Cognitive correlates of neurodegeneration related to beta-amyloid and aging in clinically normal individuals

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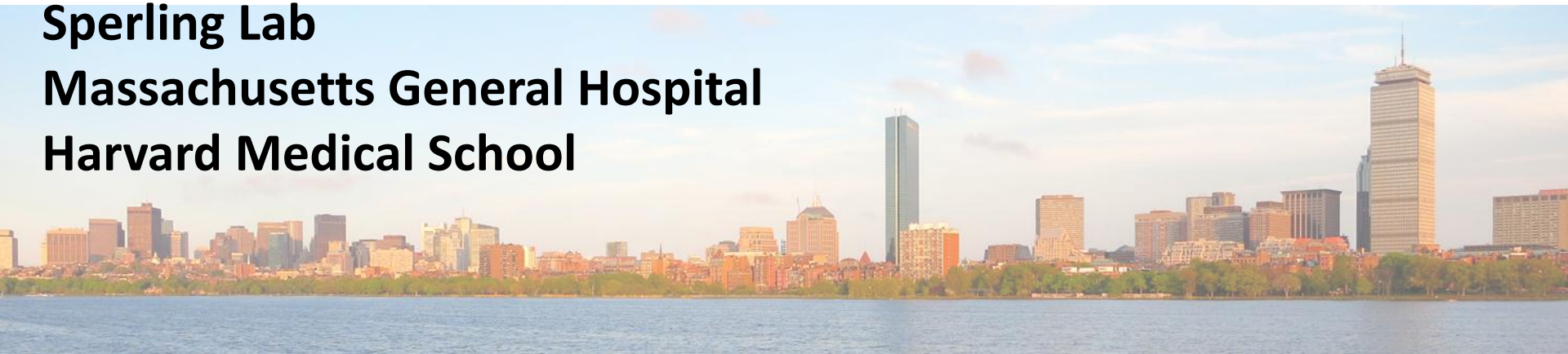


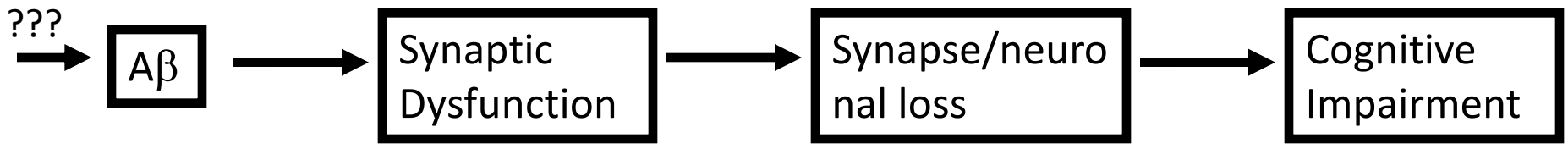
I have no financial disclosures.

Background

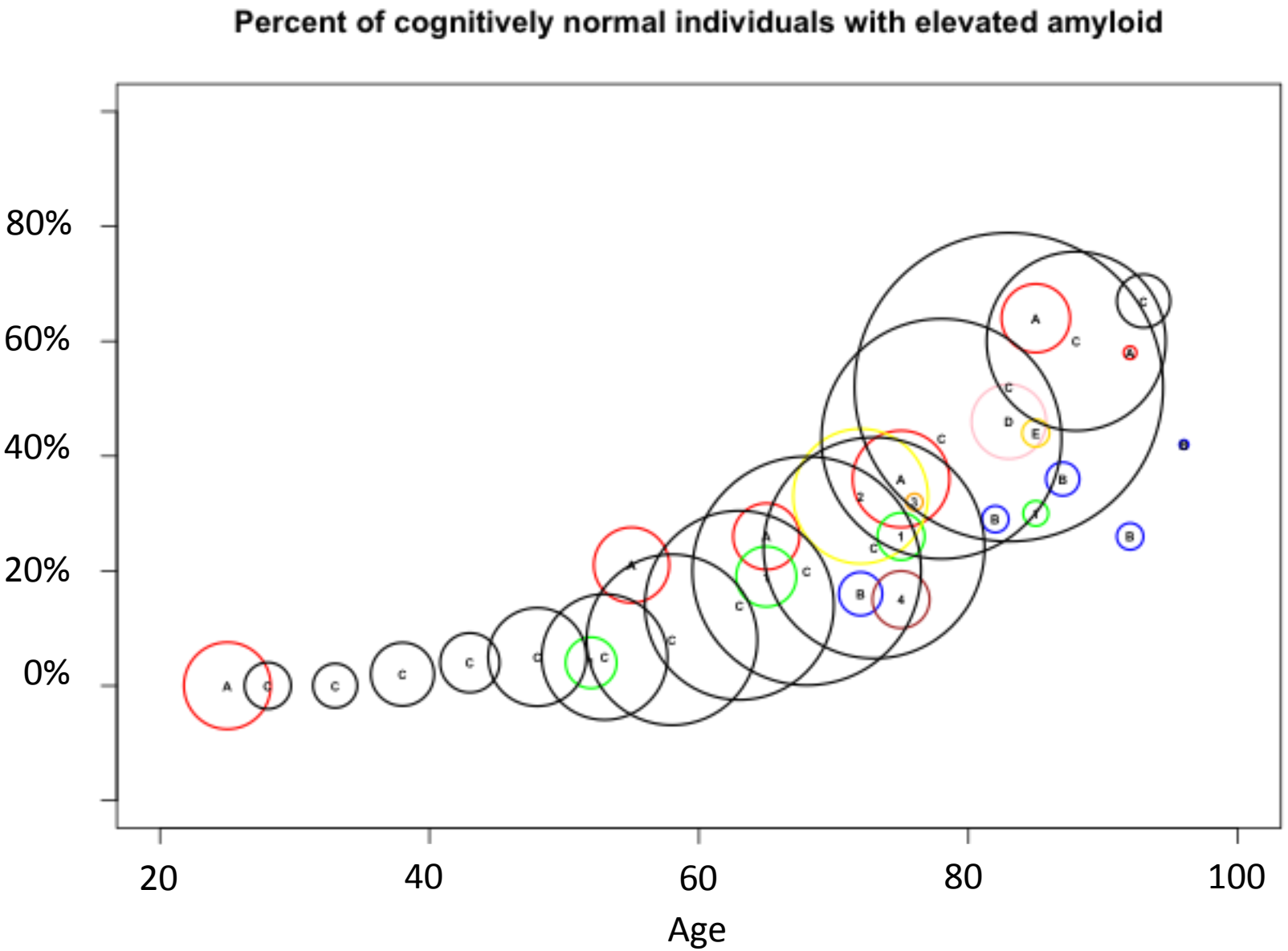
- Alzheimer's disease (AD) is the most common form of dementia (10% 65+, 40% 85+)
- Episodic memory

- Beta-amyloid (Aβ) plaques are a hallmark pathological feature of AD
- Accumulation of the Aβ peptide thought to be an *early* event that *initiates* the AD cascade ("Amyloid Hypothesis of AD")
- Amyloid imaging allows visualization of Aβ plaques in vivo

Amyloid Hypothesis of AD



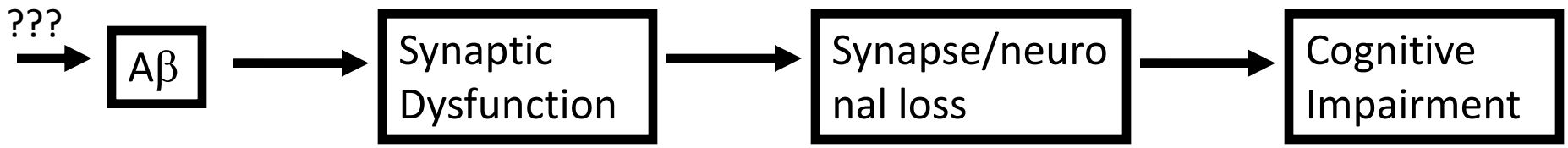
Aβ plaques are common in normals

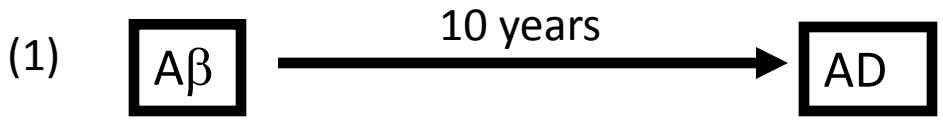


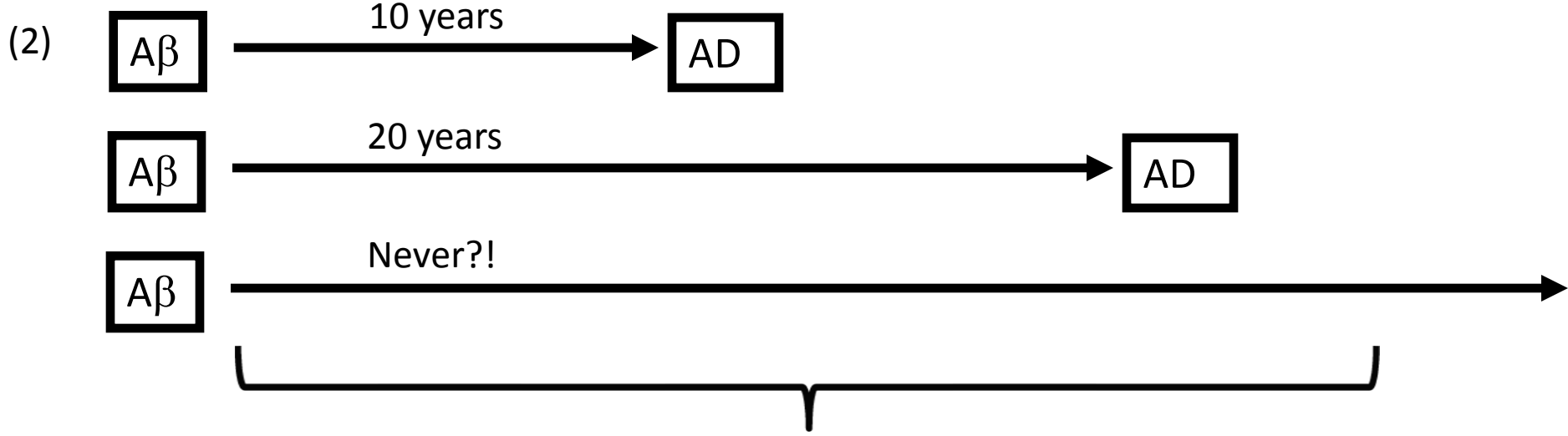
A=Kok et al. [1], CERAD moderate and frequent; B=Savva et al. [2], CERAD moderate and severe; C= Braak & Braak [3], CERAD B & C; D= Bennett et al. [4] ["Religious Orders Study"], CERAD probable and definite; E= Bennett et al. [4] ["Memory and Aging Project"], CERAD probable and definite. PIB-PET studies and corresponding criteria: 1= Morris et al. [5], global BP>0.18; 2=Rowe et al. [6], global SUVR>1.5; 3=Sperling et al. [7], posterior cingulate cortex DVR>1.6; 4=Mormino et al. [8], global DVR>1.16)

