The cortical signatures of Alzheimer's disease and Frontotemporal Degeneration: Quantitative MRI biomarkers detectable prior to dementia

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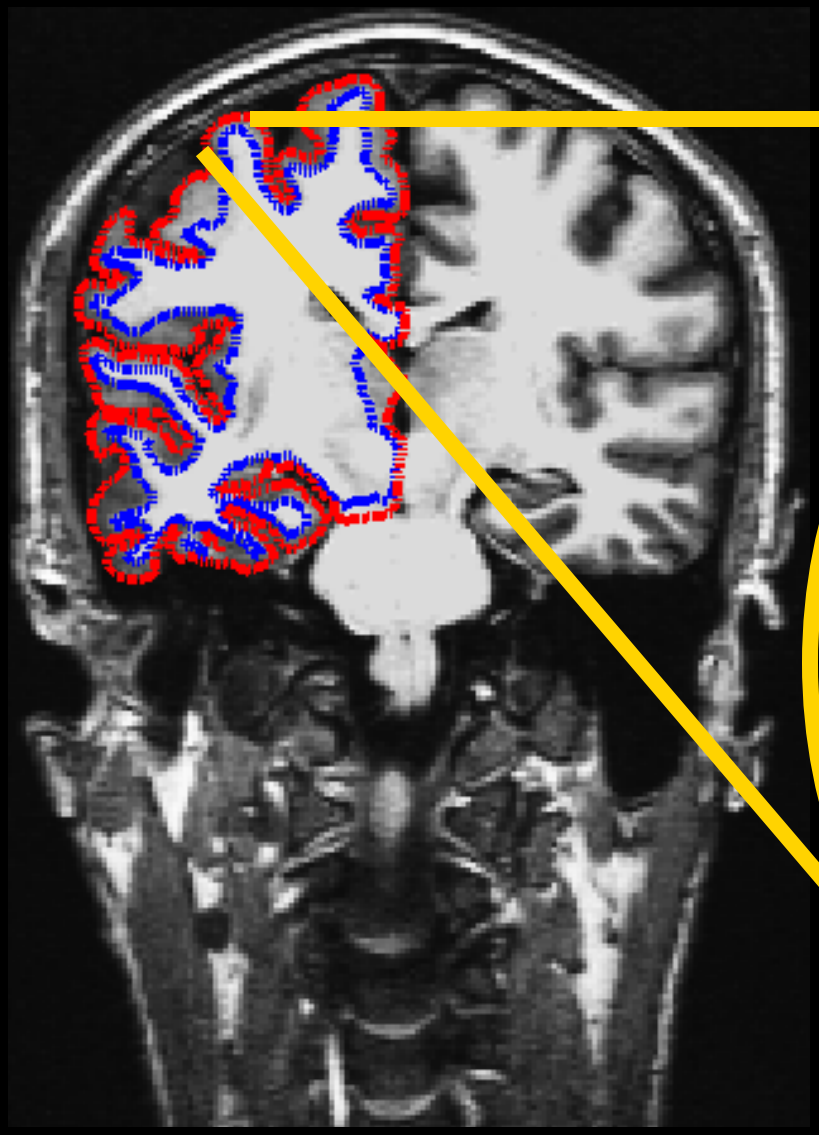
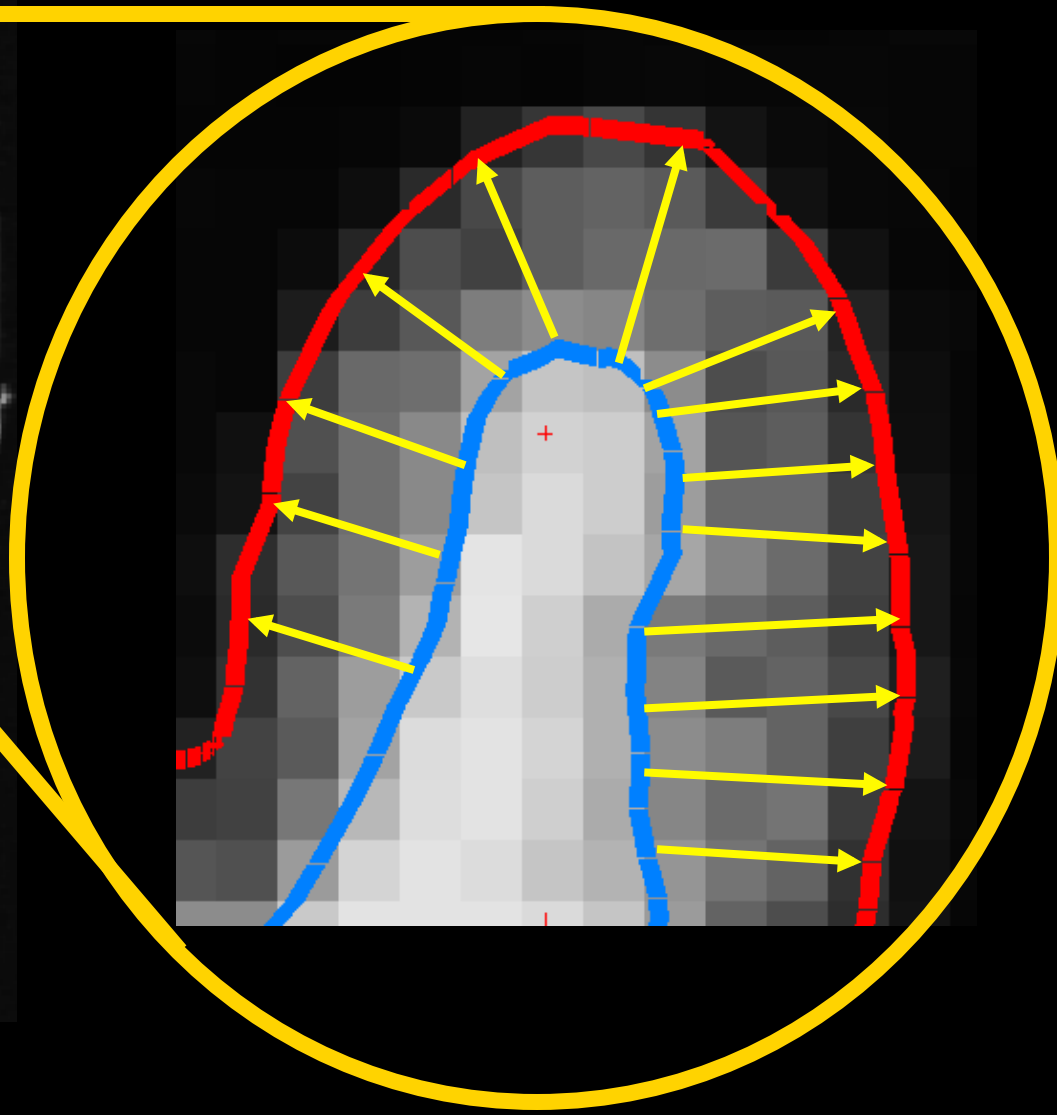
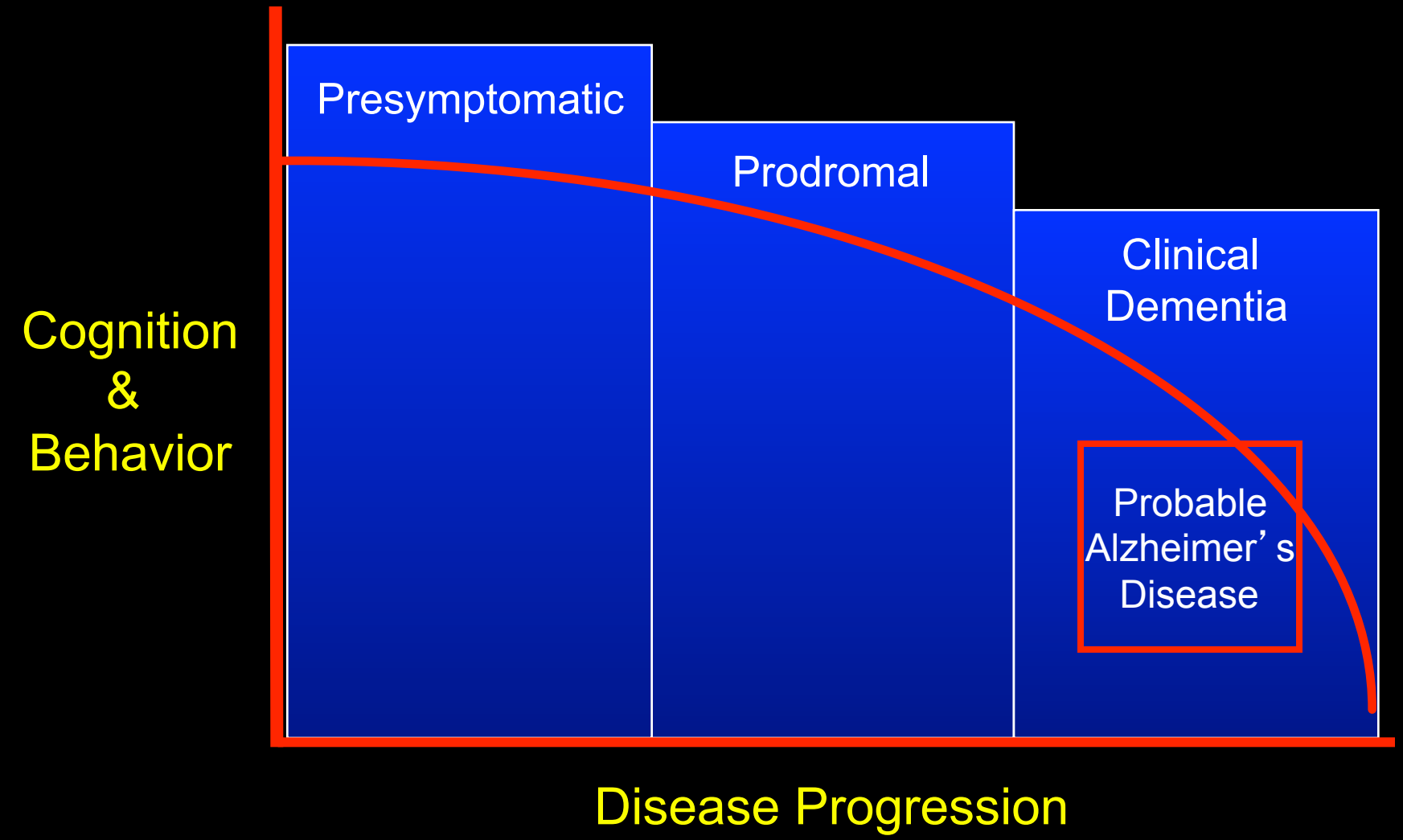
Cortical Thickness Measurement



