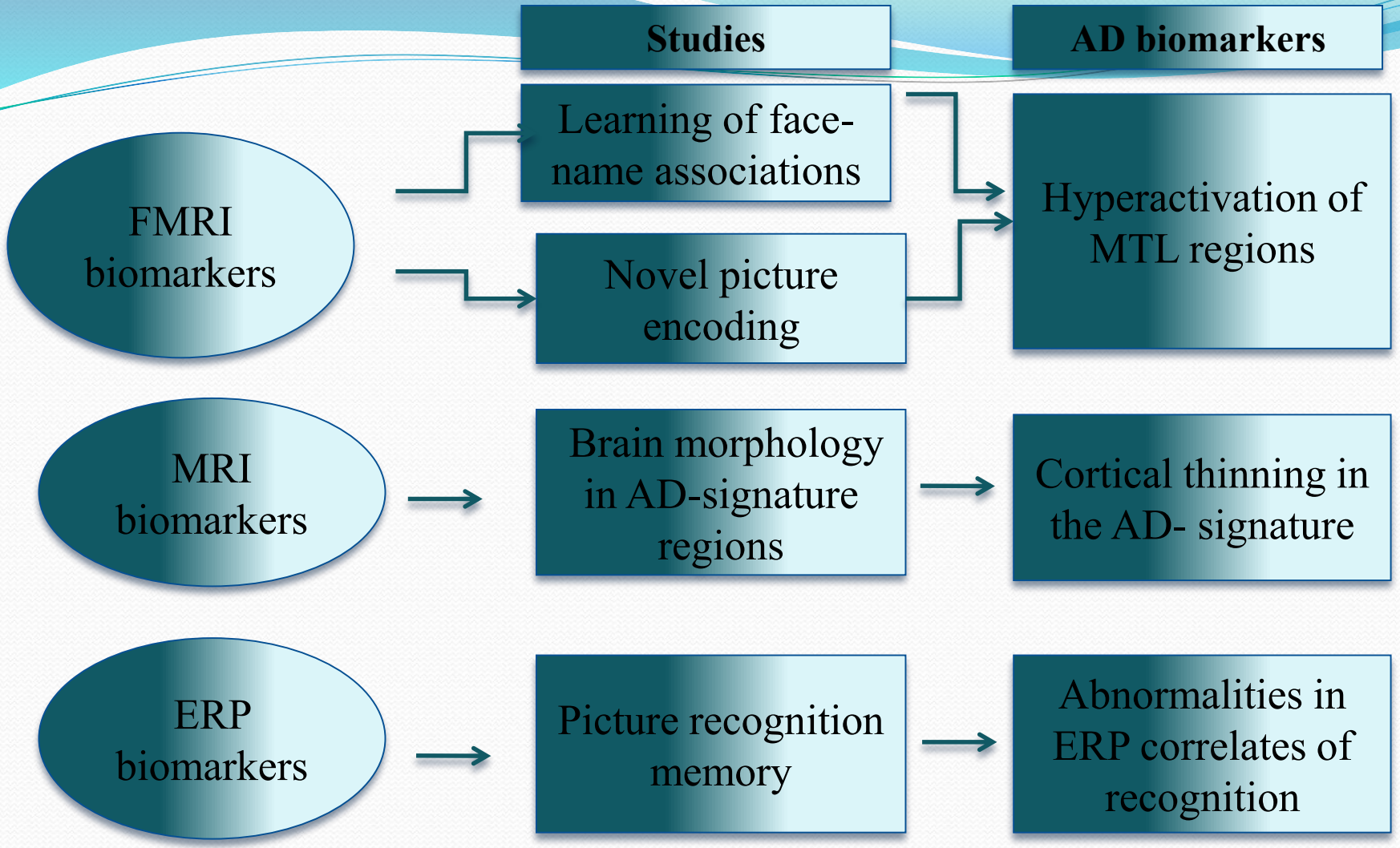


- Autosomal dominant AD (ADAD): A unique opportunity to examine early AD-related changes in cognitively-normal individuals.
- Presenilin-1 (*PSEN-1*) mutation carriers develop early-onset AD with near 100% certainty.
- The Colombian kindred has a median age of mild cognitive impairment (MCI) at 44 years (95% CI +/- 2 years), and dementia at 49 years (95% CI +/- 2 years).
- Clinical, cognitive and biomarker similarities between ADAD and late-onset Sporadic AD.

