Relationship of biomarker classification for AD to longitudinal decline among clinically normal older participants

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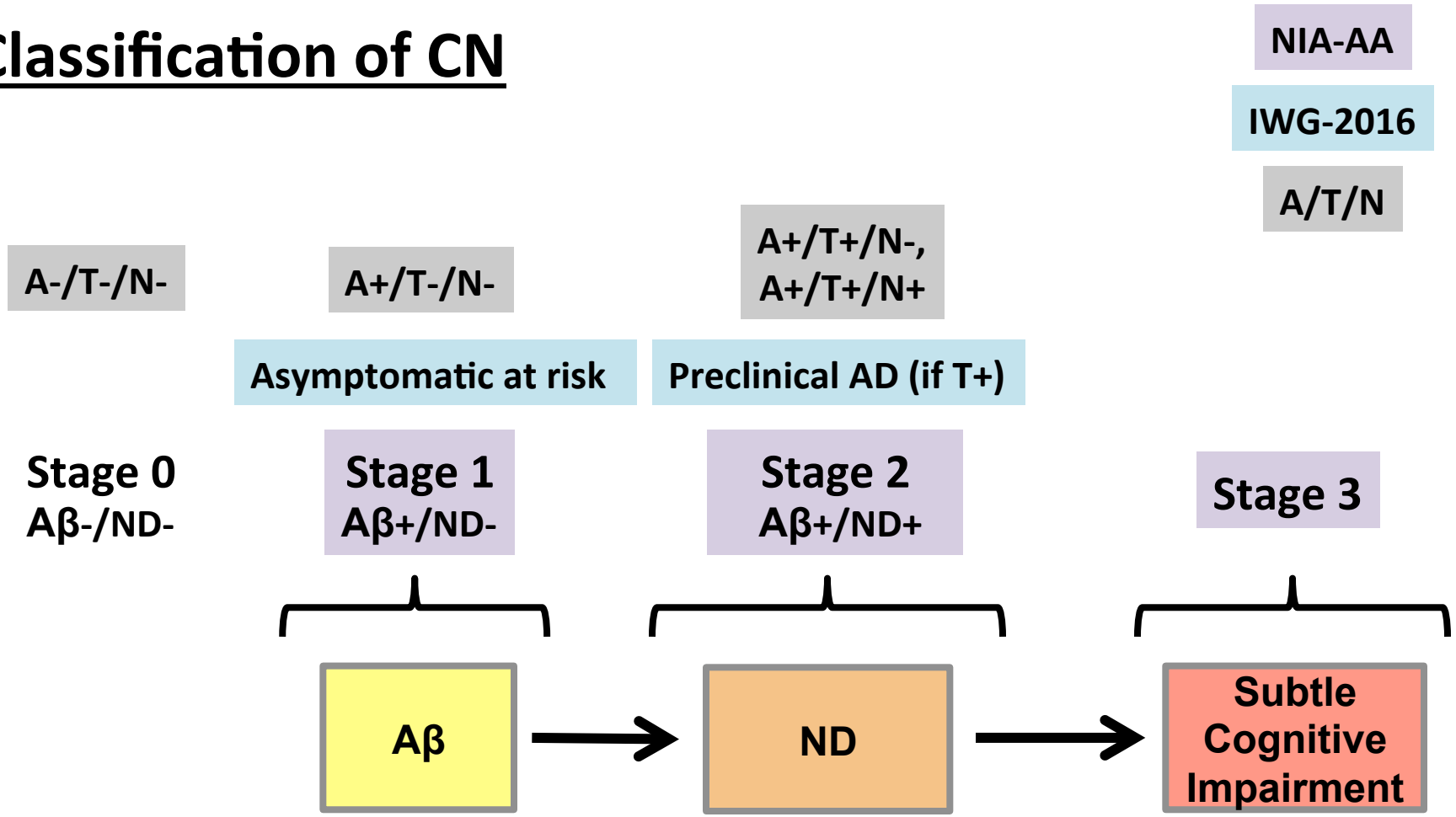
Outline

- **Biomarker classification in clinically normal participants**
- **Longitudinal decline by NIA-AA preclinical stages**
- **Associations between Aβ, ND, & Tau PET**
- **Early Aβ related cognitive changes (among Stage 1)**