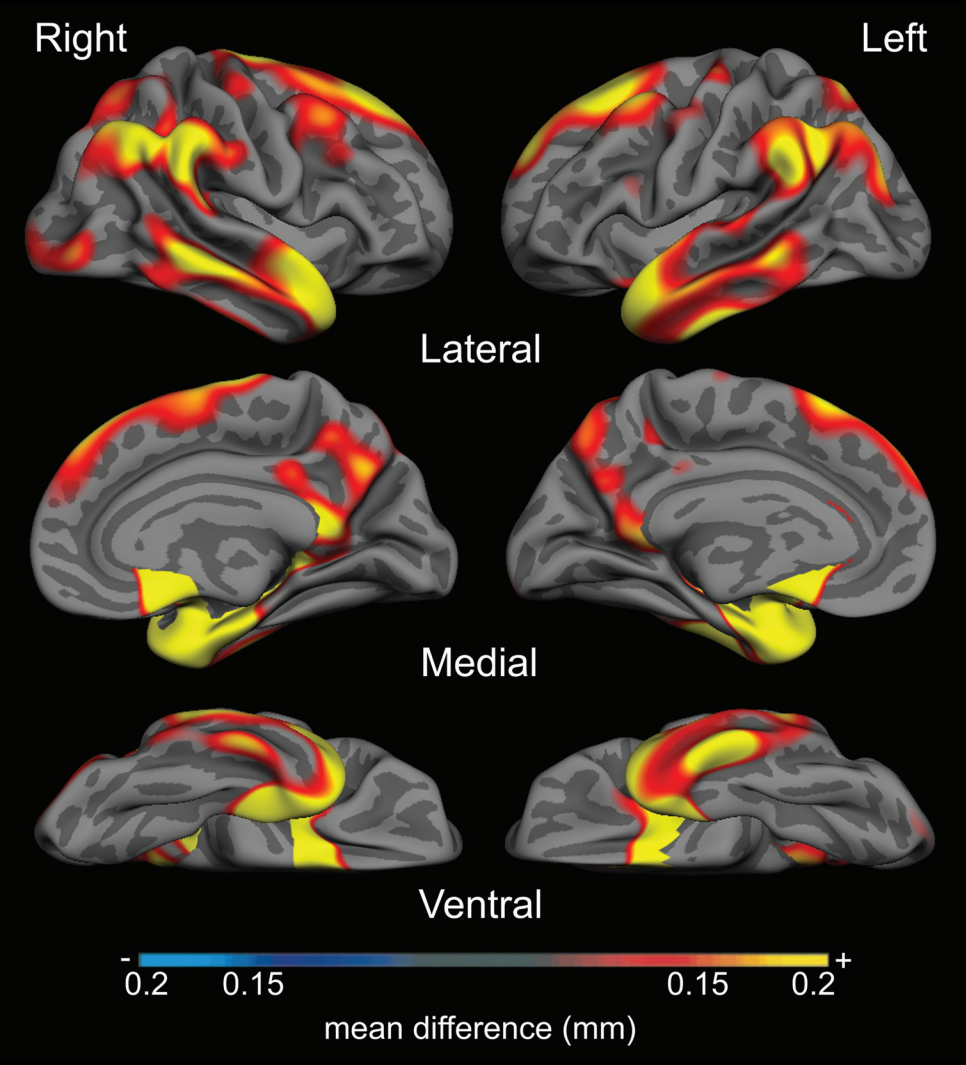


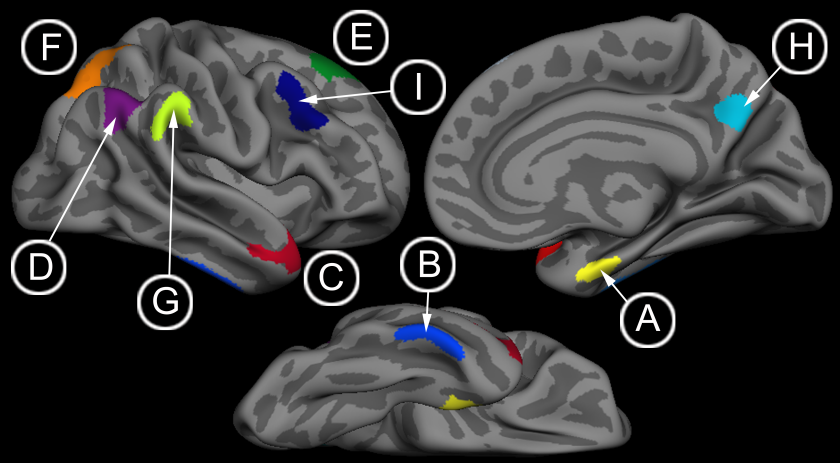
Fischl B et al, 1999/2000/2004

AD dementia


Presymptomatic
Prodromal
Clinical Dementia
Probable Alzheimer's Disease
Cognition & Behavior
Disease Progression

Cortical signature of AD: Exploratory whole brain analysis and ROI extraction



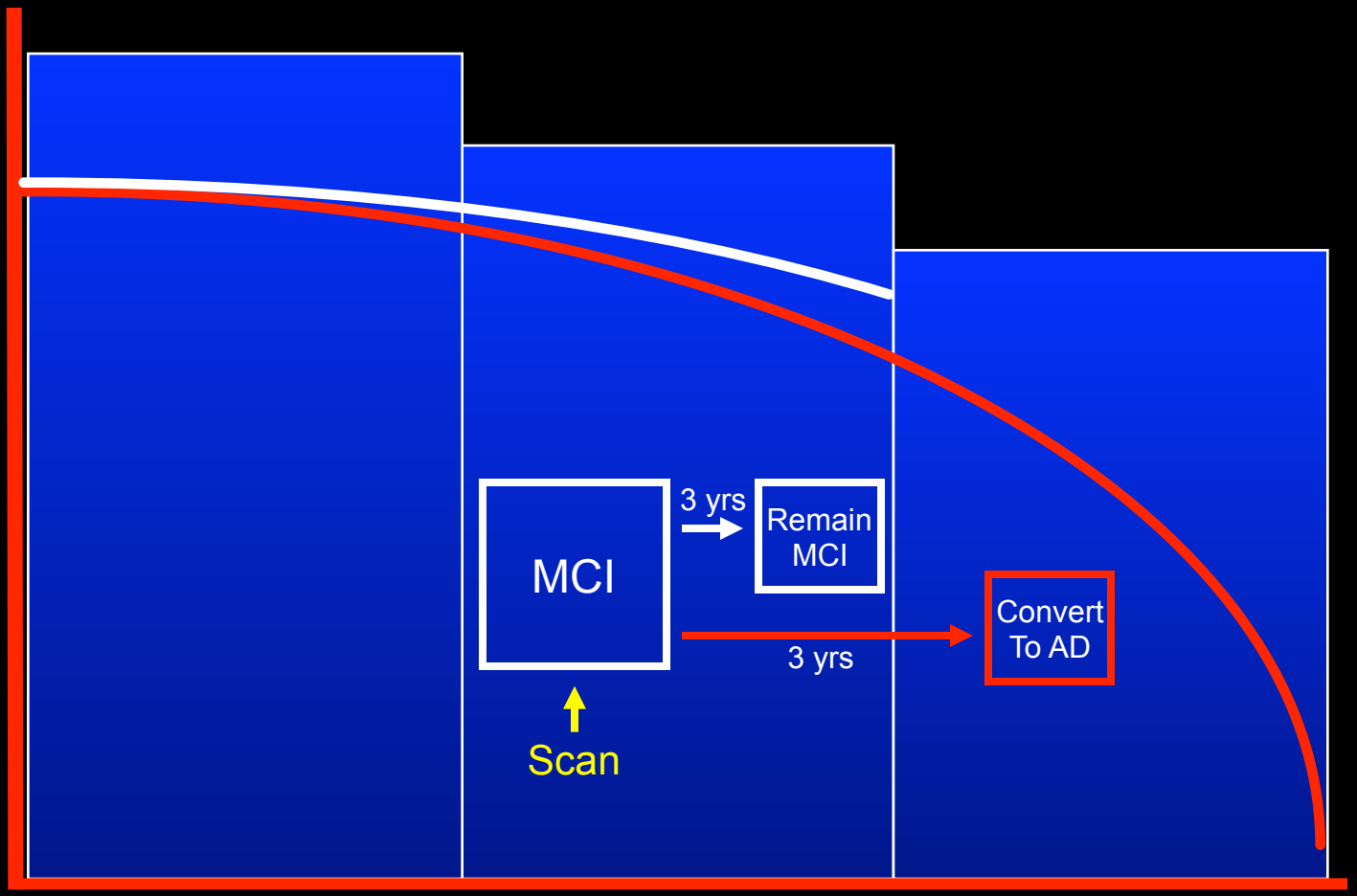


- Extracted ROIs from exploratory analysis in sample 1:

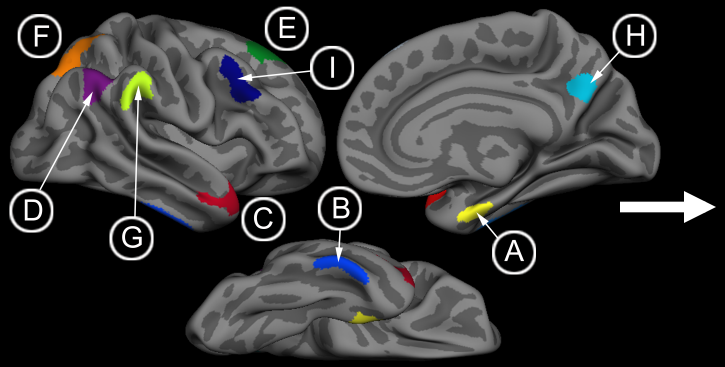
  115 OC (CDR=0) vs 29 AD (CDR=1)
- ROIs followed disease effects, not anatomical sulcal/gyral boundaries
- Reliable and valid

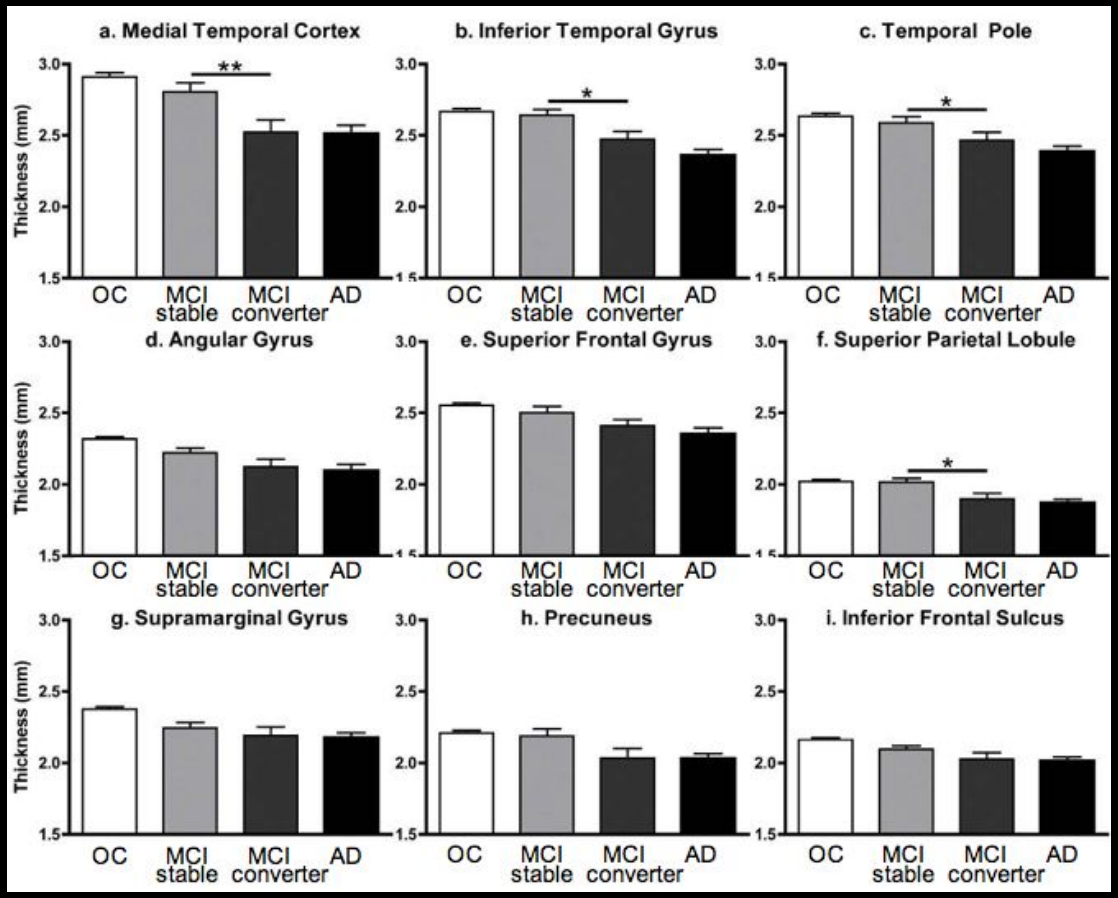
Dickerson et al, Cerebral Cortex 2009

MCI: Prodromal AD



The cortical signature of AD is detectable in MCI prior to conversion to AD dementia