Aβ in normals: possible interpretations

Amyloid Hypothesis of AD



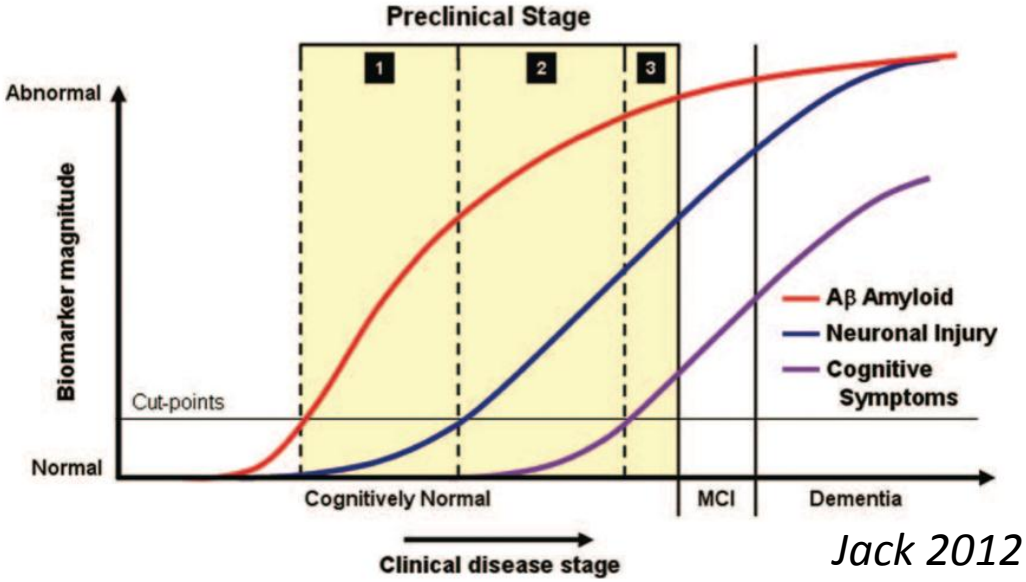




What influences this variability?

Preclinical AD Stages: Sequence between Aβ, ND, cognition

Aβ → ND → Cognition



Jack 2012

Stage 1
Asymptomatic amyloidosis
-High PET amyloid tracer retention
-Low CSF $A\beta_{1\text{-}42}$

Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on FDG-PET/fMRI
-High CSF tau/p-tau
-Cortical thinning/Hippocampal atrophy on sMRI

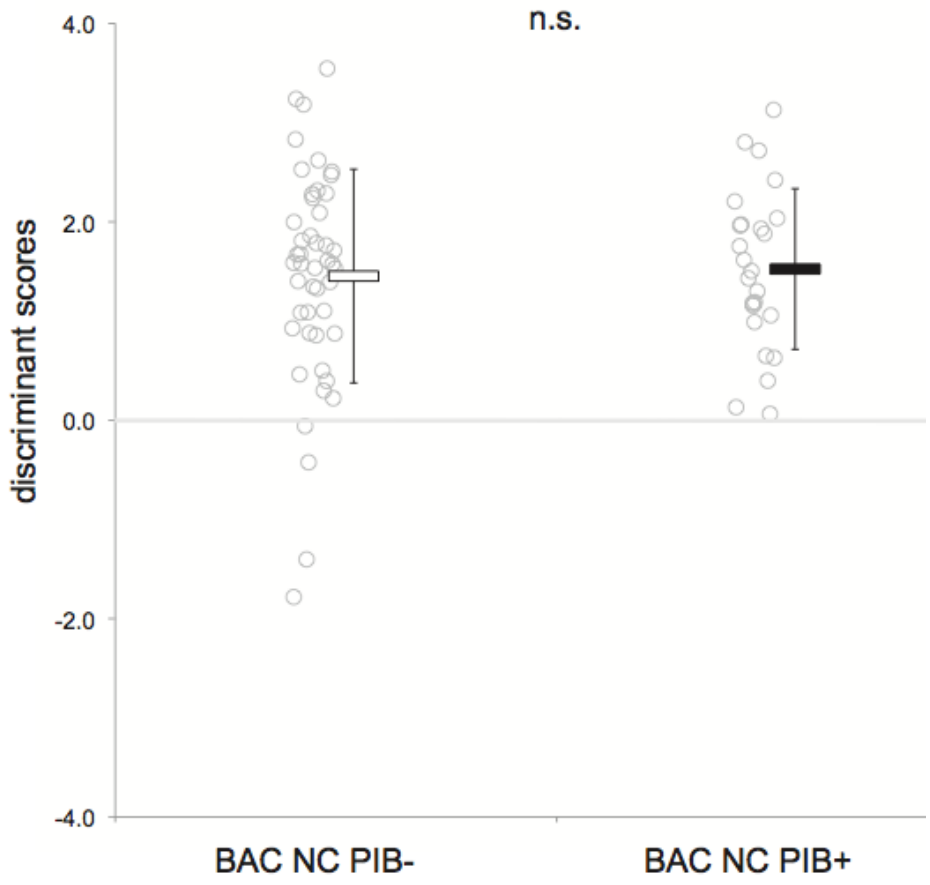
Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of subtle change from baseline level of cognition
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

MCI → AD dementia

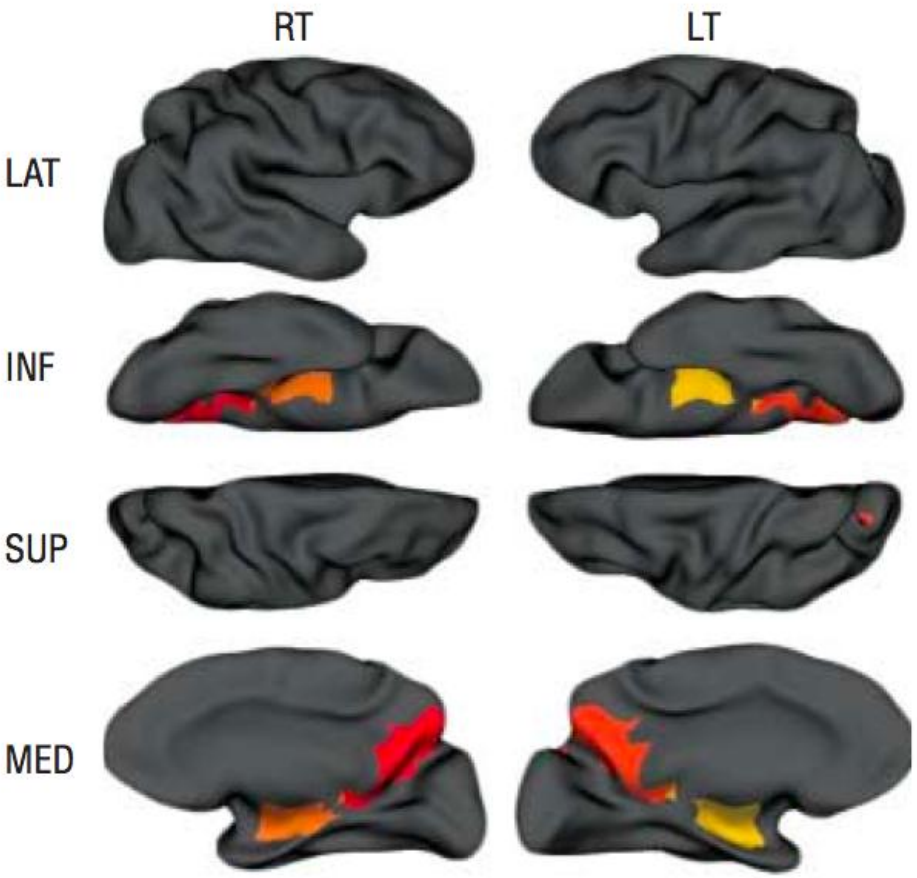
Sperling 2011

Associations between Aβ and cross-sectional ND are inconsistent

Wirth 2013 J Neurosci (N=72):
No association between Aβ and ND



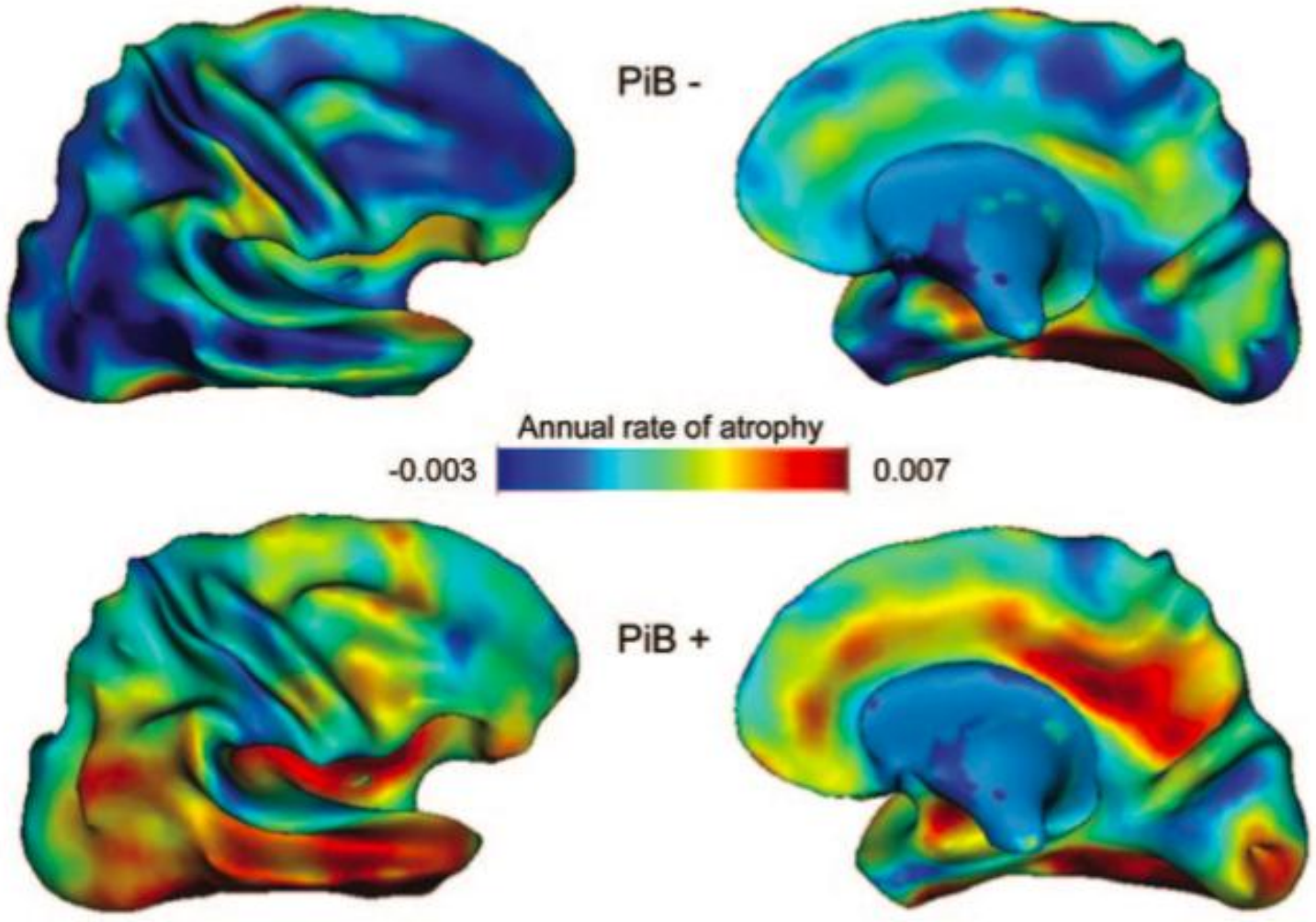
Dore 2013 JAMA Neurol (N=93):
More ND in Aβ+