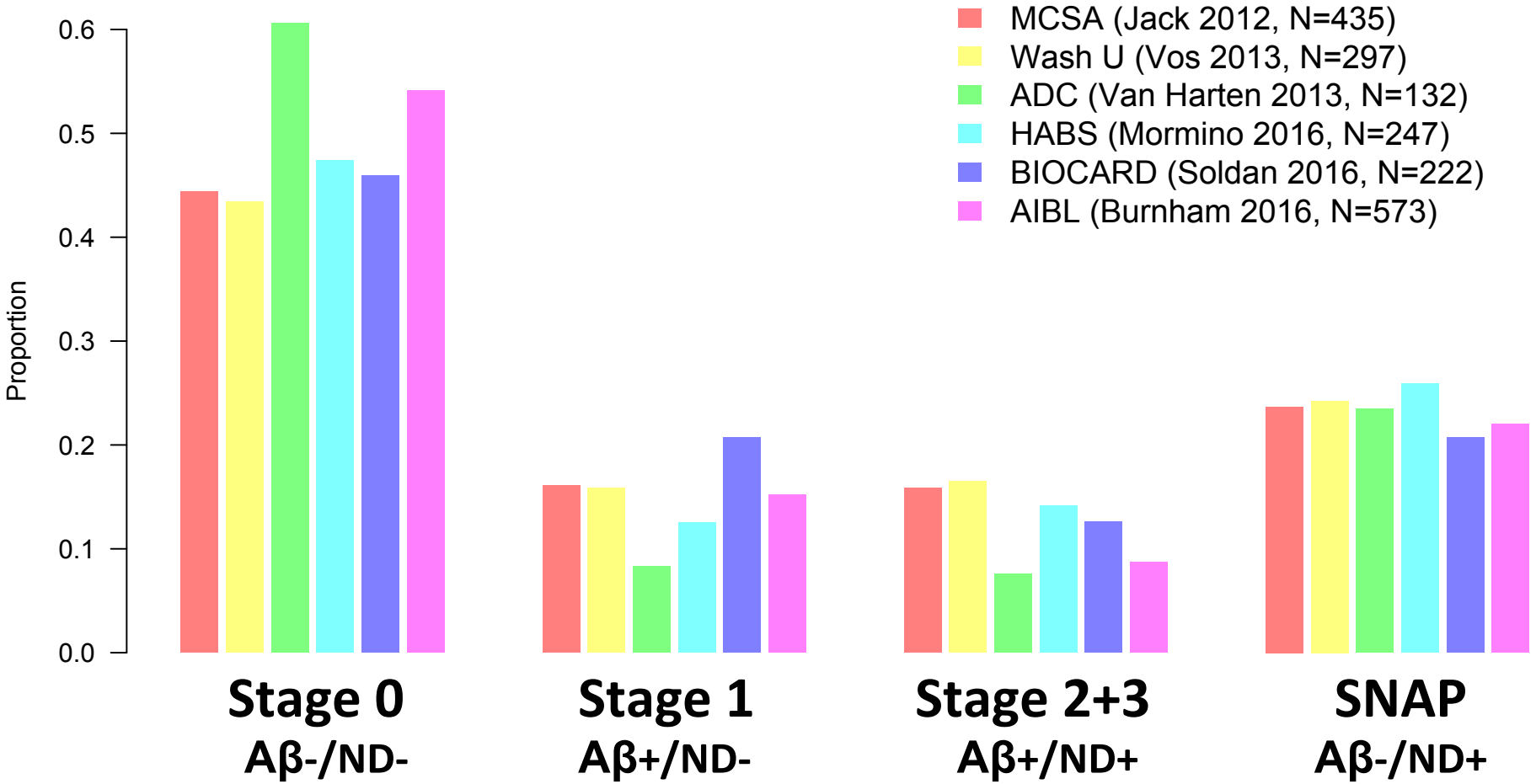
Classification of CN



NIA-AA preclinical staging

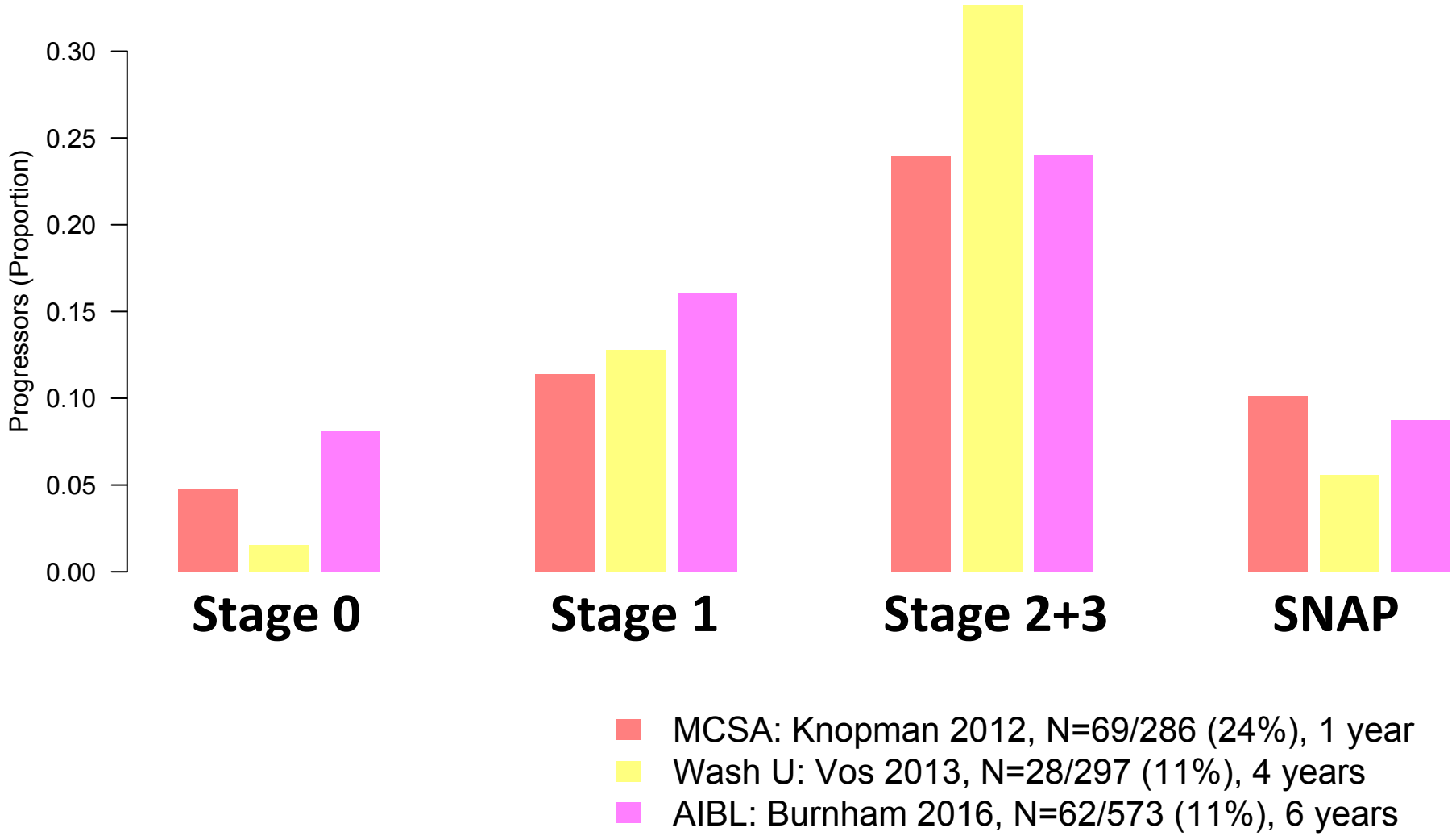
		MRI (hippocampus, AD-like) FDG (AD-like) CSF (Tau, pTau)	
		ND-	ND+
Amyloid PET CSF Aβ	Aβ-	Stage 0	SNAP
	Aβ+	Stage 1	Stage 2