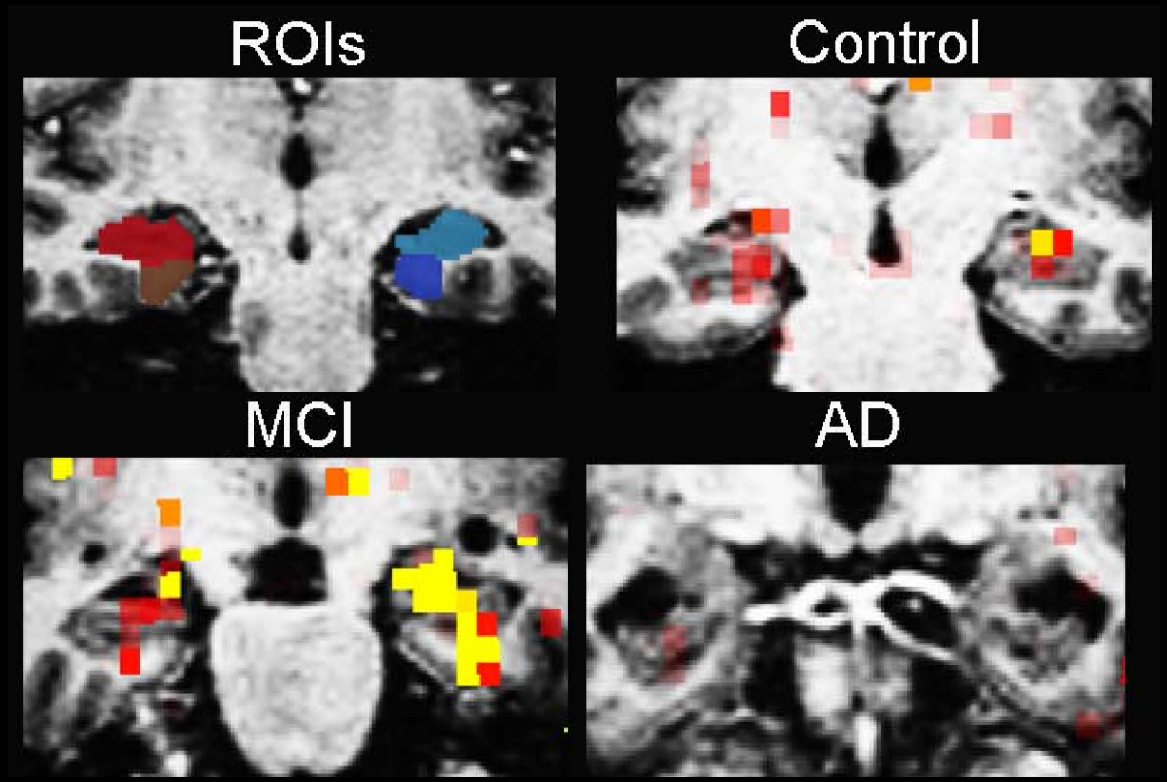




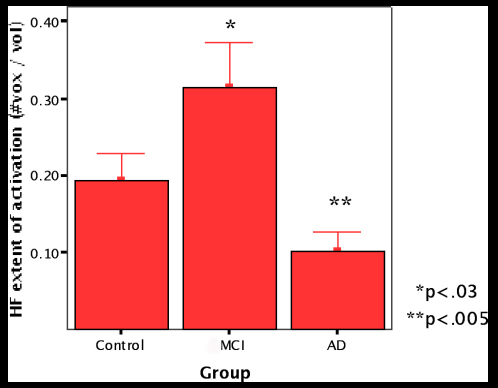
- In some regions, MCI converters suffer as much atrophy as mild ADs, but this is not true for all regions
- ROC: better than WBV, hippo vol at discriminating

Bakkour et al, Neurology 2009

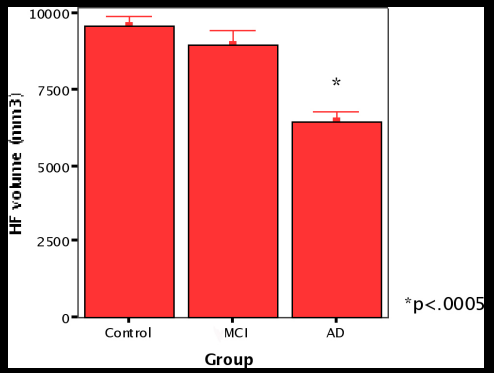
Hyperactivation in MCI: Increased hippocampal activation during memory task performance



Activation

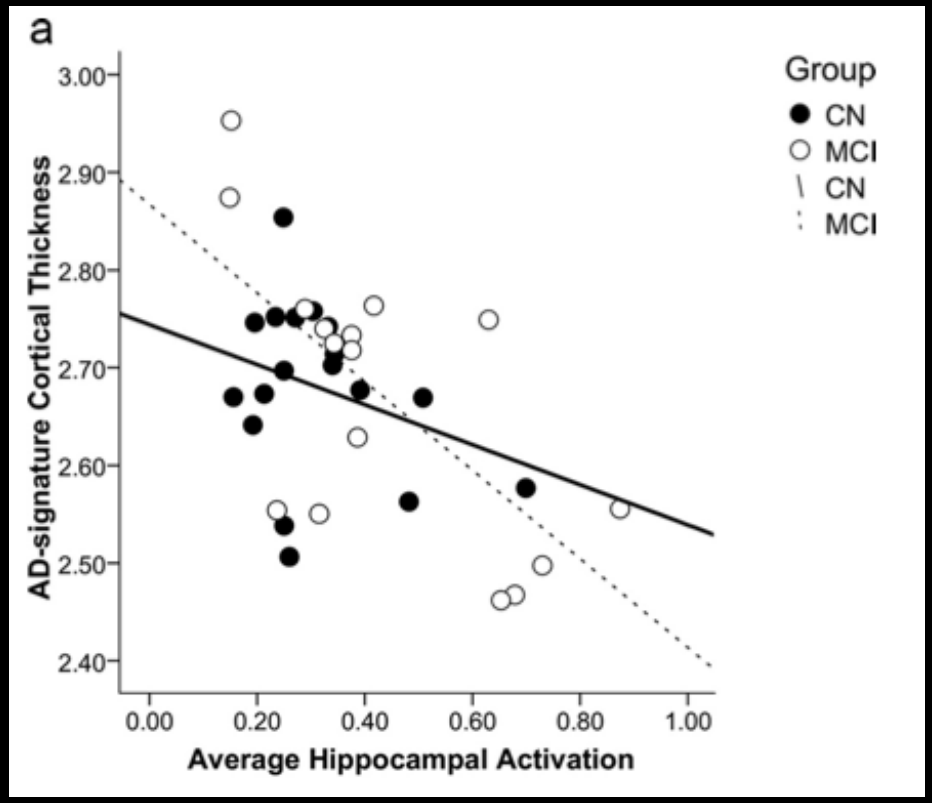


Volume



Dickerson BC et al., Neurology 2005

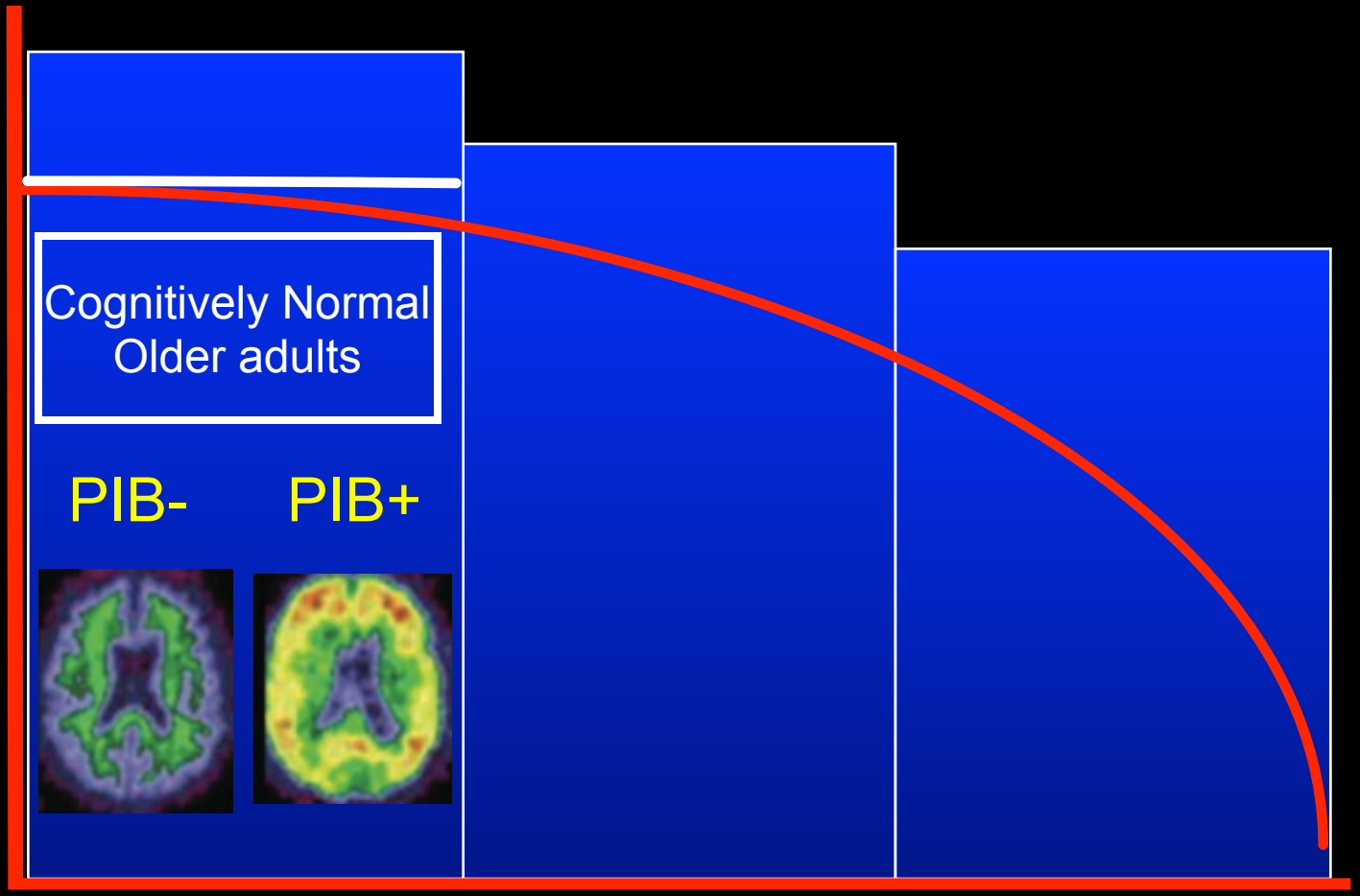
In MCI, more prominent AD-signature atrophy is associated with fMRI hippocampal hyperactivation during successful memory encoding



- More prominent hippocampal hyperactivation predicts more rapid cognitive decline (Miller S, etal, JNNP, 2008)