Also Dickerson 2009 Cerebral Cortex, Fagan 2009 Ann Neurol, Mormino 2009 Brain, Storandt 2009 Arch Neurol, Chetelat 2010 Brain, Schott 2010 Ann Neurol, Becker 2011 Ann Neurol, Oh 2011 Neuroimage, Sabuncu 2011 Cerebral Cortex

More consistent relationships with longitudinal atrophy

Chetelat 2012 Neurology (N=74):
More atrophy in Aβ+



Also Schott 2010 Annals Neurol, Dore 2013 JAMA Neurol

If sequence is true, neurodegeneration should only be present in Aβ+ subjects…

Knopman 2012 Ann Neurol

430 normals

Aβ status determined via PIB PET

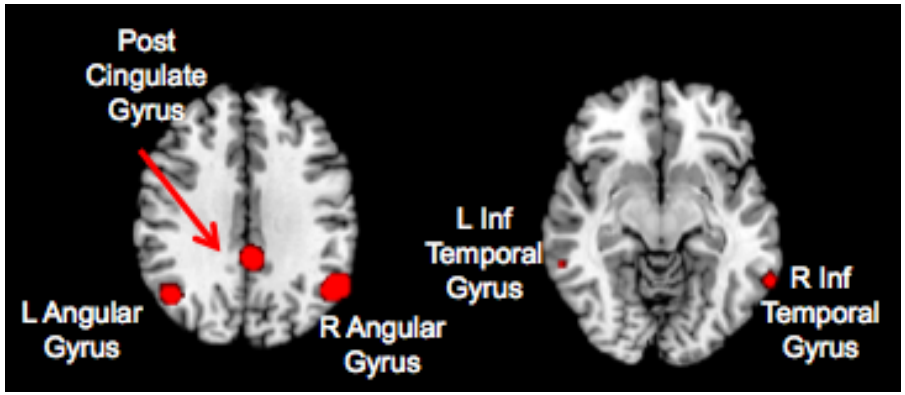
ND status determined via hippocampus volume and FDG from AD vulnerable regions

Results:

Stage 0 (Aβ-/ND-): 191 (44.4%)

Stage 1 (Aβ+/ND-): 68 (15.8%)

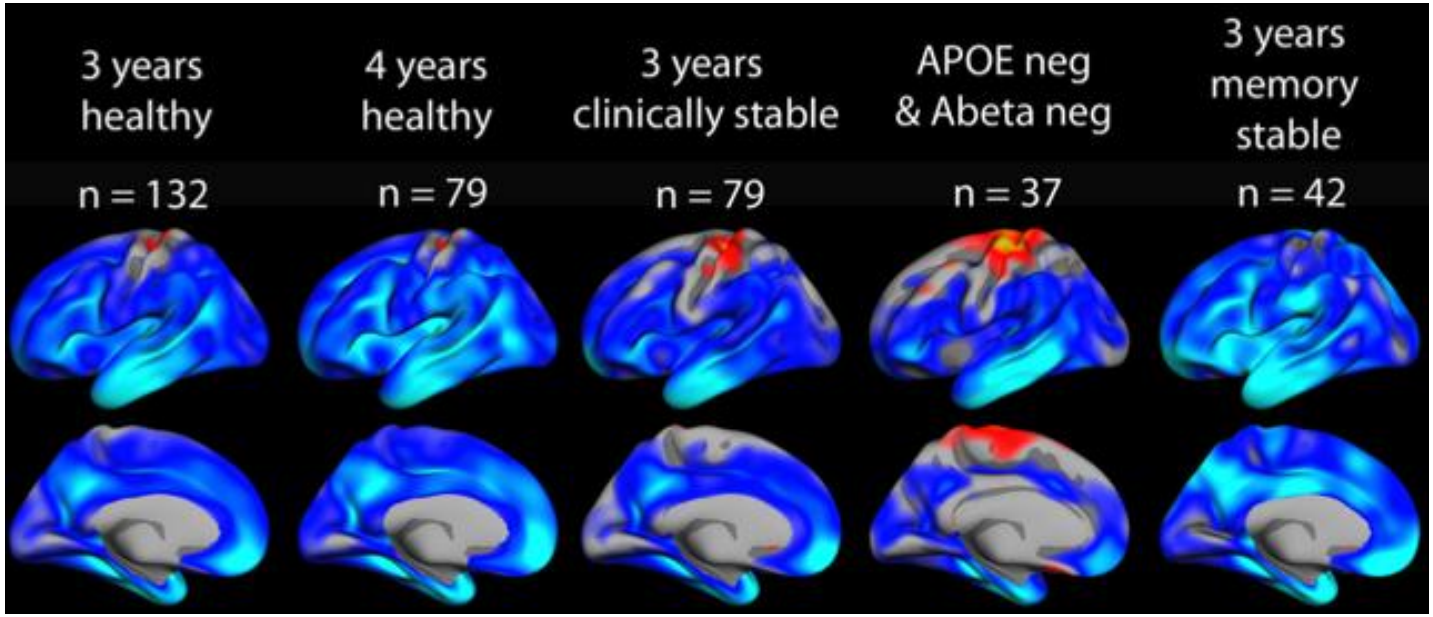
Stage 2 (Aβ+/ND+): 69 (16.0%)



Landau & Jagust, UC Berkeley FDG MetaROI methods pdf

SNAP (Aβ-/ND+): 102 (23.7%)

Consistent with SNAP, atrophy observed in low risk older subjects



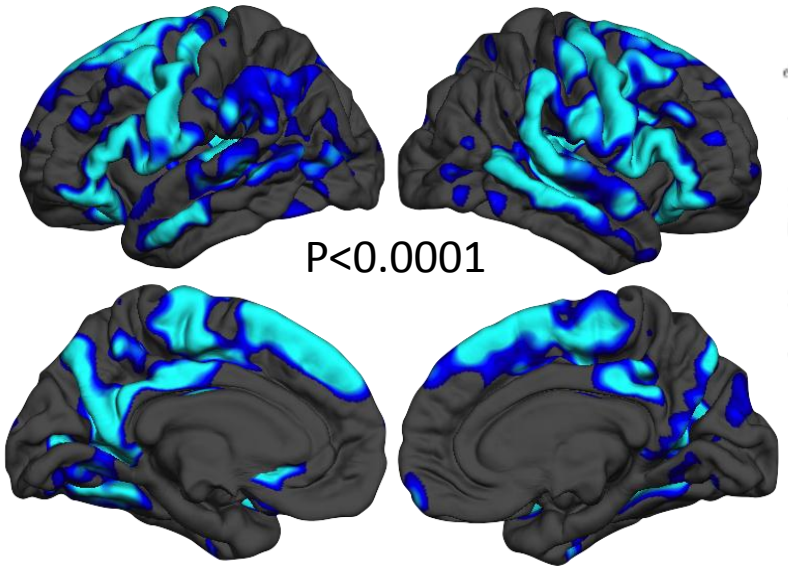
Fjell 2013 J Neurosci

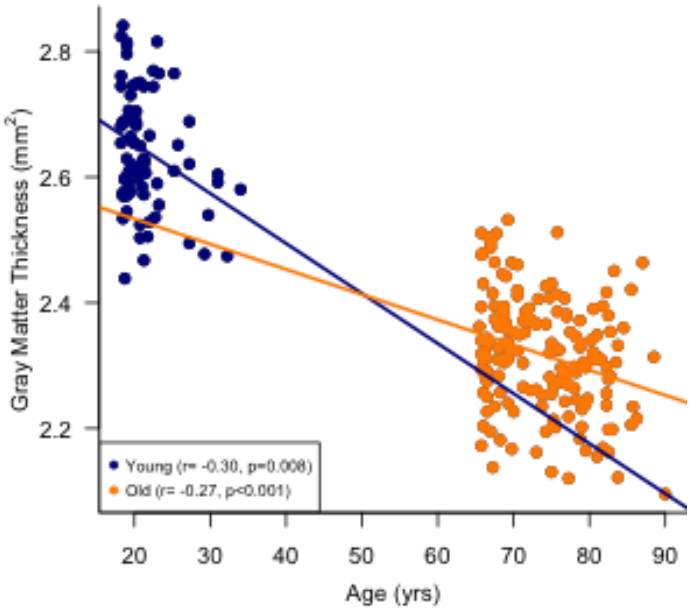
Harvard Aging Brain Study

36 Biomarker Neg Old
Aβ-, WMH-, APOE4-
Mean Age=71.2±5.7

Vs.