NIA-AA preclinical stages across cohorts



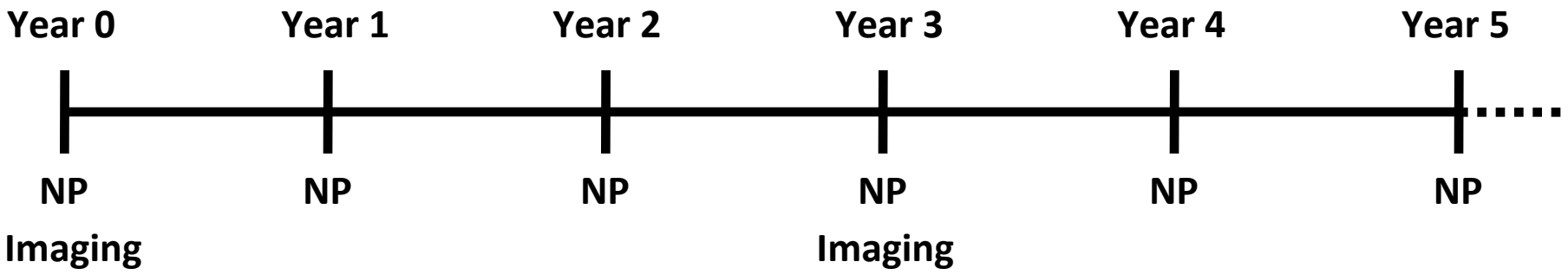
Longitudinal decline by NIA-AA preclinical stages

Greatest functional progression in Stage 2



Harvard Aging Brain Study (HABS)

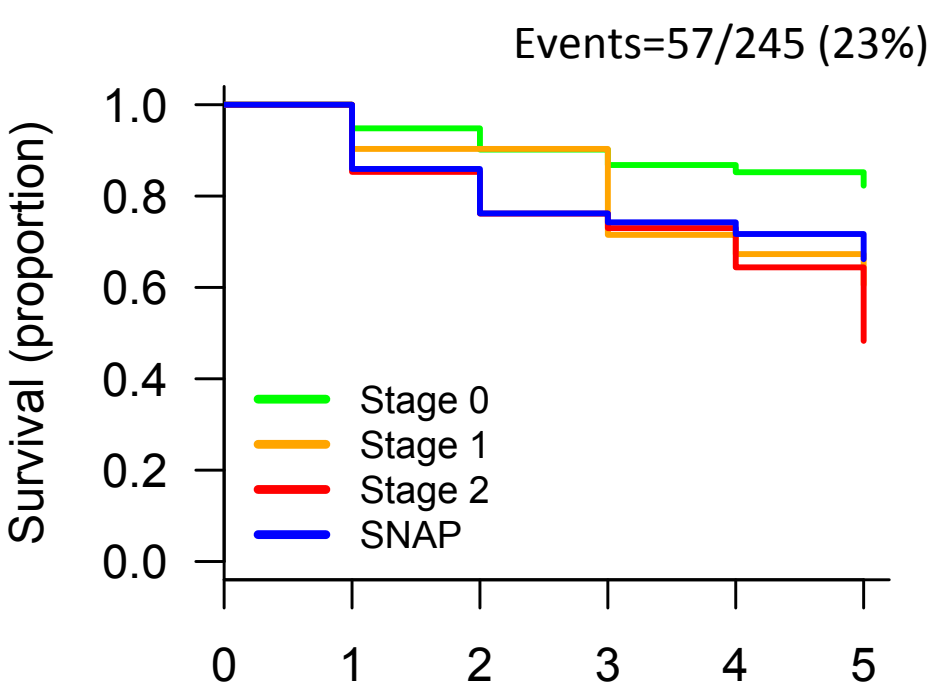
Baseline Criteria
CDR=0
Age 60-90
MMSE>25



	SNAP	Stage 0	Stage 1	Stage 2
N	64 (25.9%)	117 (47.4%)	31 (12.6%)	35 (14.2%)
Age	76.5 (71.1, 81.3)	70.0 (66.9, 75.3)	72.3 (69.3, 77.2)	76.9 (73.0, 82.2)
Female	46.9%	62.4%^	58.1%	60%
Education	16 (12, 18)	16 (13, 18)	16 (14, 18)	16 (16, 18)
APOE4+	17.8%	15.0%	64.3%	53.1%
Follow Up	3.6 (2.2, 4.2)	3.9 (2.1, 4.4)	4.0 (2.7, 4.2)	4.1 (3.0, 5.0)