Putcha D, et al, J Neurosci 2011

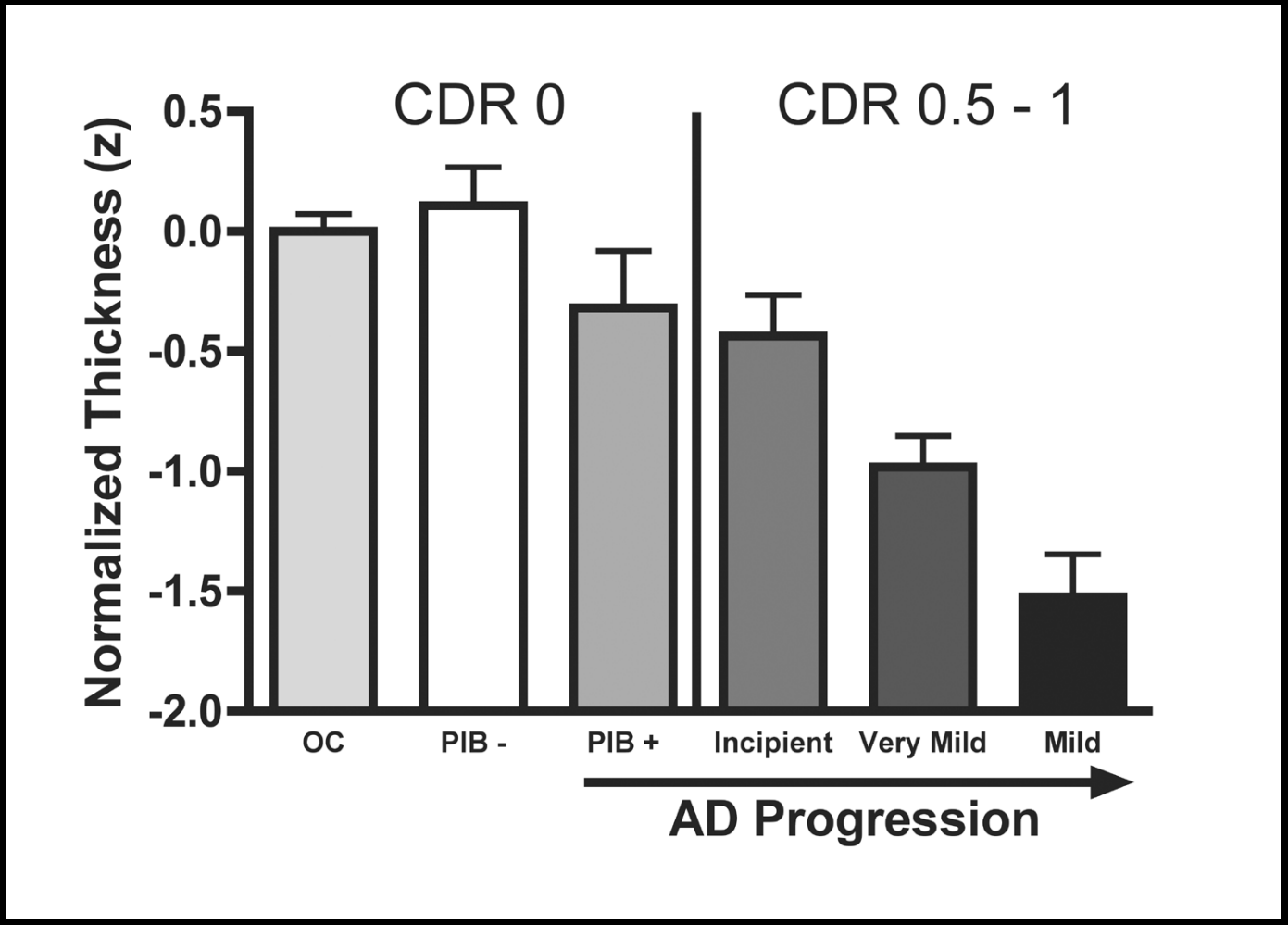
Preclinical AD



Cognition & Behavior

Disease Progression

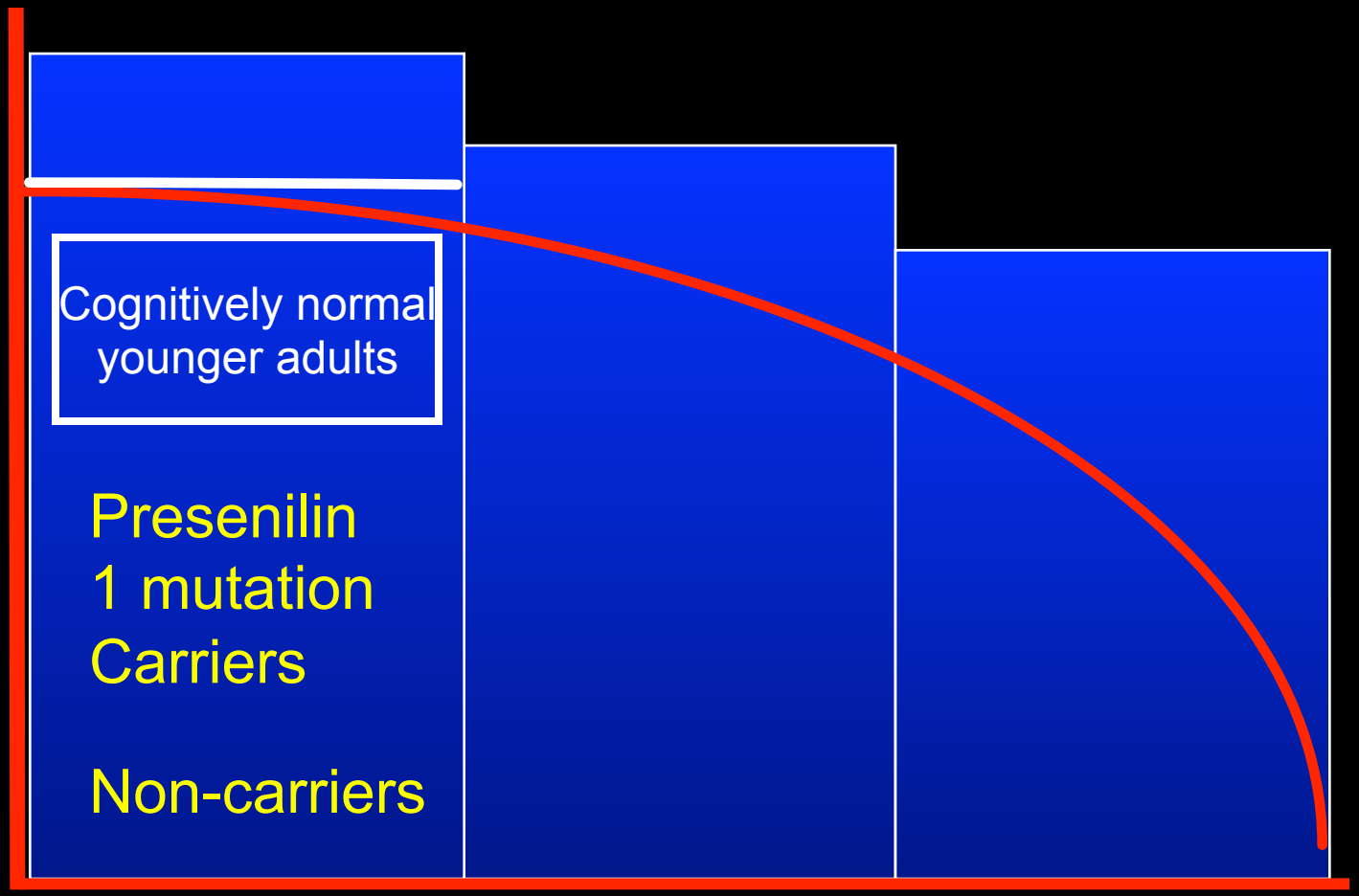
Cortical atrophy is present in amyloid PIB positive normals



Mean thickness of all "AD signature" regions, adjusted for age

Dickerson BC, et al., Cerebral Cortex, 2009

Presymptomatic AD



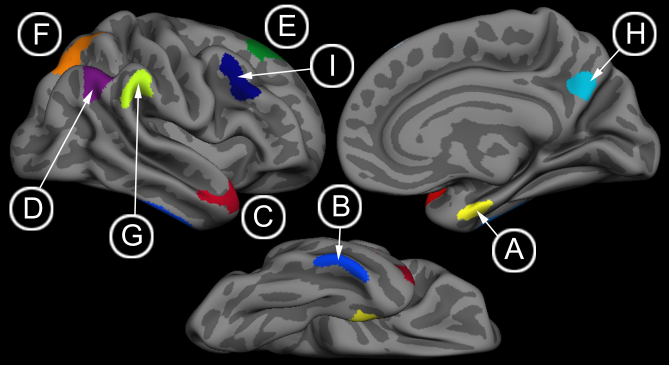
Cognition & Behavior

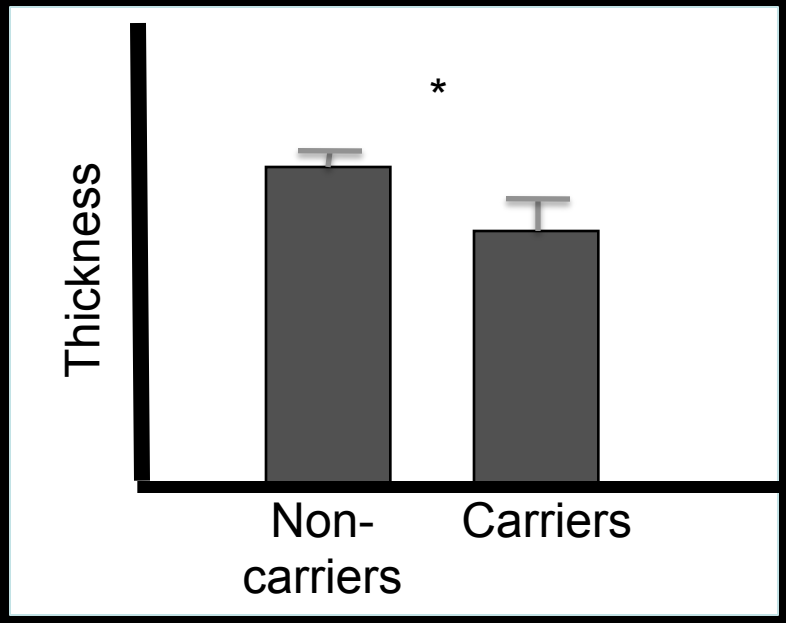
Disease Progression

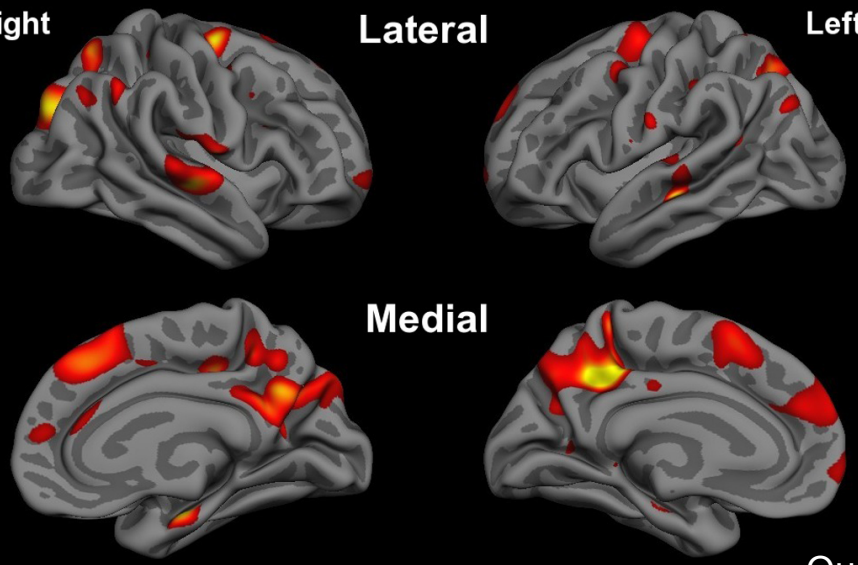
Quiroz & Dickerson et al., JNNP 2012

Asymptomatic Presenilin 1 E280A mutation carriers (n=18) vs. non-carriers (n=22), mean age 37.1 (average 7 years prior to symptom onset)