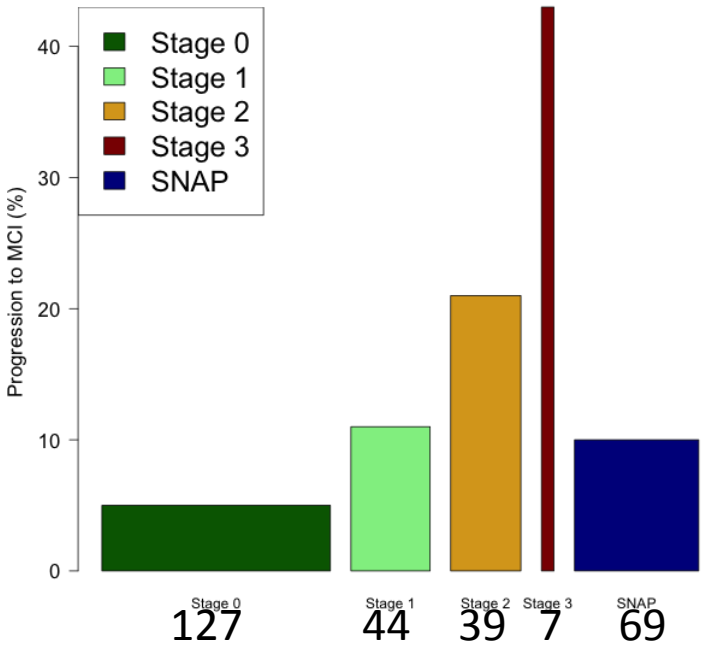
75 Young
Mean Age=22.0±4.0





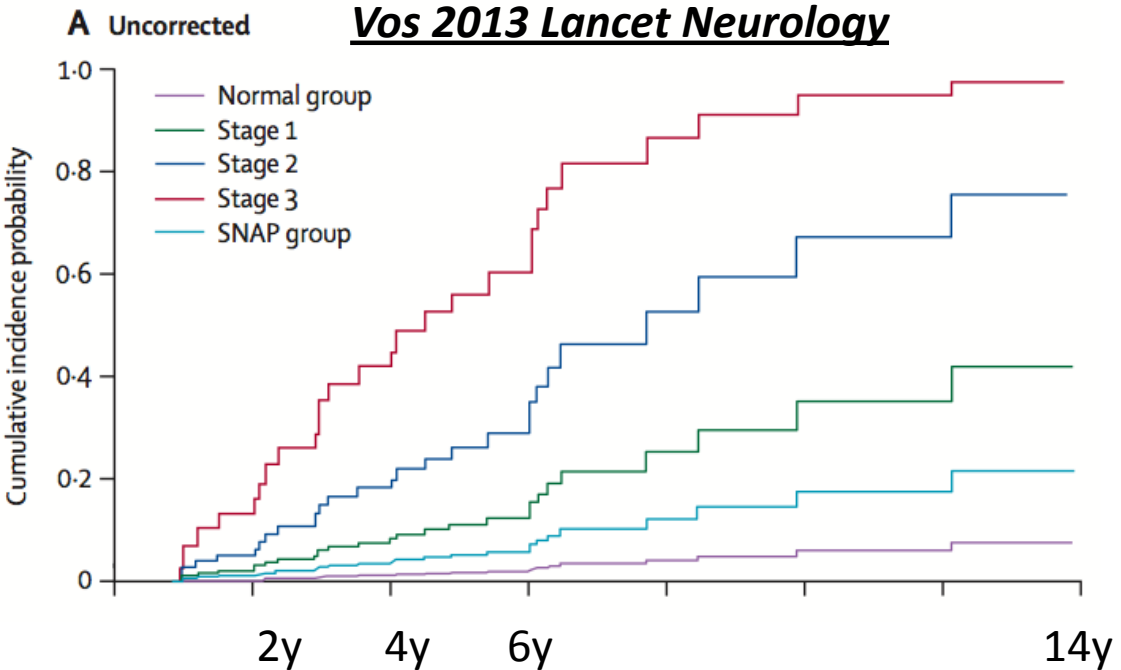
Aβ in conjunction with ND associated with worse cognition

Knopman 2012 Ann Neurol



Median FU=1.3 years

Vos 2013 Lancet Neurology



Study Aims

- **Clarify association between Aβ and ND in HABS and ADNI.**
- **Apply preclinical staging to HABS.**
- **Examine associations between preclinical stages and cognition in HABS.**

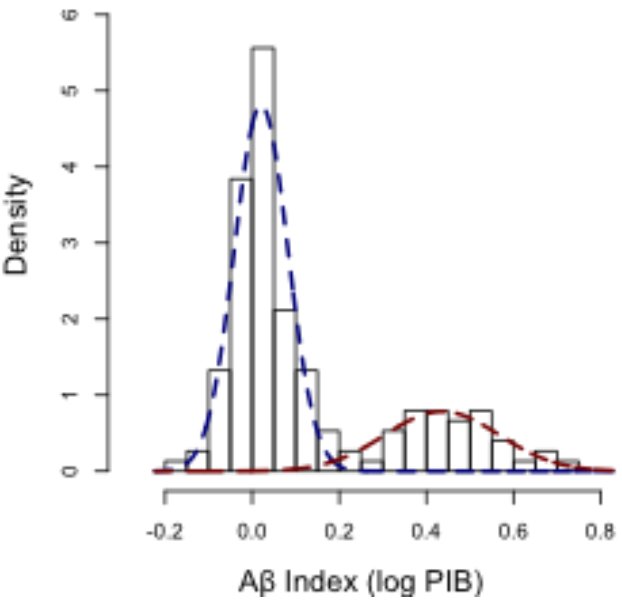
Demographics

	HABS	ADNI2
N*	191	252*
Age#	74.5 (6.0)	75.6 (6.6)
% Female	58%	51%
Education	16.0 (2.9)	16.3 (2.7)
Aβ Status#	135 Low, 7 Ambig, 49 High	120 Low, 72 Ambig, 60 High
% *APOE4+*	27%	27%

*N=196 with v5.1 hippocampus volume available online @ LONI
#HABS CN versus ADNI CN ($p<0.10$)

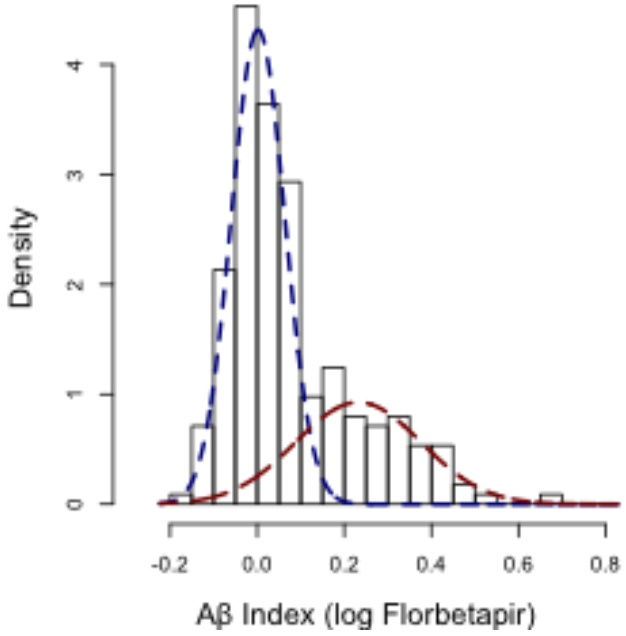
Defining Aβ Cut Offs: Gaussian Mixture Modeling

HABS (PIB)



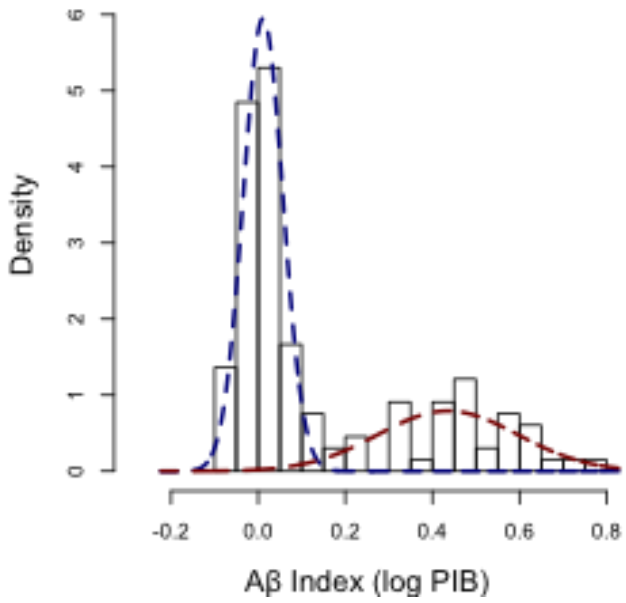
22% Aβ+
74% Aβ-
4% Ambiguous

ADNI (AV45)