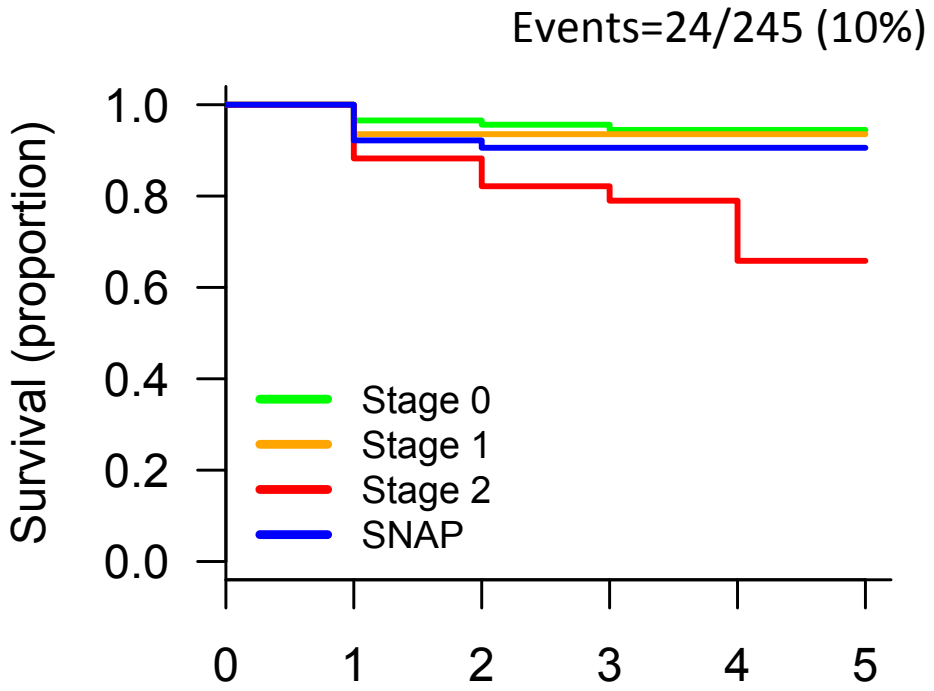
Functional progression in HABS (follow up=4 years)

Time to CDR 0.5



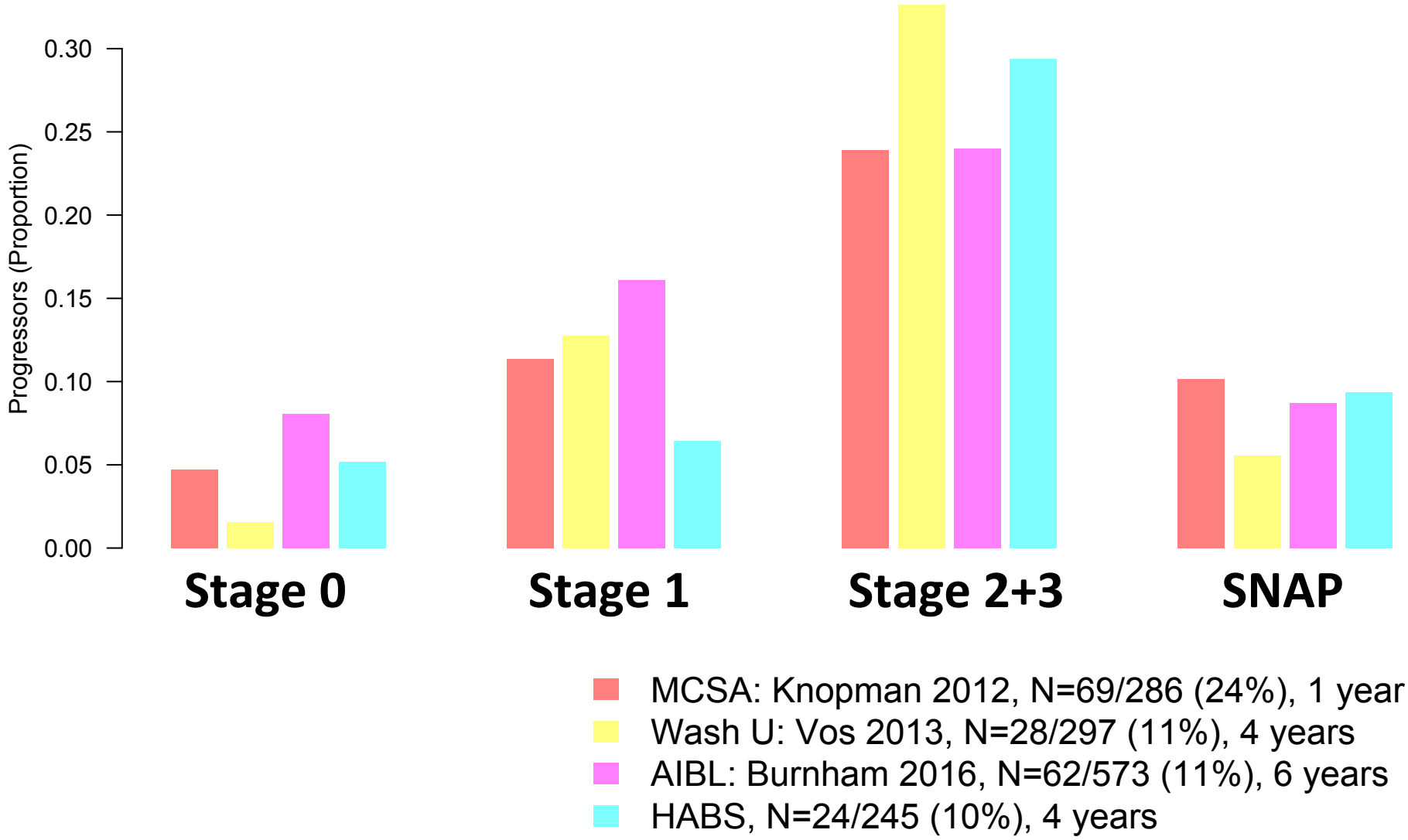
	N	HR
Stage 0	14%	-
Stage 1	32%	2.23*
Stage 2	38%	2.90*
SNAP	28%	2.16*