A priori AD-signature ROIs

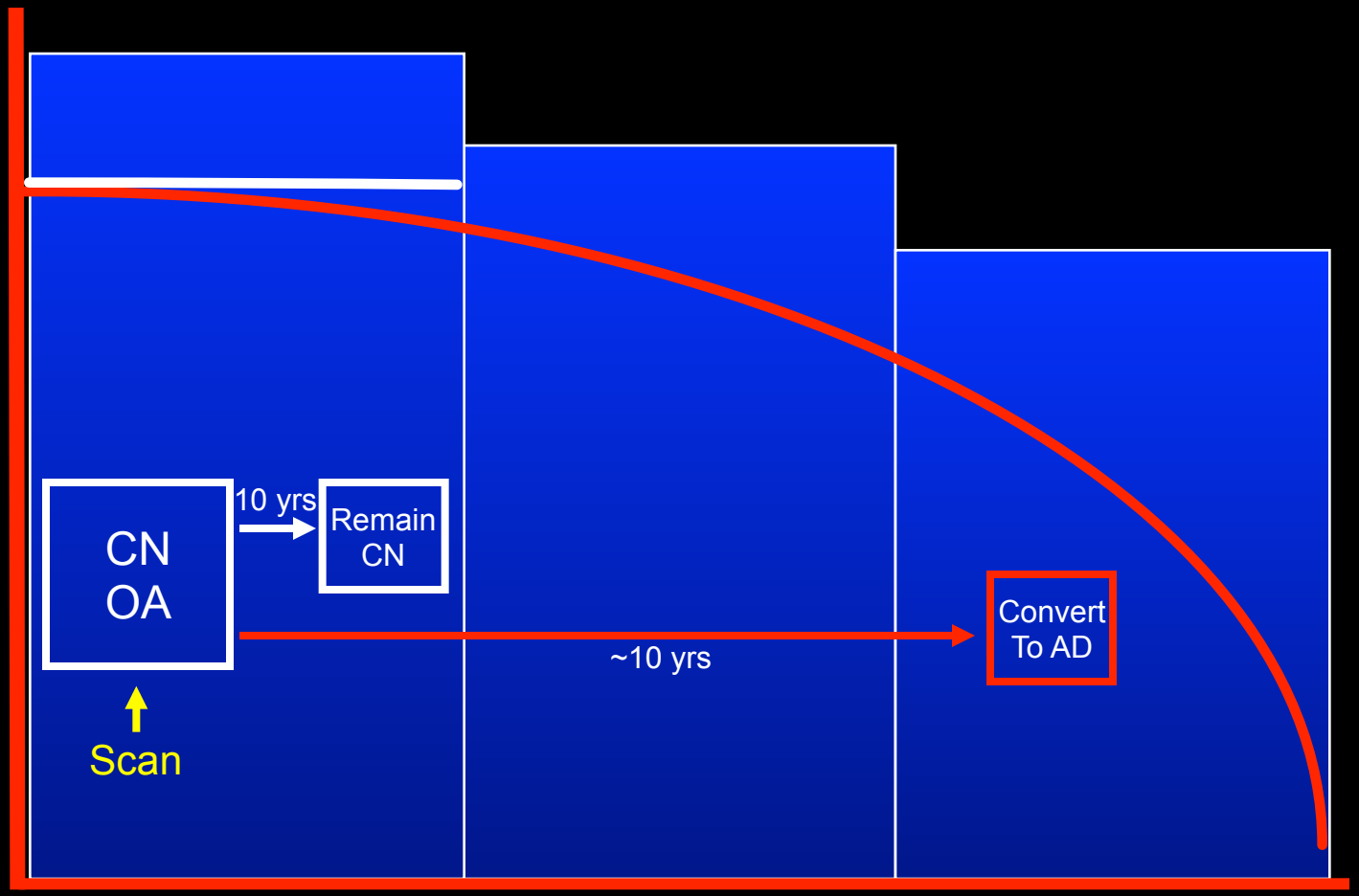






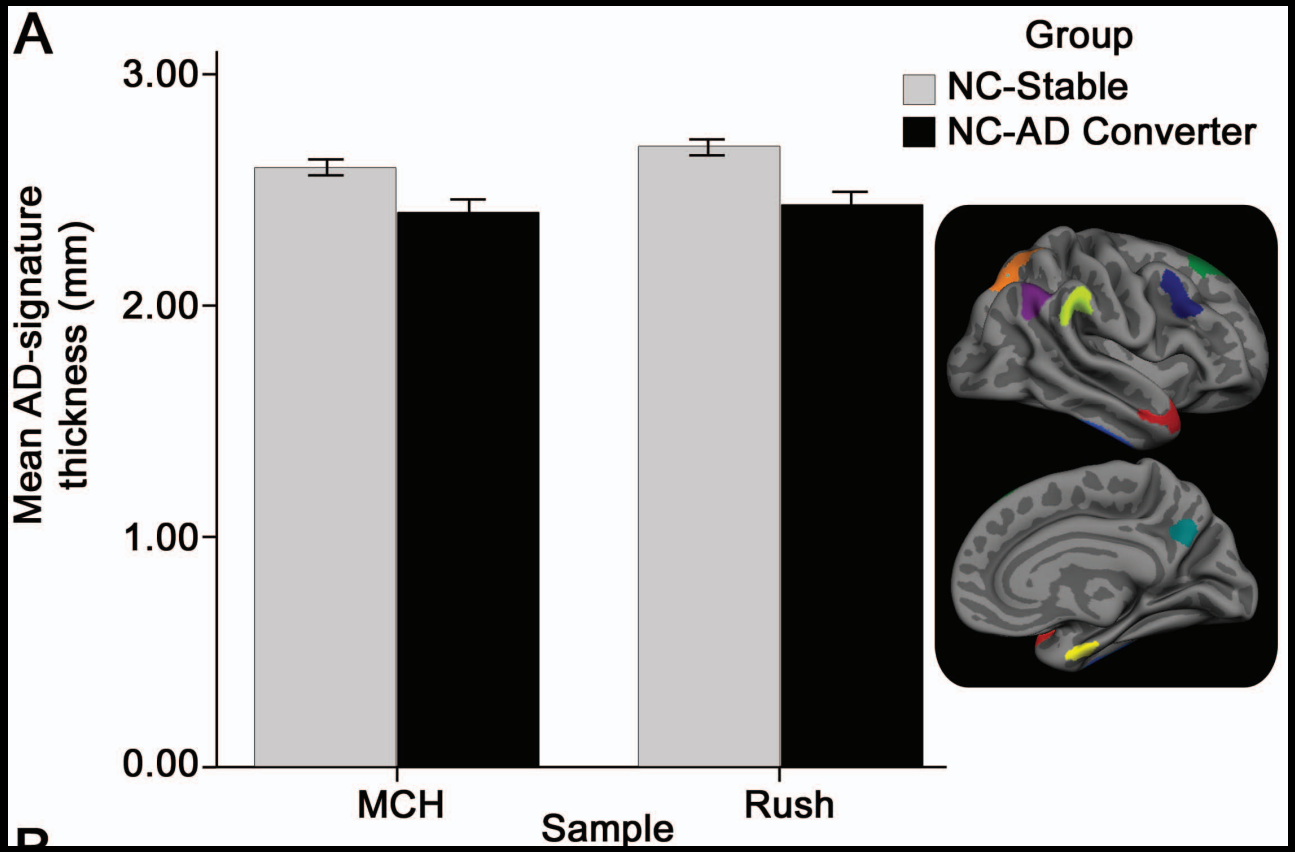
Quiroz & Dickerson et al., JNNP 2012

Presymptomatic AD



Dickerson BC, et al., Neurology, 2011

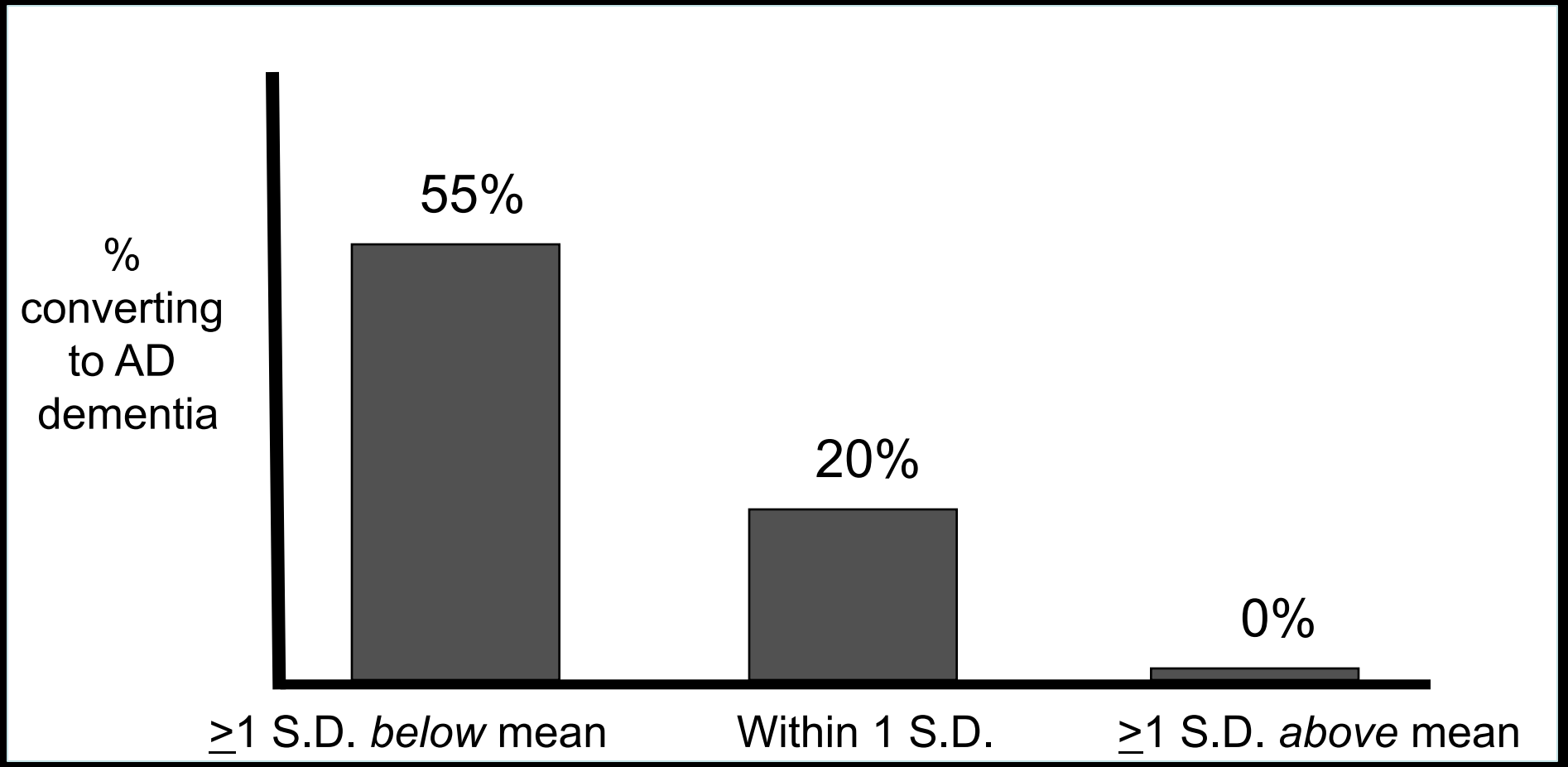
The cortical signature of AD is detectable in small groups of subjects at the stage of preclinical AD



- MGH: 0.20mm, Cohen's d effect size = 1.3
- Rush: 0.19mm, Cohen's d effect size = 1.2

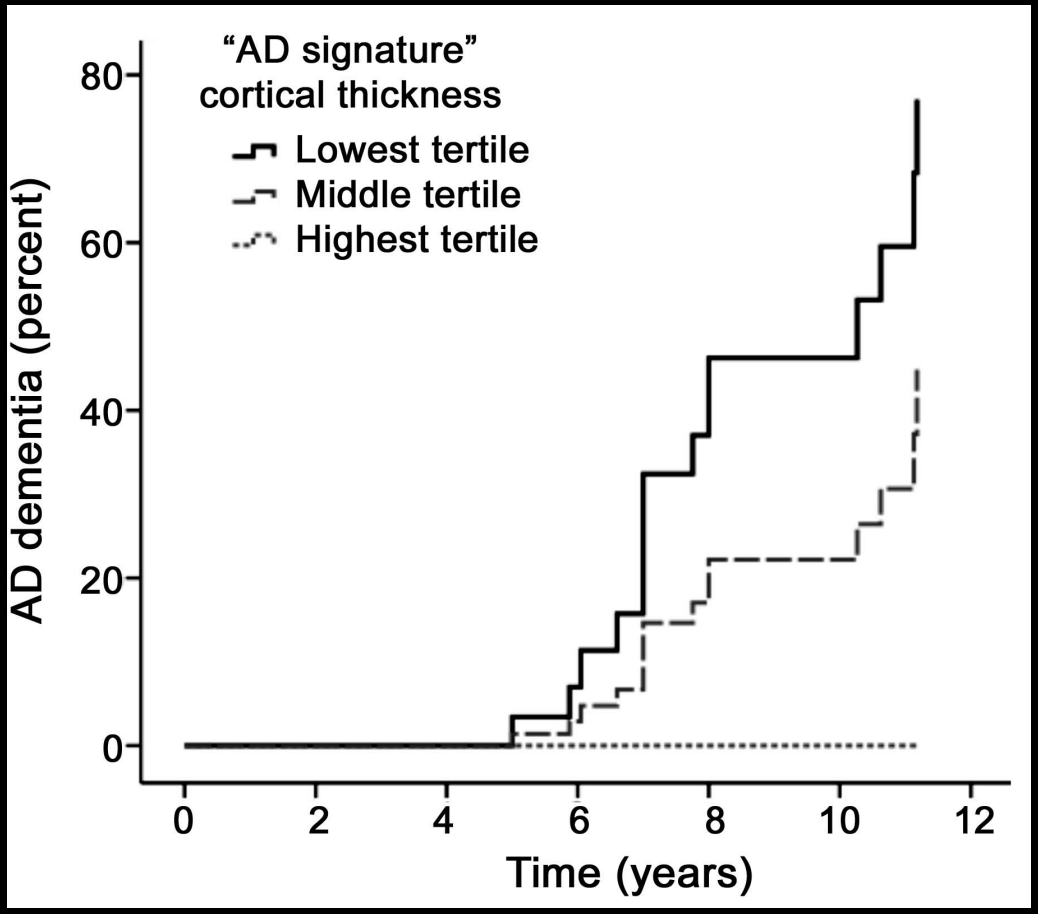
Dickerson BC, et al., Neurology, 2011

The expression of this MRI biomarker of AD-related cortical atrophy provides information about risk of AD dementia