Lopera *et al*, JAMA 1997; Acosta-Baena et al, 2011

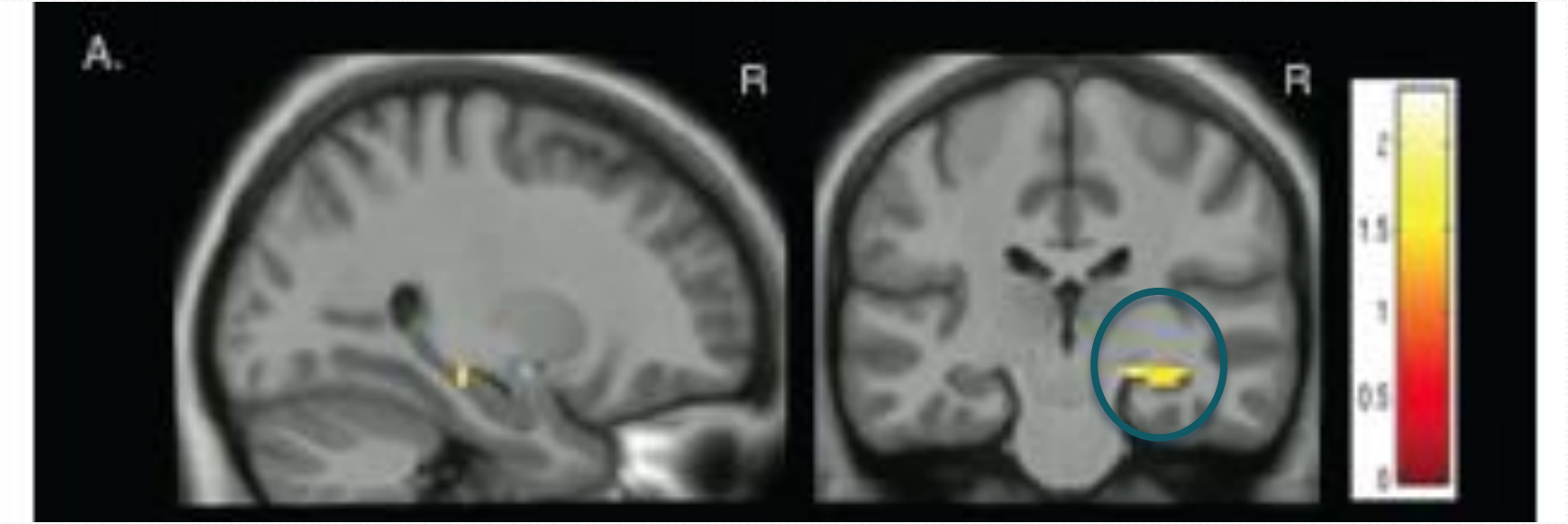
***Are there changes in the brain of mutation carriers years before the onset of AD symptoms?***

***What are the earliest brain changes associated with the predisposition to Alzheimer's disease?***


Studies
AD biomarkers
FMRI biomarkers
Learning of face-name associations
Novel picture encoding
Hyperactivation of MTL regions
MRI biomarkers
Brain morphology in AD-signature regions
Cortical thinning in the AD- signature
ERP biomarkers
Picture recognition memory
Abnormalities in ERP correlates of recognition