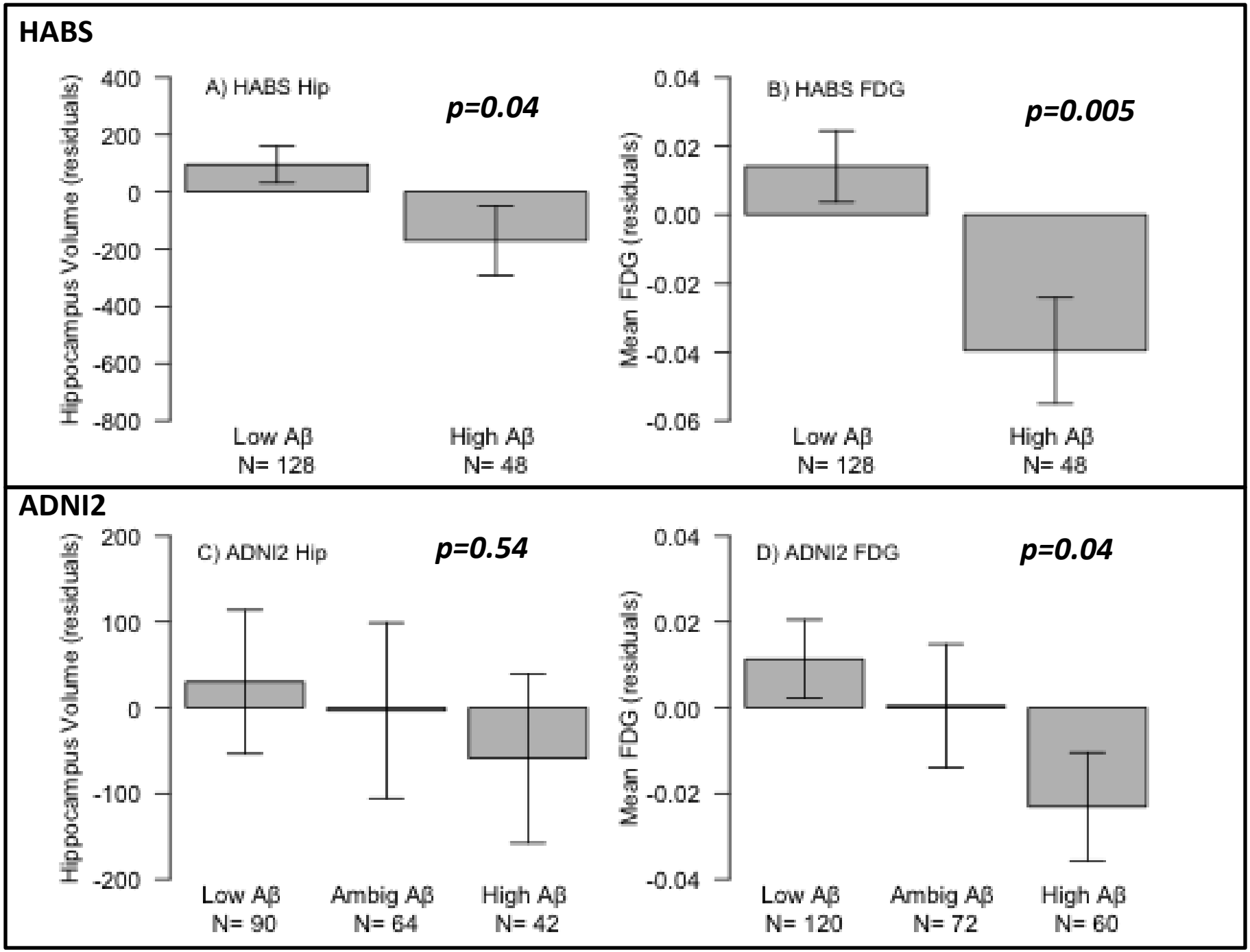


24% Aβ+
48% Aβ-
28% Ambiguous

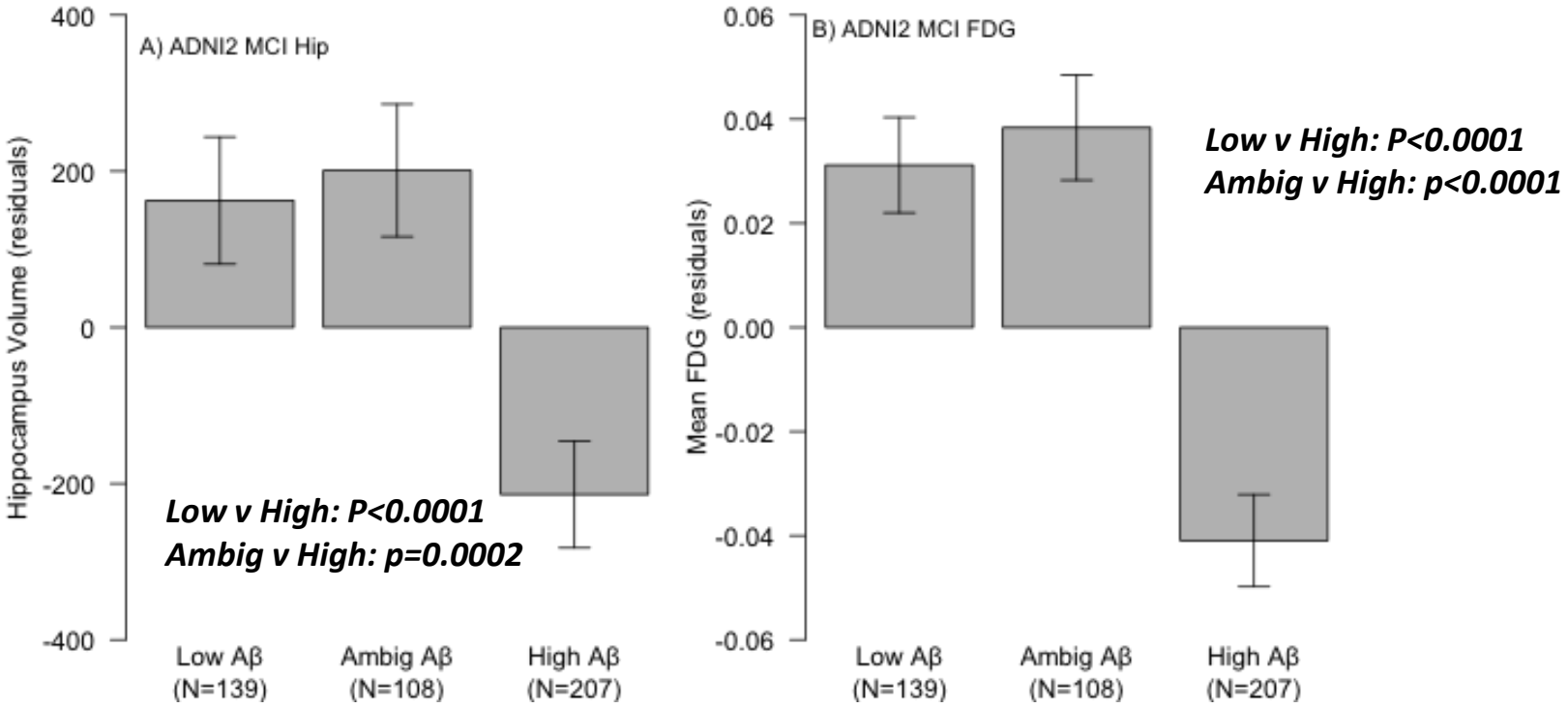
AIBL (PIB)



31% Aβ+
66% Aβ-
4% Ambiguous

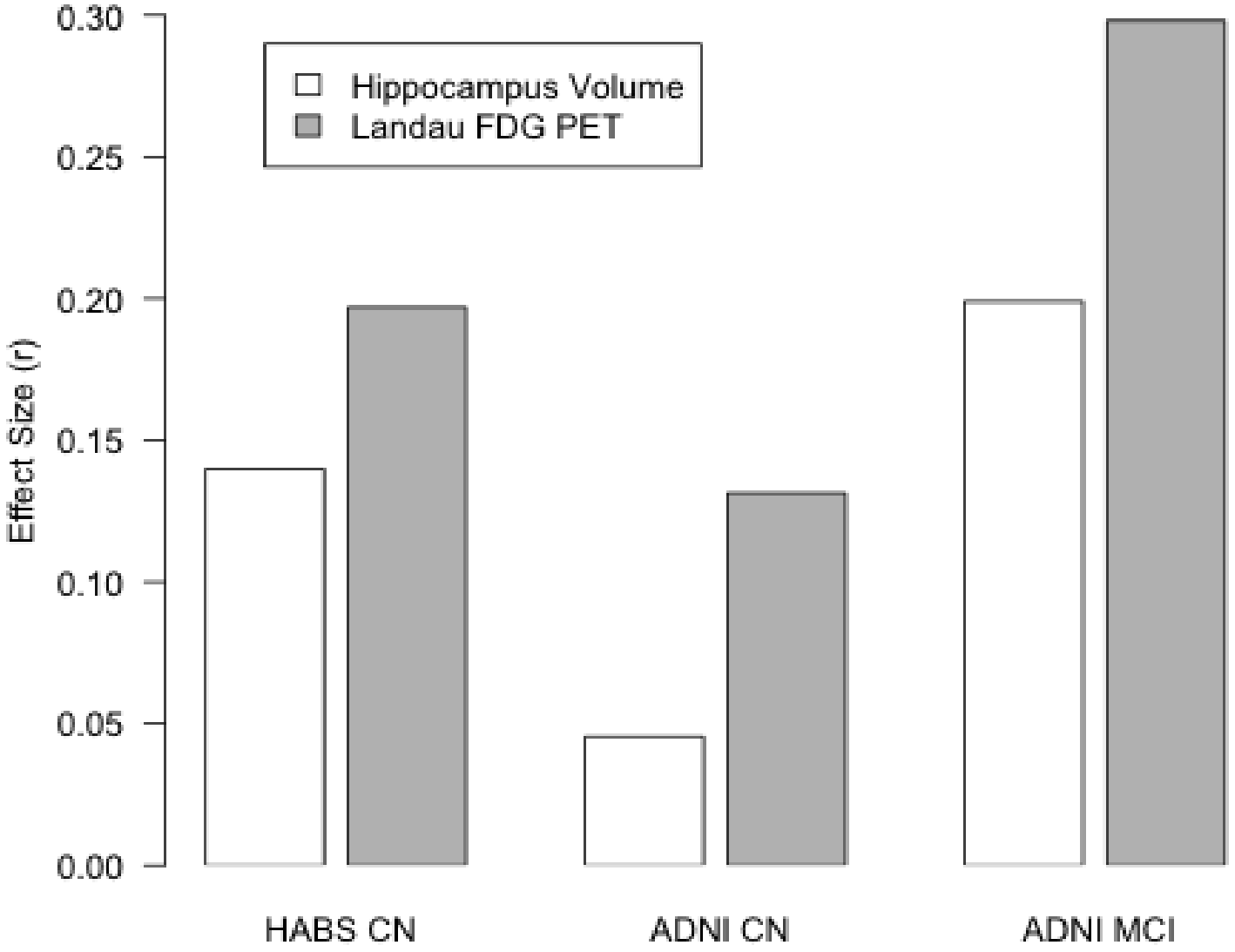

HABS
A) HABS Hip
p=0.04
Hippocampus Volume (residuals)
400
200
0
-200
-400
-600
-800
Low Aβ
N= 128
High Aβ
N= 48
B) HABS FDG
p=0.005
Mean FDG (residuals)
0.04
0.02
0.00
-0.02
-0.04
-0.06
Low Aβ
N= 128
High Aβ
N= 48
ADNI2
C) ADNI2 Hip
p=0.54
Hippocampus Volume (residuals)
200
100
0
-100
-200
Low Aβ
N= 90
Ambig Aβ
N= 64
High Aβ
N= 42
D) ADNI2 FDG
p=0.04
Mean FDG (residuals)
0.04
0.02
0.00
-0.02
-0.04
Low Aβ
N= 120
Ambig Aβ
N= 72
High Aβ
N= 60

	ADNI2 MCI
N	**454**
Age	**72.3 (8.0)**
% Female	**44%**
Education	**16.1 (2.7)**
% Aβ+	**60%**
Aβ Status	**139 Low, 108 Ambig, 207 High**
% *APOE4+*	**47%**