Dickerson BC, et al., Neurology, 2011

The signature of AD-related cortical atrophy predicts time to AD dementia



Cox proportional hazards model:

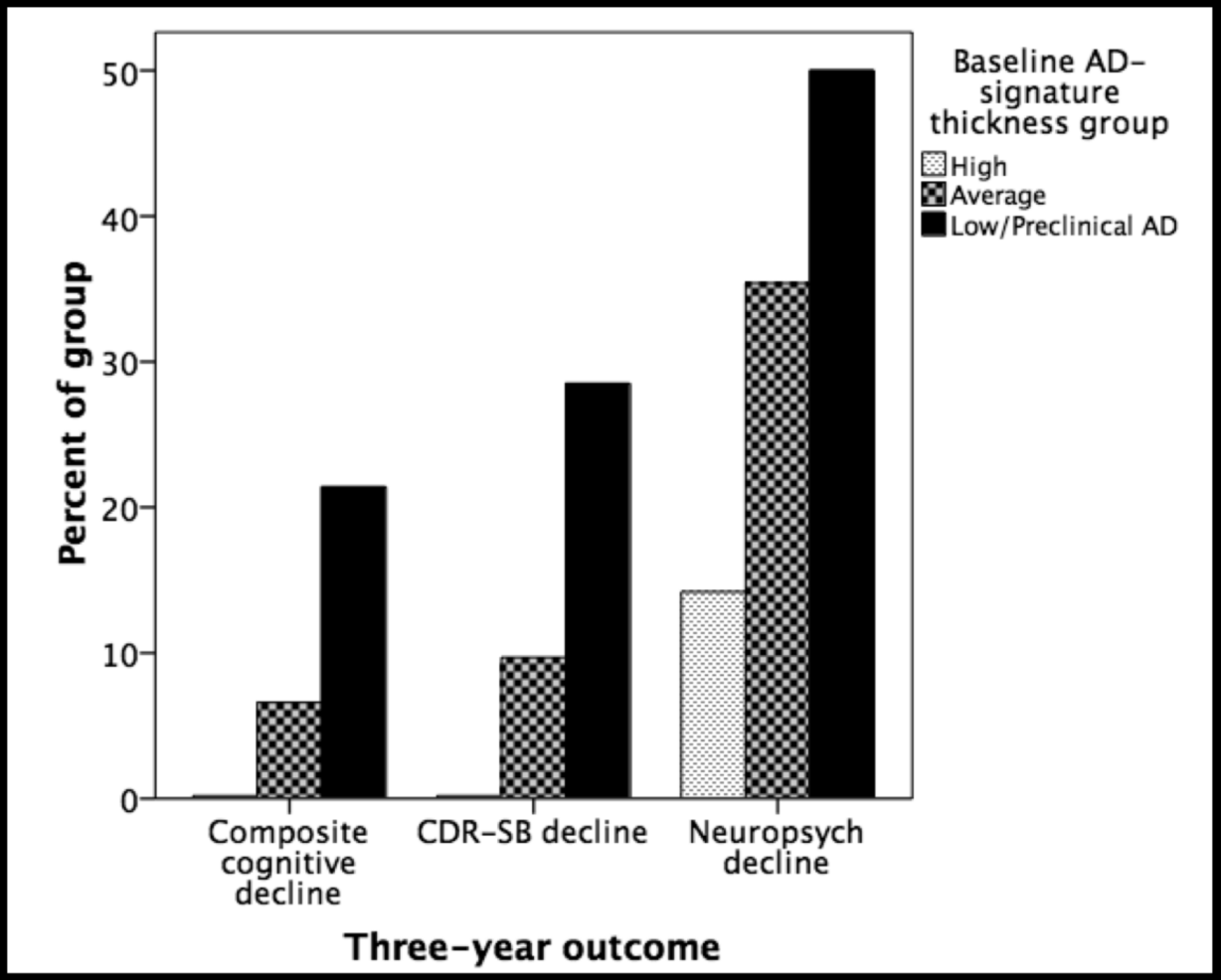
- cortical thickness marker can predict time-to-conversion to dementia over 8 years (H.R.=3.4, 95%C.I.=1.7-6.9, $p<0.005$)
- for every 1 S.D. of regional thinning, the risk of dementia is elevated by 3.4

Using MRI-based AD signature as part of Preclinical AD diagnostic criteria

- Study questions
  - Can we use previous information about relationship of AD signature to progression from asymptomatic to dementia to identify cutoffs applicable to individual people that would enable us to essentially implement this as a biomarker consistent with “Preclinical AD?”
  - Do people with normal cognition who express this biomarker have greater likelihood of short-term cognitive decline suggestive of early AD symptoms?
  - Are people with normal cognition who express this biomarker more likely to have cerebrospinal fluid levels of amyloid-b consistent with AD?

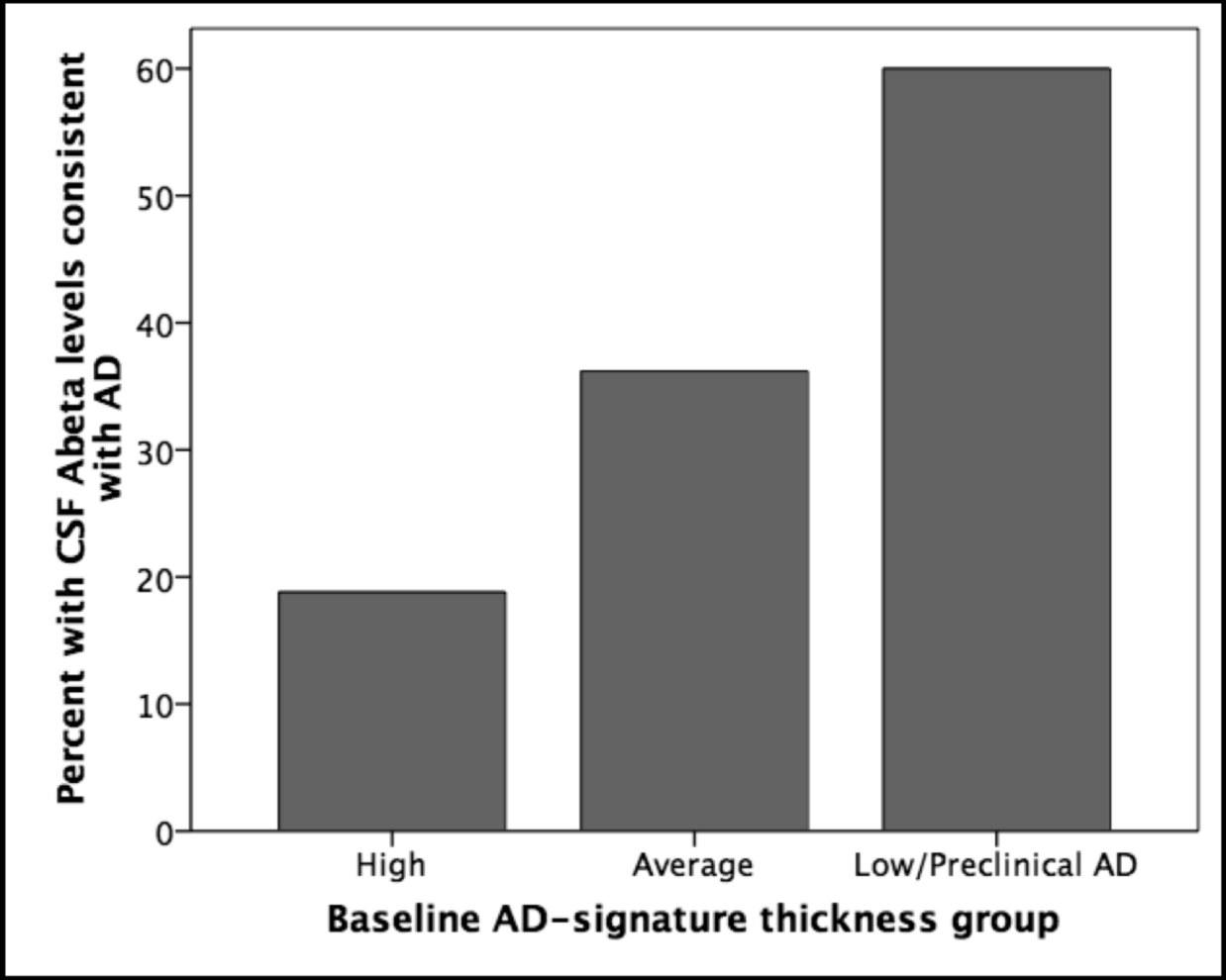
Dickerson BC, et al., Neurology, 2012

People with normal cognition who express this MRI biomarker consistent with Preclinical AD are more likely to develop cognitive decline over 3 years



Dickerson BC, et al., Neurology, 2012

People with normal cognition who express this MRI biomarker consistent with Preclinical AD are more likely to harbor abnormal CSF protein levels consistent with molecular evidence of AD