***Is brain hyperactivity one of the earliest signs of AD-related neurodegeneration?***

# Hippocampal Hyperactivation

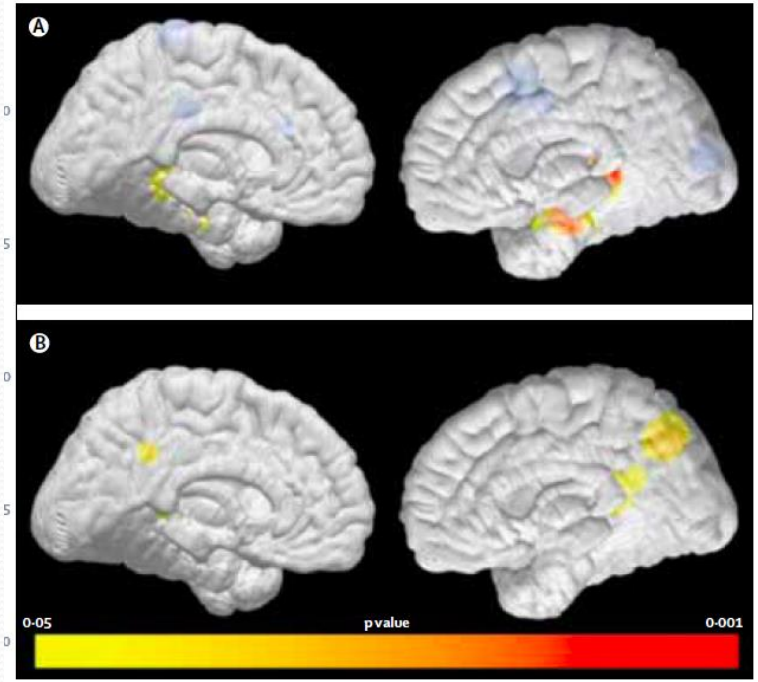



Statistical Parametric Maps (SPMs) for the comparison PSEN1 mutation carriers versus controls for the contrast novel face-name pairs versus repeated face-name pairs. Color bar represents *t*-statistic values for all activated voxels within the anatomical mask.

*Quiroz et al. (2010) Annals of Neurology*

# Younger group of carriers (18-25 years)

Carriers had greater right hippocampal and parahippocampal activation, and less precuneus and posterior cingulate deactivation