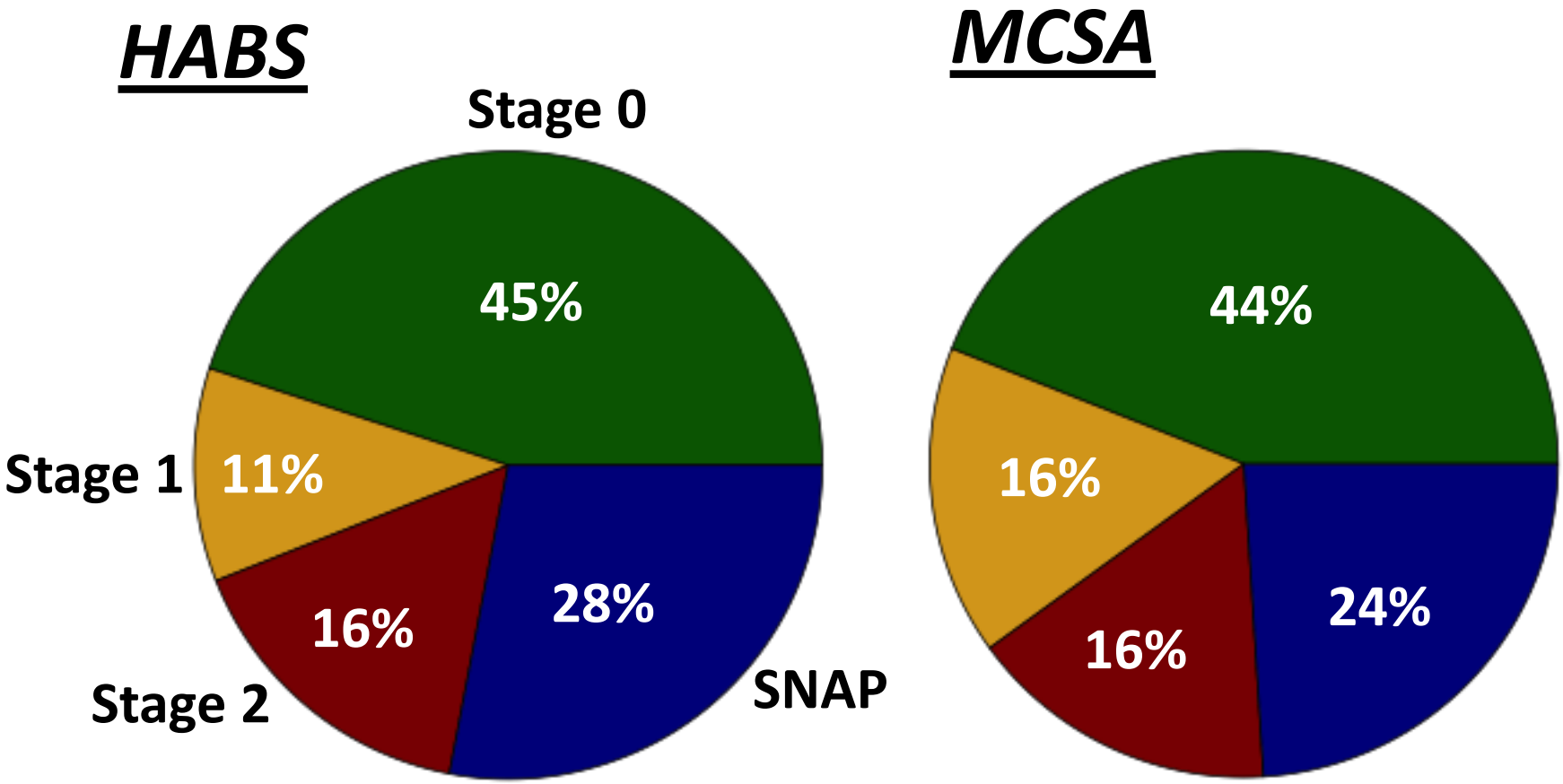
Effect Sizes

r effect size
Small=0.1 (1%)
Medium=0.3 (9%)
Large=0.5 (25%)



Apply preclinical staging to HABS

	Aβ-	Aβ+
ND-	Stage 0	Stage 1
ND+	SNAP	Stage 2



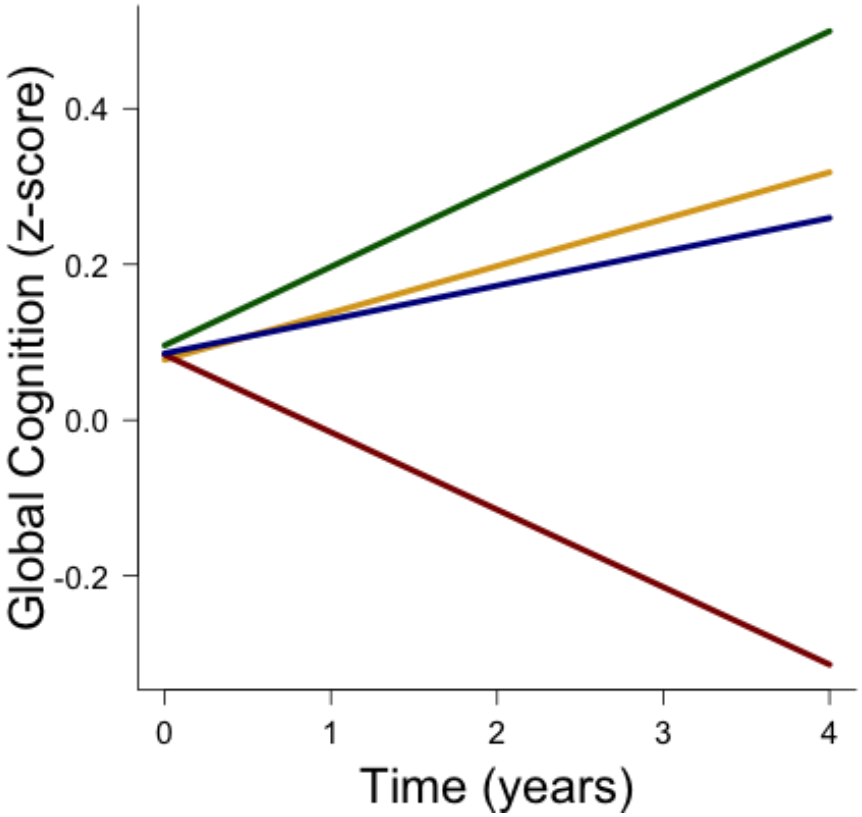
Demographics by preclinical stage

	Stage 0	Stage 1	Stage 2	SNAP
N	93	22	32	58
Age	70 (67, 76)	73 (70, 78)	77 (74, 82)	77 (72, 81)
Education	16 (14, 18)	16 (14, 18)	16 (15, 18)	16 (12, 18)
% Female	61%	59%	63%	40%
% APOE4+	17%	63%	54%	16%

Do preclinical groups show different patterns of cognitive decline?

Aβ + ND associated with greatest decline

Median Follow Up: 2 years



Aβ+ x Time: p<0.0001
ND+ x Time: p=0.0002
Aβ+ x ND+ x Time: p=0.035

Comparison	p
SNAP v Stage 0	0.038
SNAP v Stage 1	0.666
Stage 1 v Stage 0	0.270
Stage 2 v Stage 0	<0.0001
Stage 2 v Stage 1	<0.0001
Stage 2 v SNAP	<0.0001

Stage 0 (Aβ-/ND-)
Stage 1 (Aβ+/ND-)
Stage 2 (Aβ+/ND+)
SNAP (Aβ-/ND+)

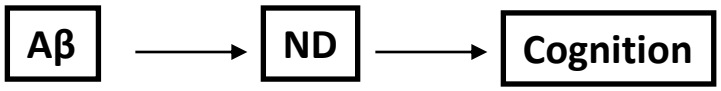
Global cognition composite score: Logical Memory delayed recall, Face-Name (CRN), Selective Reminding Test delayed recall, Trails B-A, Categories, FAS, Digit Symbol, MMSE

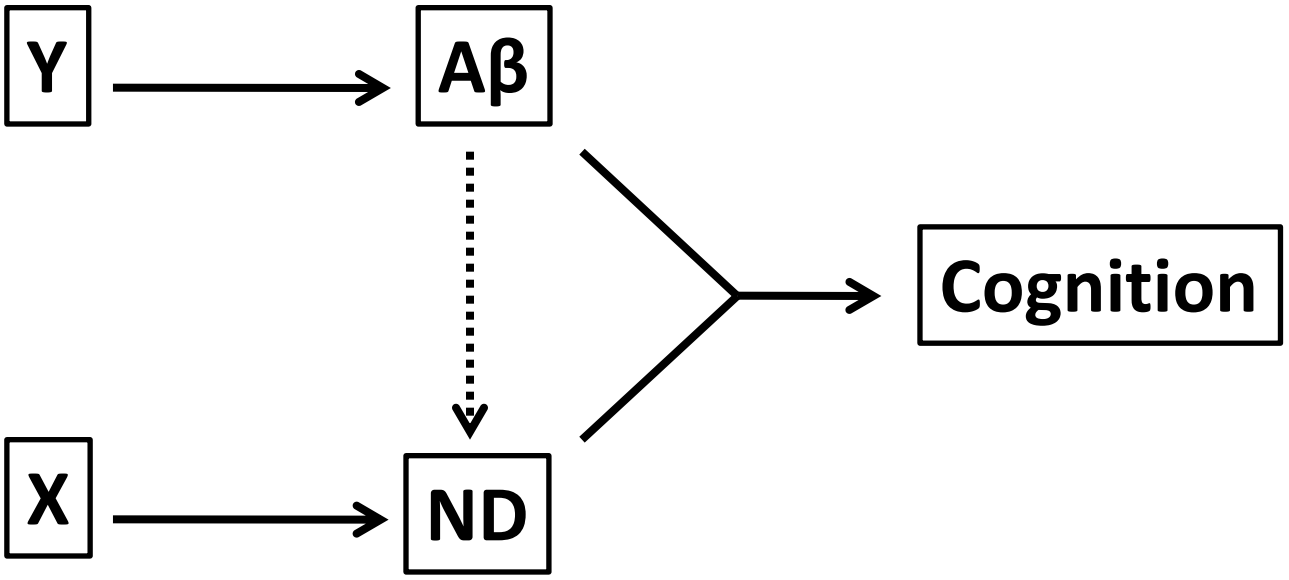
Summary

- **Subtle associations between ND and Aβ in normals (sometimes)**
  - **ND present in the absence of elevated Aβ**

- **Cognition impaired in subjects with BOTH ND and Aβ**
  - **Single factor insufficient**

Potential Model





Risk Factors for Aβ (Y): Genetics, neural activity?
Risk Factors for ND (X): Tau, Vascular disease, other age related pathologies, lifestyle factors?

Thank you!