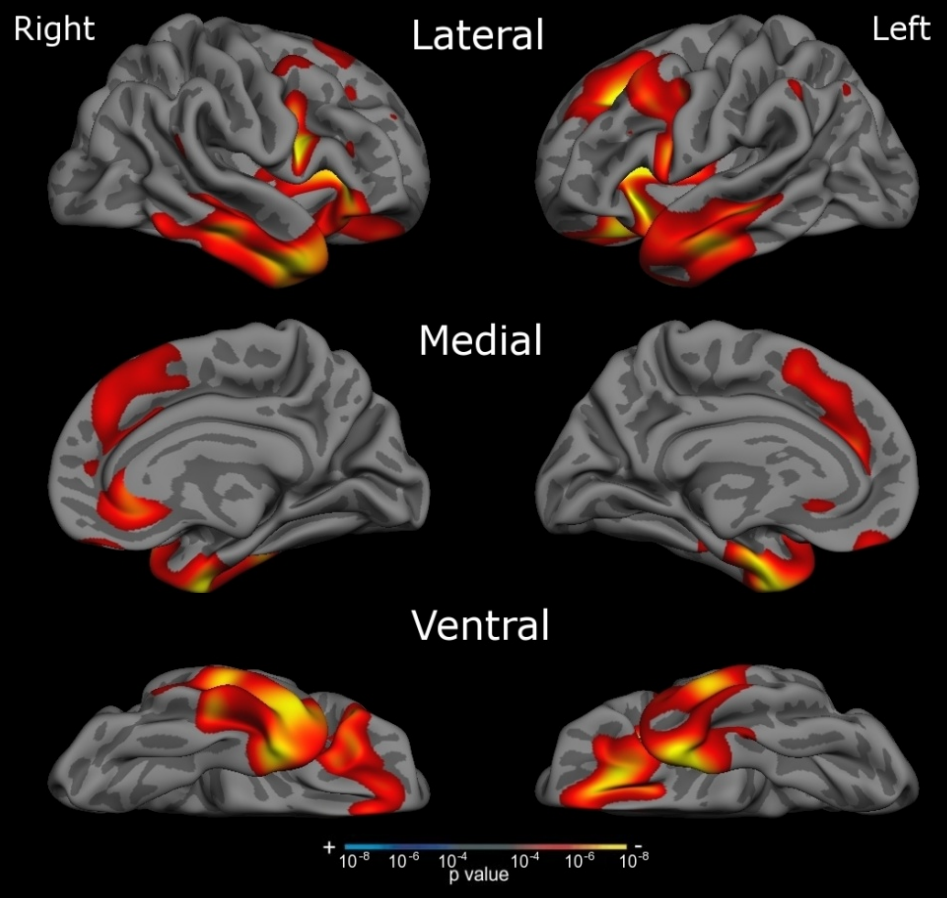


Dickerson BC, et al., Neurology, 2012

Implications

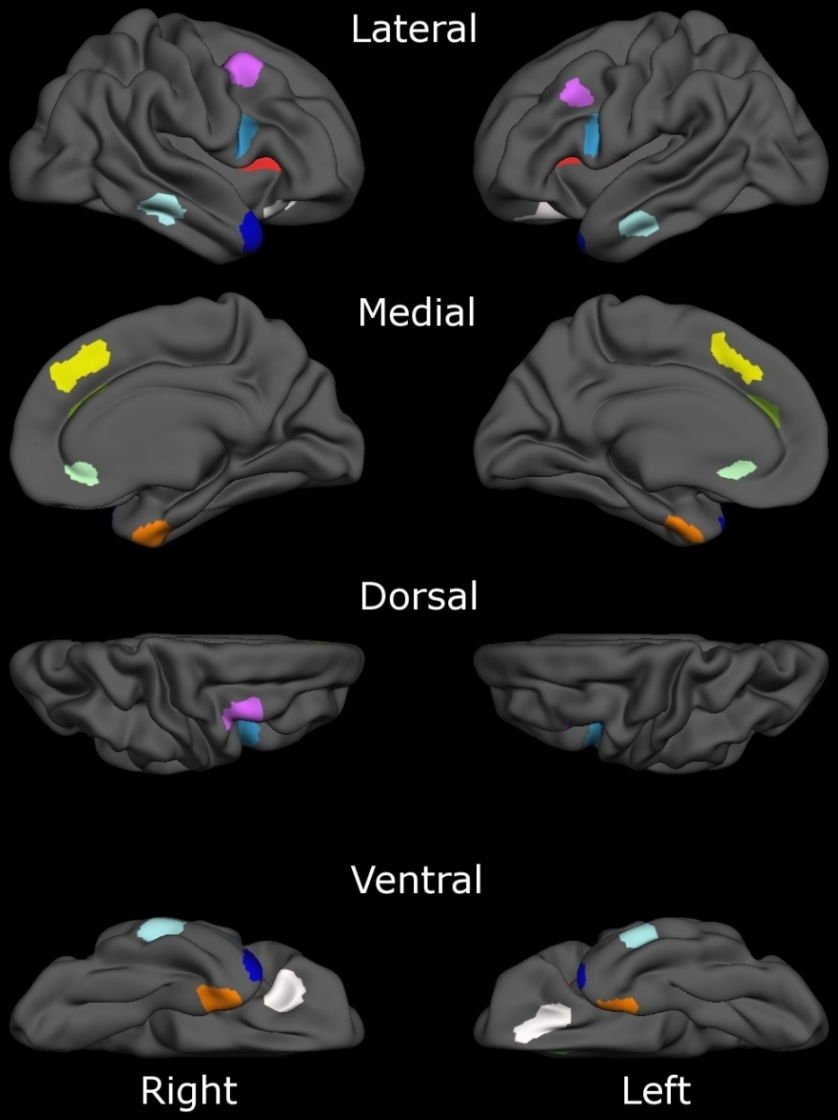
- Could potentially consider MRI as one way to screen cognitively normal older adults (~10 min)
- Could use results to
  - identify those at high risk for cognitive decline consistent with early symptoms of prodromal AD
  - Identify those likely to harbor silent AD pathology
- Need further investigations of cognitively normal individuals to better understand population distribution of these changes in relation to longitudinal course

Cortical signature of very mild/ mild FTD Dementia



FTD Dementia (n=33, mean age 65, CDR 0.5 or 1)
vs. Controls (n=33, mean age 72, CDR 0)

FTD-Sig ROIs

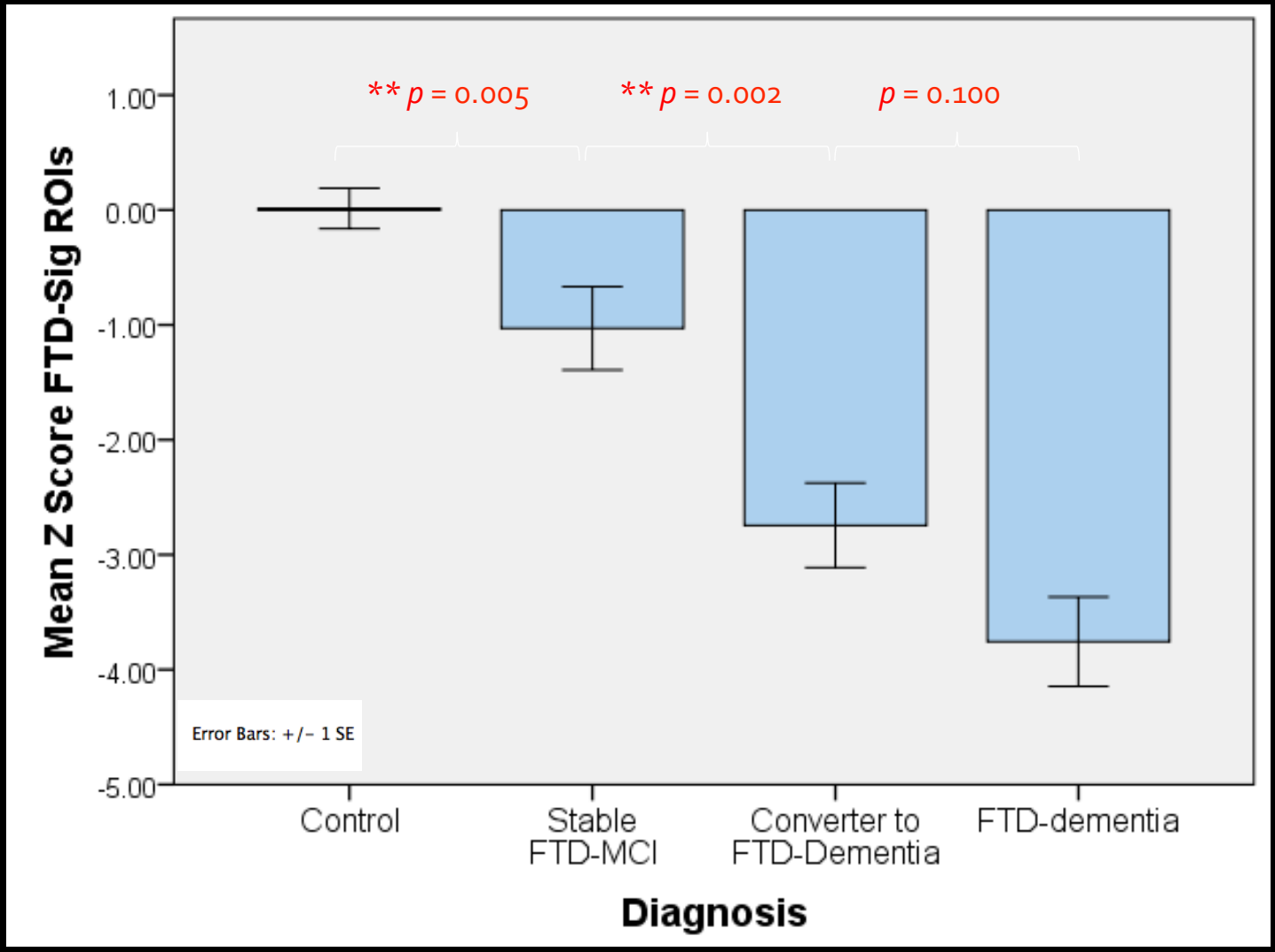


FTD-MCI

- Clinical phenotype of early FTD (PPA or bvFTD)
- Met clinical criteria for MCI at initial visit
  - Self/family expressed concern regarding symptoms
  - Impairment in 1(+) cognitive / behavioral domain
    - PASS/SIRS rating scales
  - Not demented (CDR 0 or 0.5; Largely independent in daily activities; usually MMSE minimally impaired)

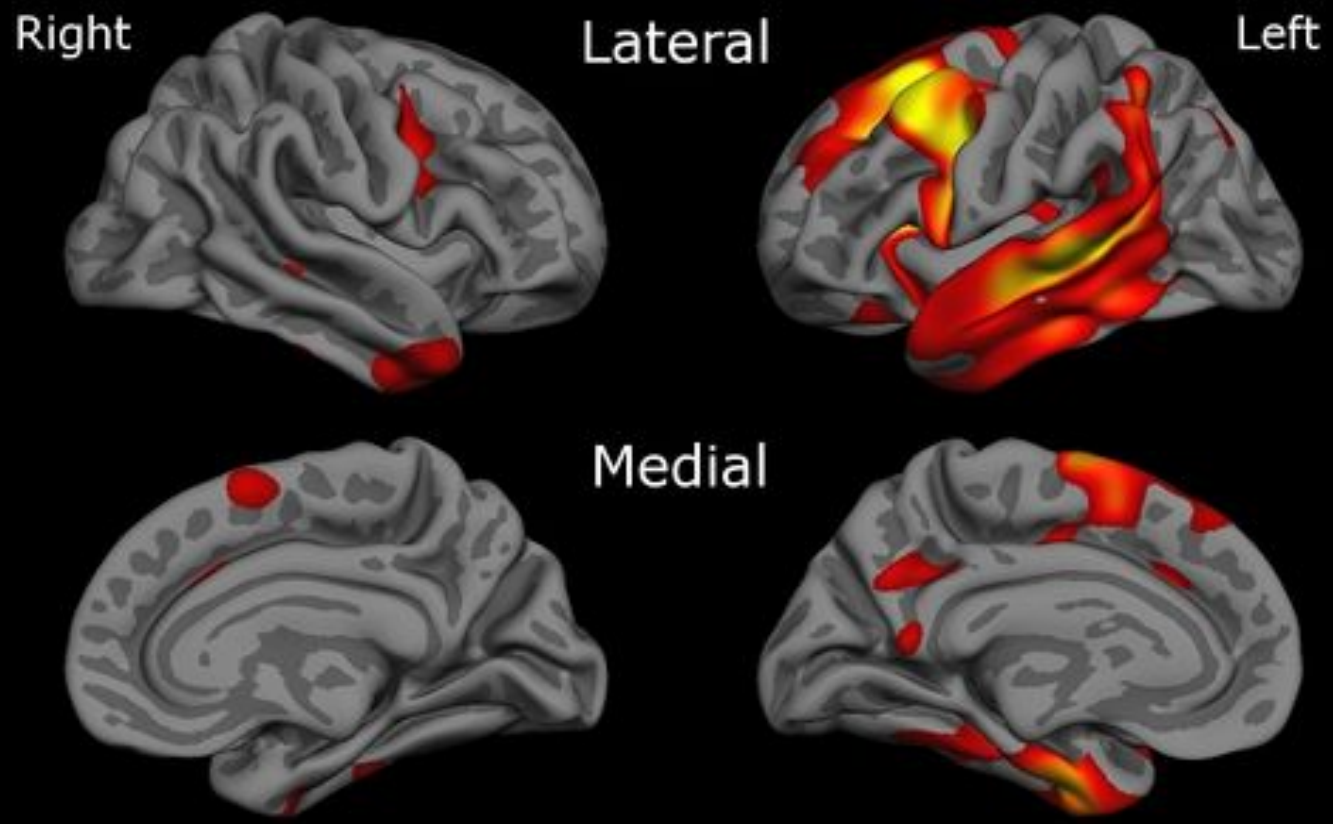
Diagnosis	N [F]	Disease Duration (yrs)	Longitudinal Follow up (yrs)	Time to convert (yrs)
FTD-MCIs	17 [8]	5.35 (1.58)	2.16 (1.25)	---
FTD-MCIc	17 [11]	7.35 (2.11)	3.42 (1.08)	1.5 (1)