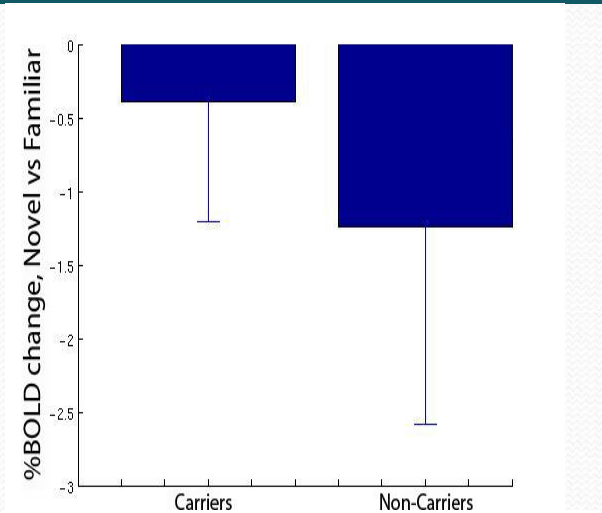
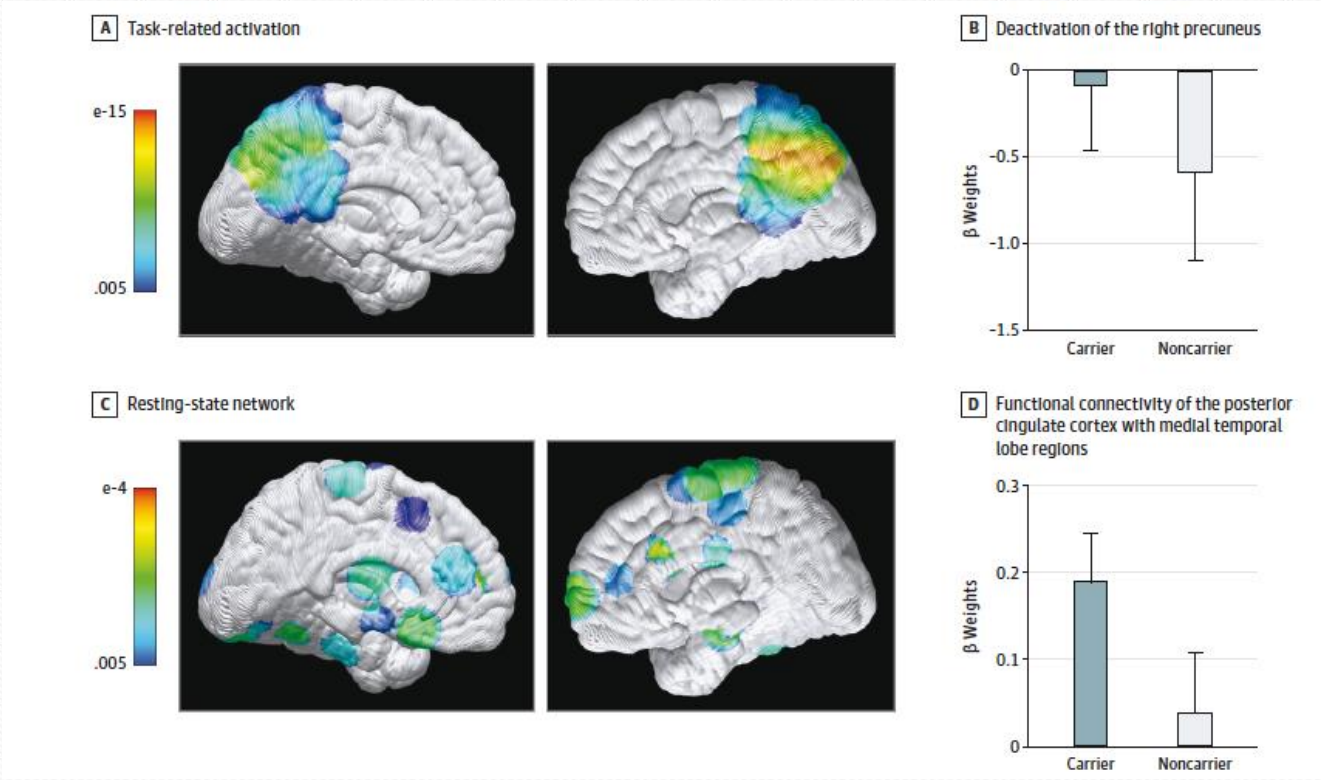




Figure 2. Reduced %BOLD suppression during face/name associated encoding in young pre-symptomatic E280A mutation carriers vs non-carriers (p=0.013).