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ADNI

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HARVARD AGING BRAIN

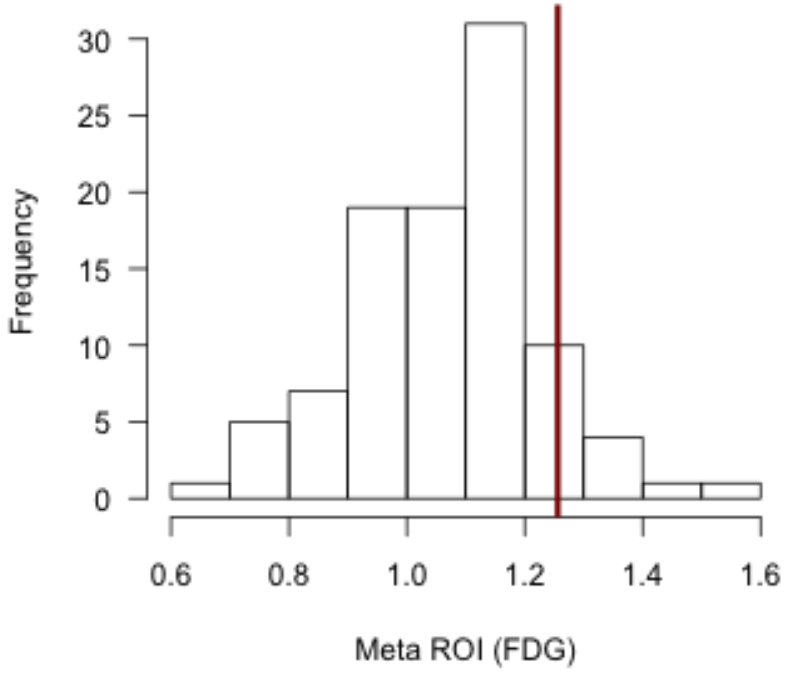
Massachusetts General Hospital - Harvard Medical School - Brigham and Women's Hospital

EXTRA

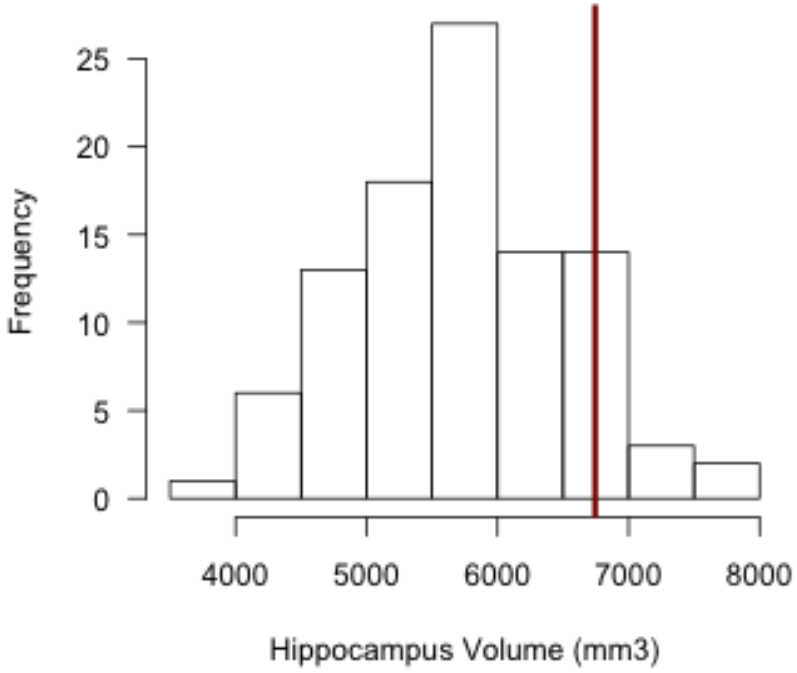
Deriving Cut Offs using ADNI AD

	ADNI AD
N	127
Age	75.9 (7.6)
Gender	43%
Education	15.8 (2.8)
% Aβ+	88%
% *APOE4+*	70%

FDG Cut off=1.256

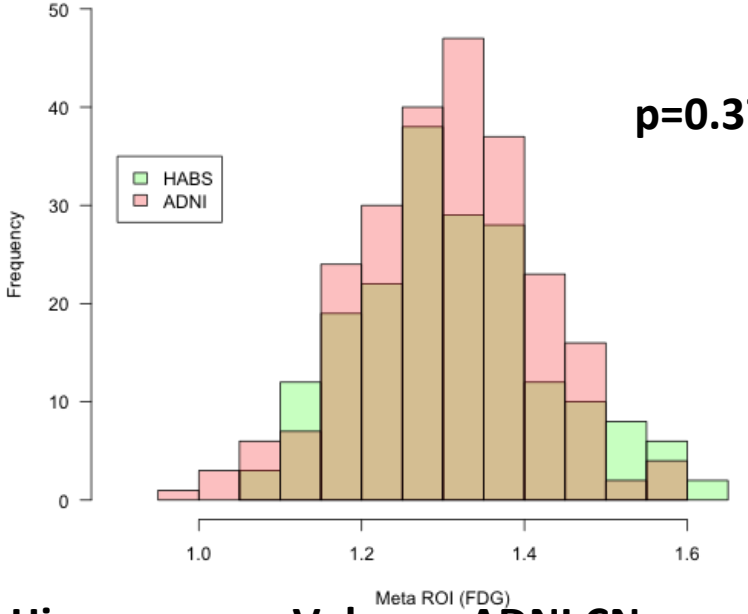


Hip Cut off=6745mm^3



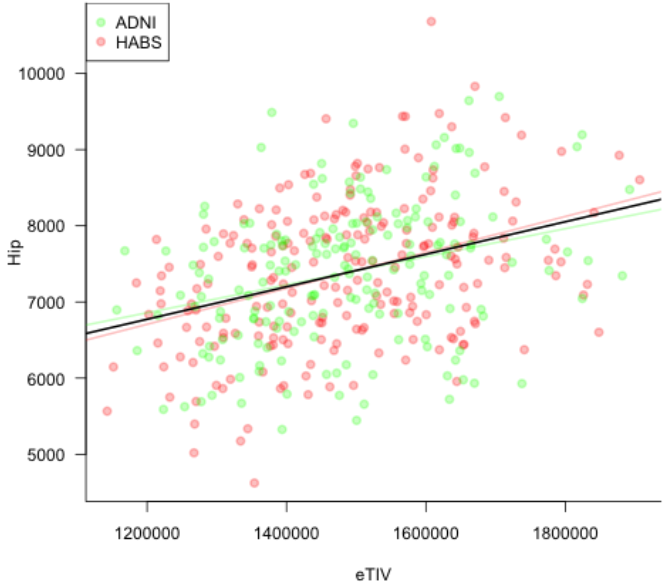
Comparing CN distributions

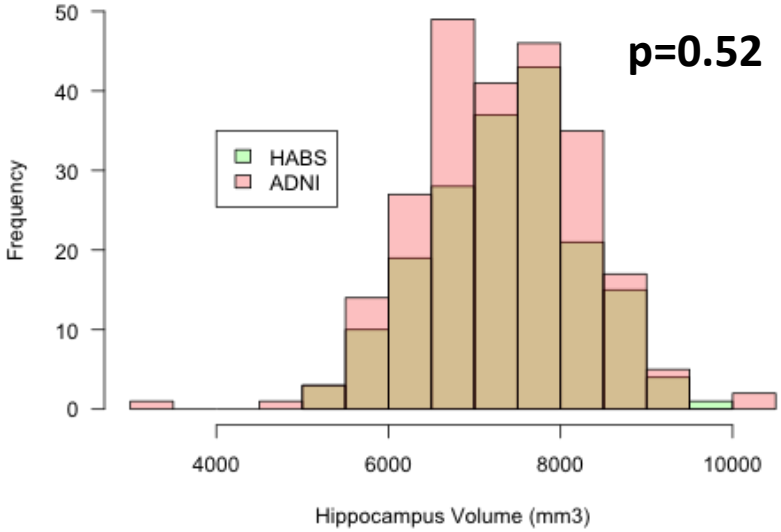
Meta ROI FDG: ADNI CN versus HABS CN



	FDG-	FDG+
Hip-	114 (58%)	44 (22%)
Hip+	17 (9%)	22 (11%)

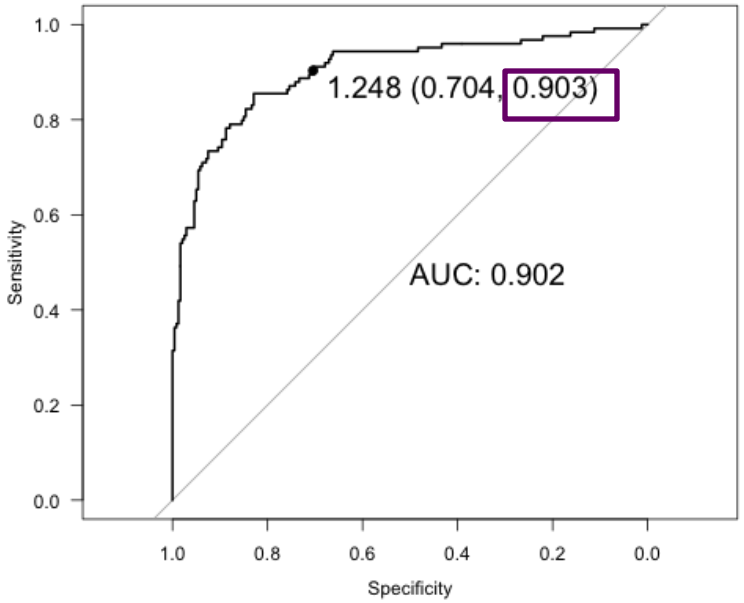
Hippocampus Volume: ADNI CN versus HABS CN