Cortical atrophy in FTD-signature ROIs is detectable at the stage of MCI and predicts conversion to dementia



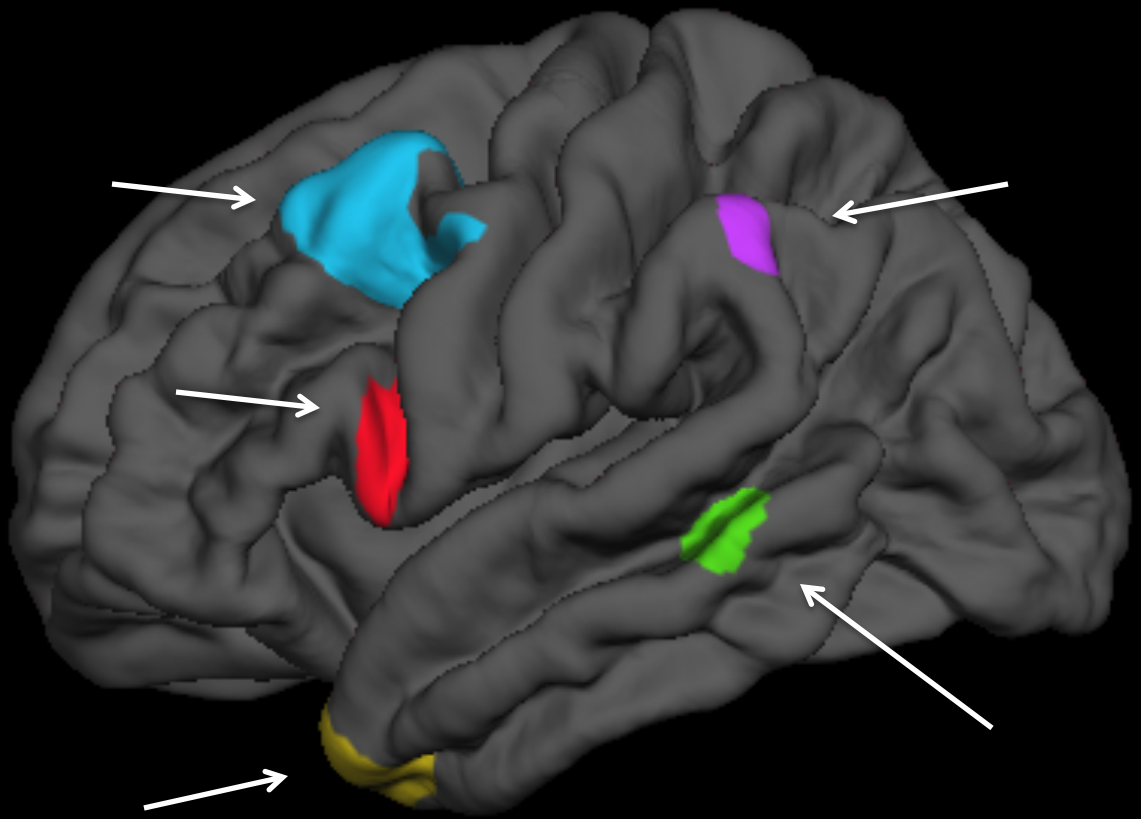
Domoto-Reilly & Dickerson et al, in prep

Cortical atrophy in PPA



Sapolsky et al Neurology 2010

PPA subtypes: most prominent regions of atrophy



Resting state language circuitry

Seed ROI from PPA pts

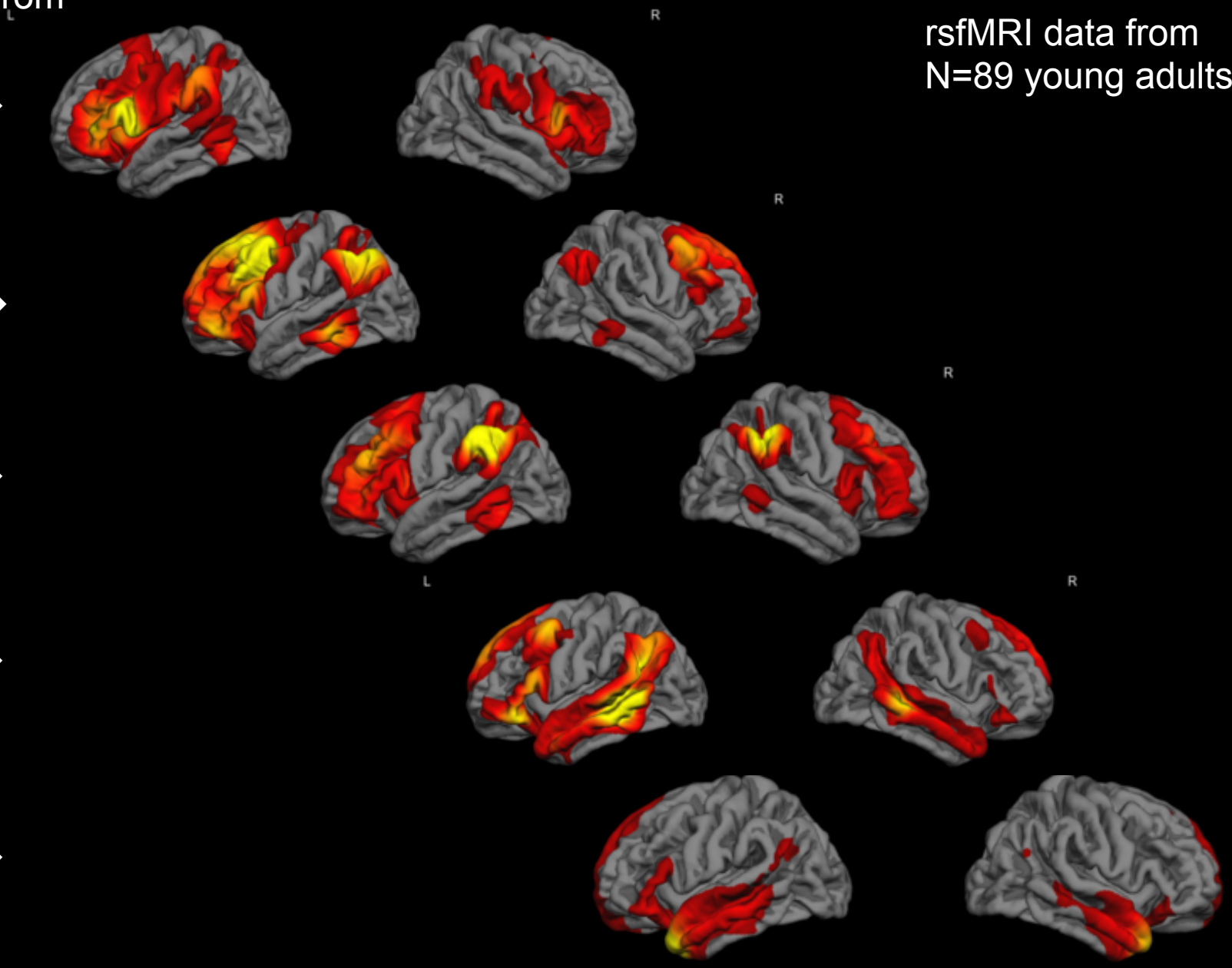
cIFG ➔

cMFG ➔

IPL ➔

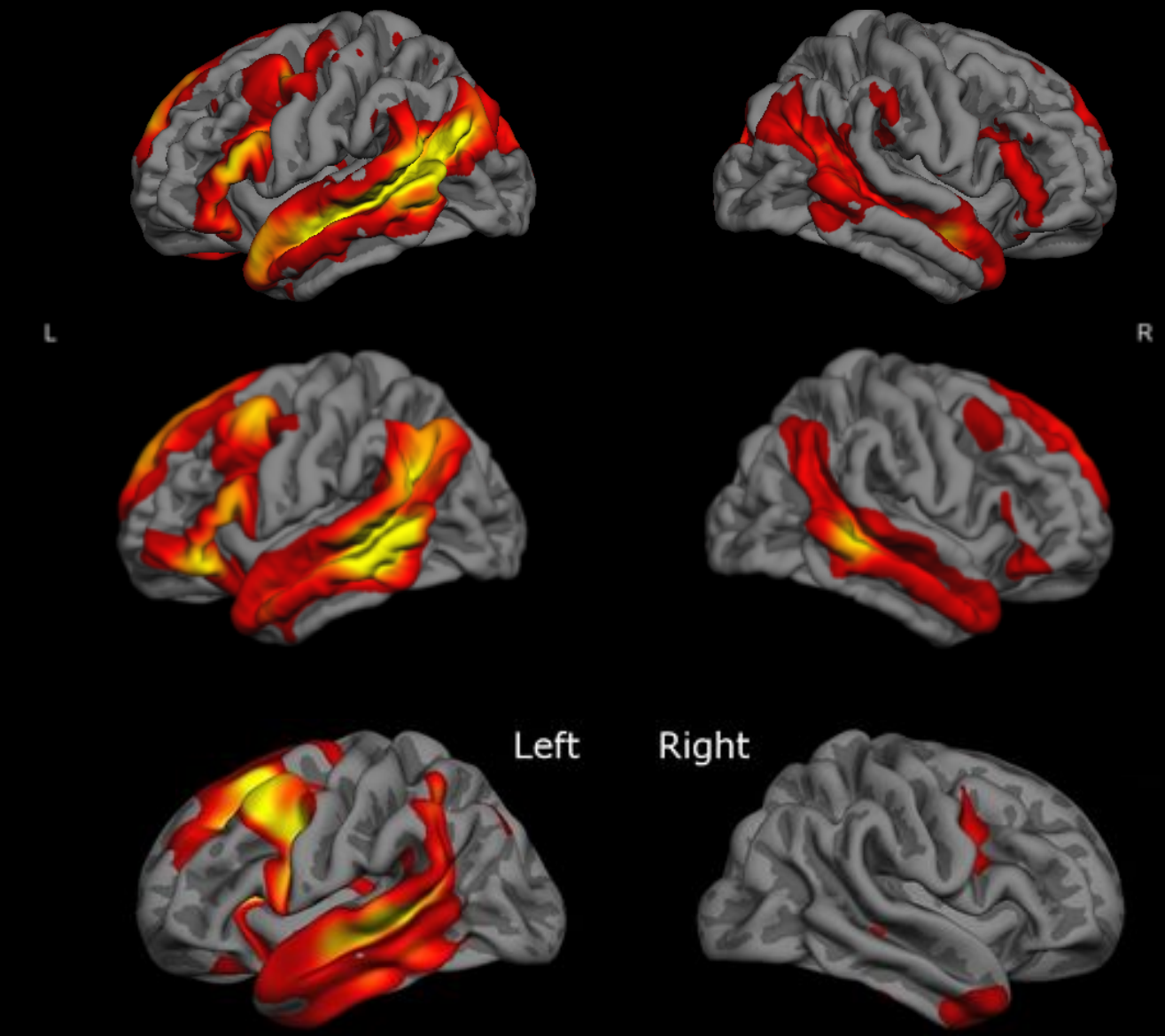
cMTG ➔

TPole ➔



rsfMRI data from N=89 young adults

Large-scale Language Network



fMRI task activation

Resting state fcMRI

PPA atrophy

Looking ahead:
Biomarkers of MCI and earlier stages in neurodegenerative dementias

Clinical practice:

- Early diagnosis of mildly symptomatic individuals
- More confident diagnosis of atypical MCI/dementia cases

Research:

- Risk assessment in asymptomatic individuals
- Identification of candidates for clinical trials
- Predicting effects of treatment
- Monitoring of effects of treatment

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