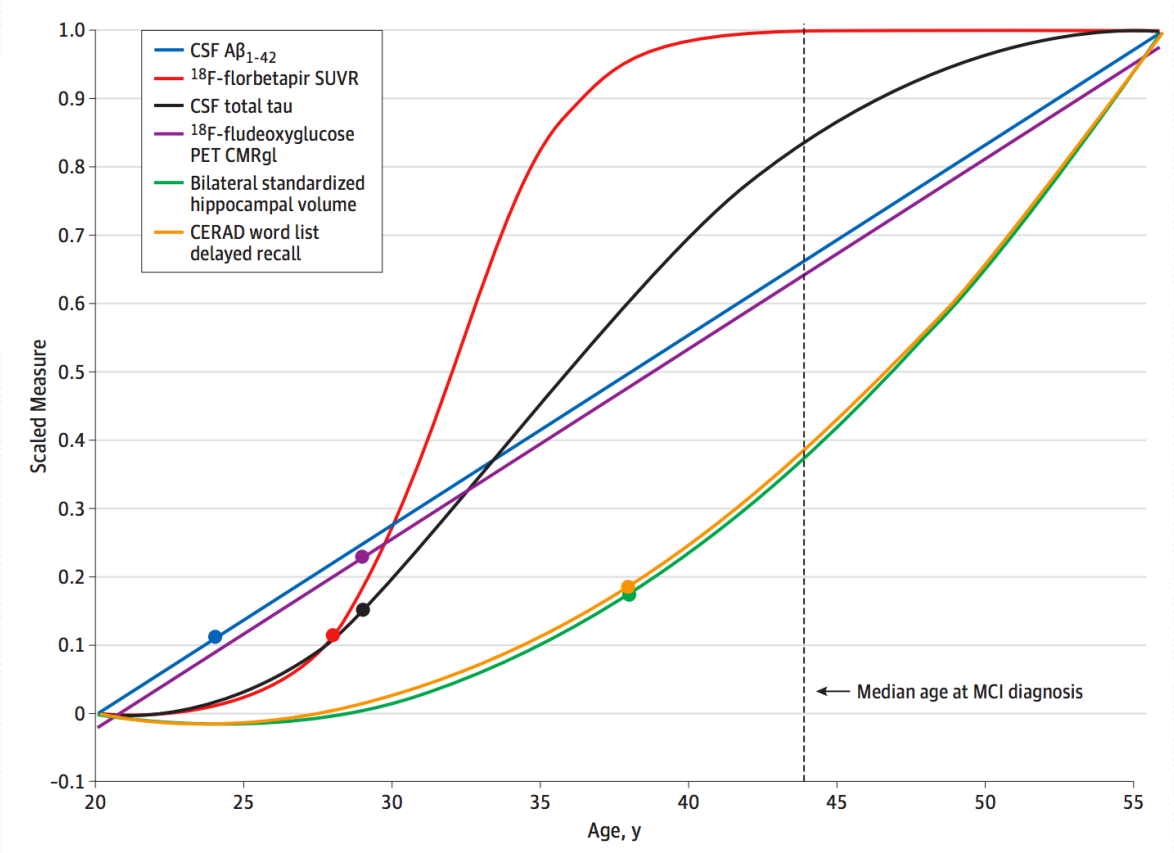
*Reiman, Quiroz et al. (2012), Lancet Neurology*

# Children/Adolescents (9-18 years)

## Carriers had less parietal deactivation (Novel>Familiar)



# Biomarker abnormalities in preclinical PSEN1 E280A carriers




Fleisher et al, 2012; 2015

ALZHEIMER'S PREVENTION INITIATIVE

# Objective:

To characterize the relationship between amyloid burden and tau accumulation in the brains of *PSEN1* E280A mutation carriers and non-carriers from the Colombian kindred with autosomal dominant AD.

Hypotheses being tested:

- Abnormal levels of tau will be evident in the brains of asymptomatic *PSEN1* mutation carriers.
- Amyloid- beta deposition will precede tau tangle formation both within and beyond the medial temporal lobe.

# Methods

19 members of the Colombian kindred with *PSEN1* mutation traveled to Boston (USA) for tau PET using [F18] AV1451 and amyloid PET using [11C] PIB. Ten mutation carriers aged 28-44, and 9 non-carriers were included.

| | MCI (n=2) (individual values) | Asymptomatic Carriers (n=8) | Noncarriers (n=9) | P-value |
|---|---|---|---|---|
| Age: mean (SD) | 43, 44 | 33 (5) | 38 (11) | 0.28 |
| Education | 5, 11 | 9 (4) | 11 (3) | 0.13 |
| MMSE | 18, 26 | 28 (1.4) | 29 (0.5) | 0.23 |
| CERAD Word List: | | | | |
| Immediate Learning | 8, 11 | 19 (5) | 22 (4) | 0.18 |
| Delayed Recall | 2, 7 | 7 (2) | 8 (1) | 0.21 |
| Semantic Fluency (Animals) | 14, 25 | 22 (6) | 21 (4) | 0.78 |

# Aβ pathology measured with mean cortical 11C PiB for *PSEN1* mutation carriers> controls

# [18F] AV1451 binding for *PSEN1* carriers and controls

# Conclusions:

# Limitations:

# Next Steps

- Characterize the relationship between tau deposition, decreased cognitive function, and neurodegenerative changes in preclinical ADAD.
- Compare the ability of tau biomarker measurements to predict subsequent cognitive decline in mutation carriers.
- Longitudinal study of tau biomarkers in preclinical ADAD.
- Compare findings from ADAD studies to preclinical late-onset AD (Harvard Aging Brain Study)

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***PSEN1***
***Colombian families***

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