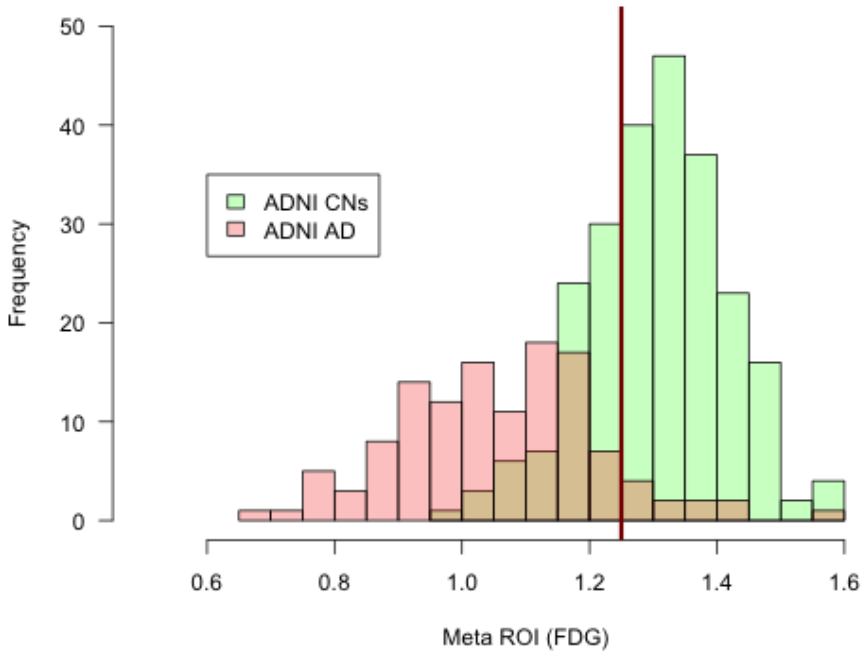


Find cut off with 90% sensitivity

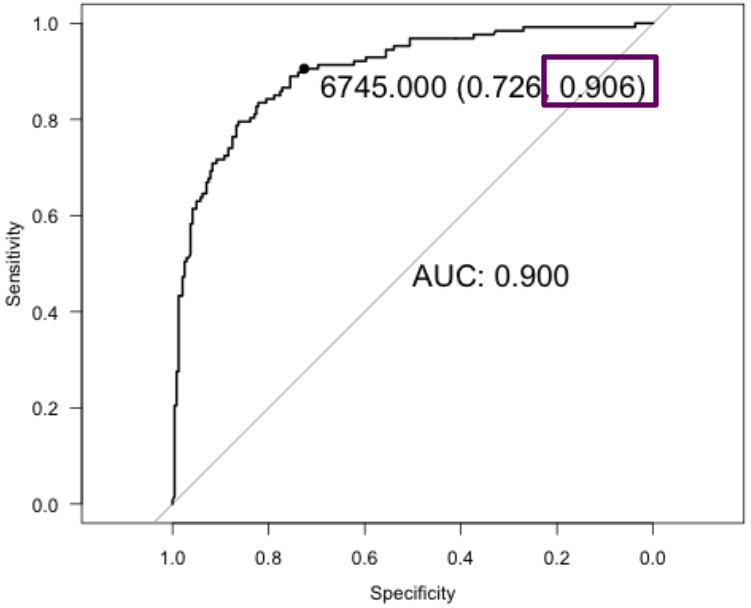
Meta ROI FDG

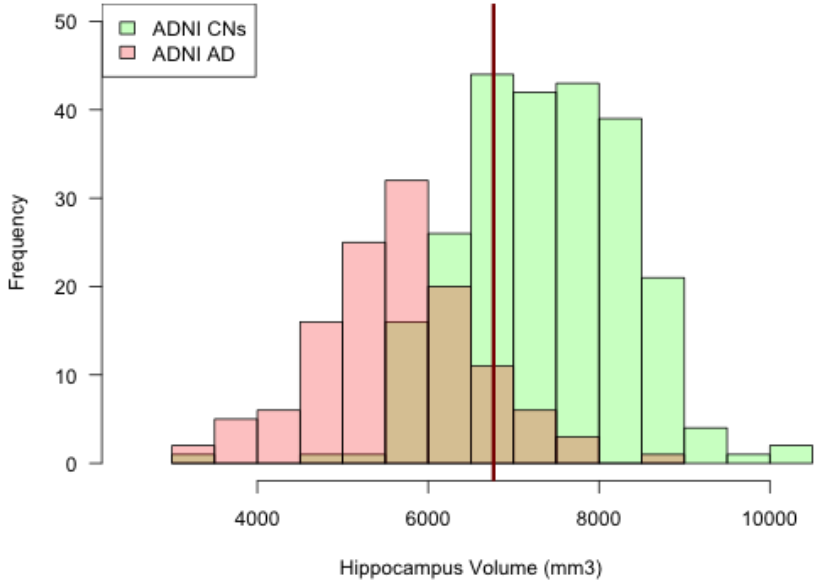


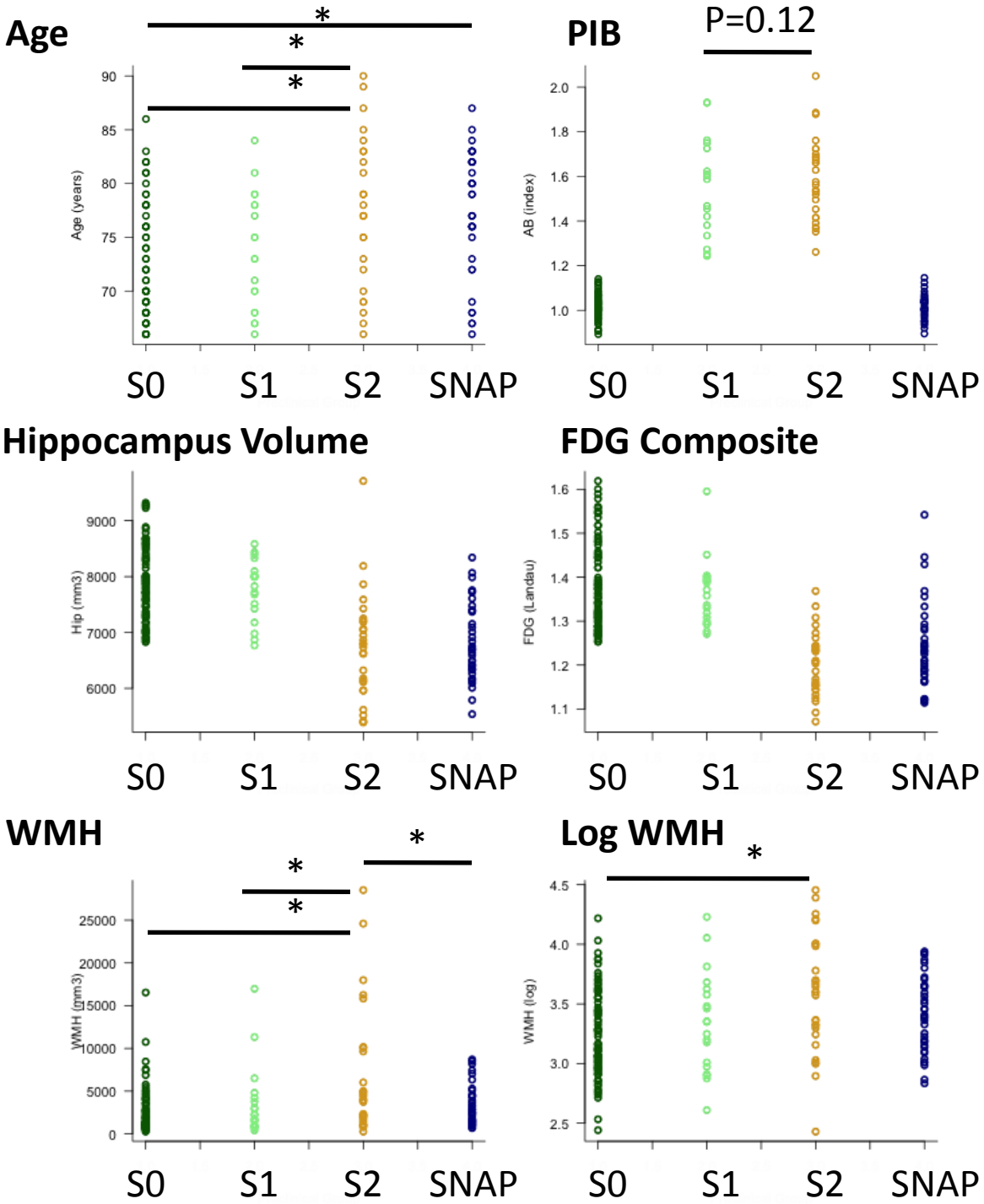
ADNI CN versus ADNI AD

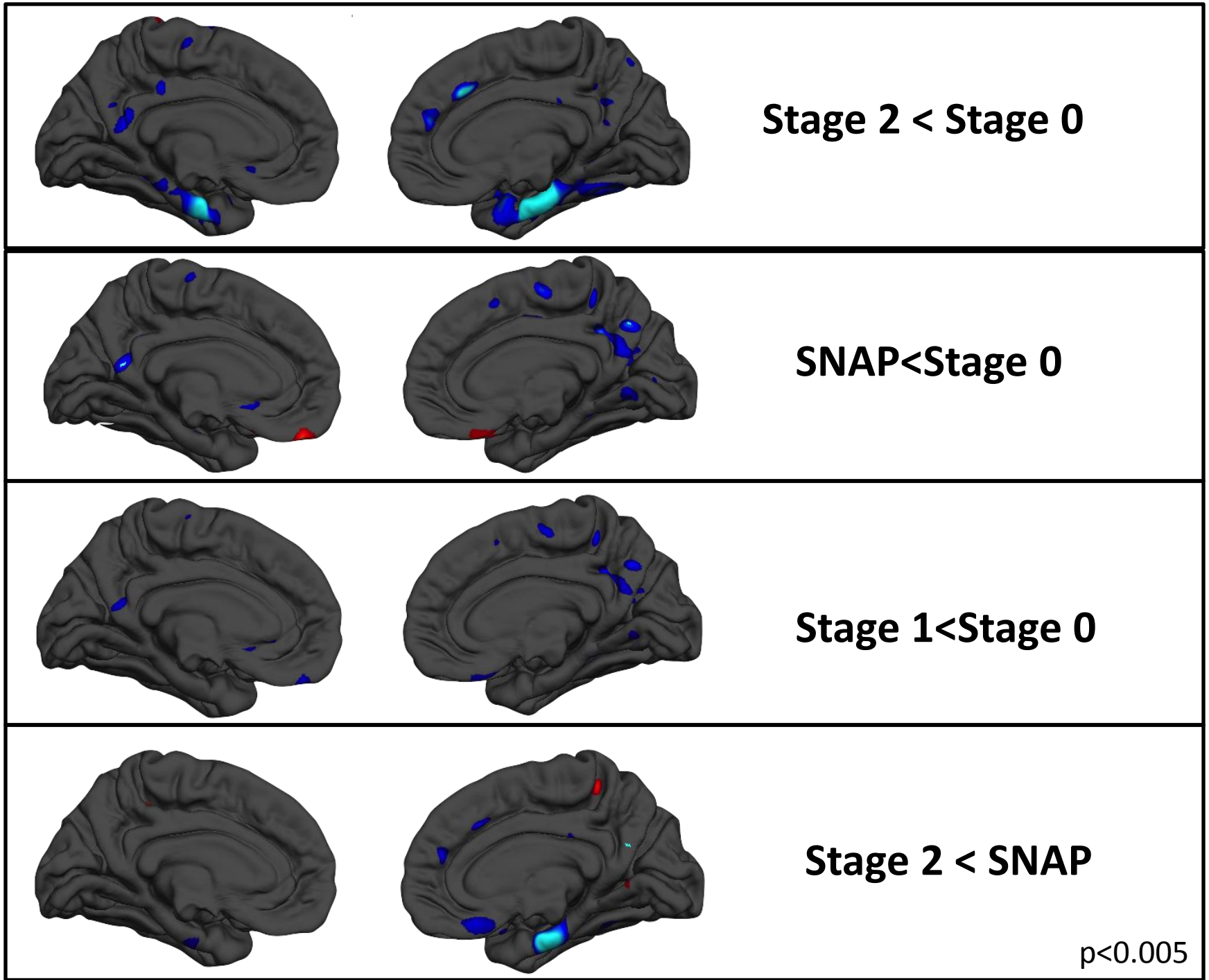


Hippocampus Volume






Age
*
*
*
90
85
80
75
70
Age (years)
S0
S1
S2
SNAP
PIB
P=0.12
2.0
1.8
1.6
1.4
1.2
1.0
AB (index)
S0
S1
S2
SNAP
Hippocampus Volume
9000
8000
7000
6000
Hip (mm3)
S0
S1
S2
SNAP
FDG Composite
1.6
1.5
1.4
1.3
1.2
1.1
FDG (Landau)
S0
S1
S2
SNAP
WMH
*
*
*
25000
20000
15000
10000
5000
0
WMH (mm3)
S0
S1
S2
SNAP
Log WMH
*
4.5
4.0
3.5
3.0
2.5
WMH (log)
S0
S1
S2
SNAP


Stage 2 < Stage 0
SNAP<Stage 0
Stage 1<Stage 0
Stage 2 < SNAP
p<0.005