Time to "consistent" CDR 0.5



	N	HR
Stage 0	5%	-
Stage 1	6%	1.26
Stage 2	29%	6.92*
SNAP	9%	2.14

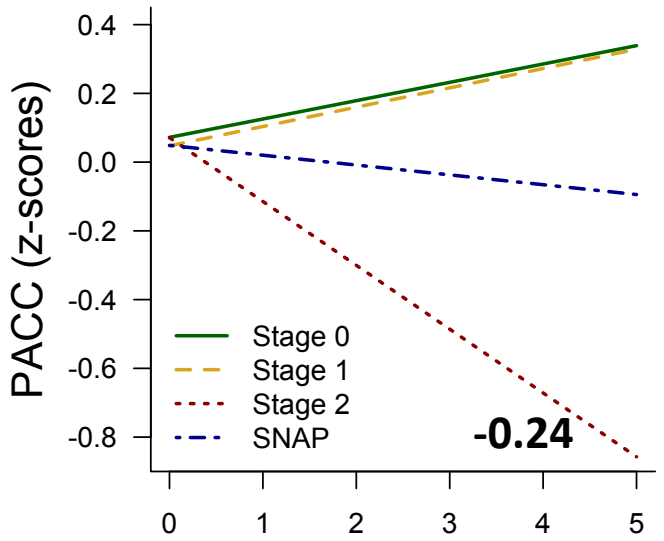
Summary of Progression by NIA-AA preclinical stages



Cognitive decline by NIA-AA Stages

HABS

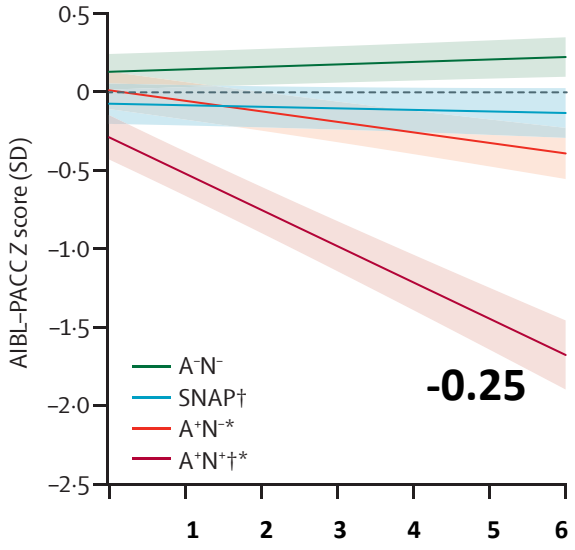
N=247
4 years
Age=74
ND=Hip Vol
Or FDG



Mormino 2016 JAMA Neurol

AIBL

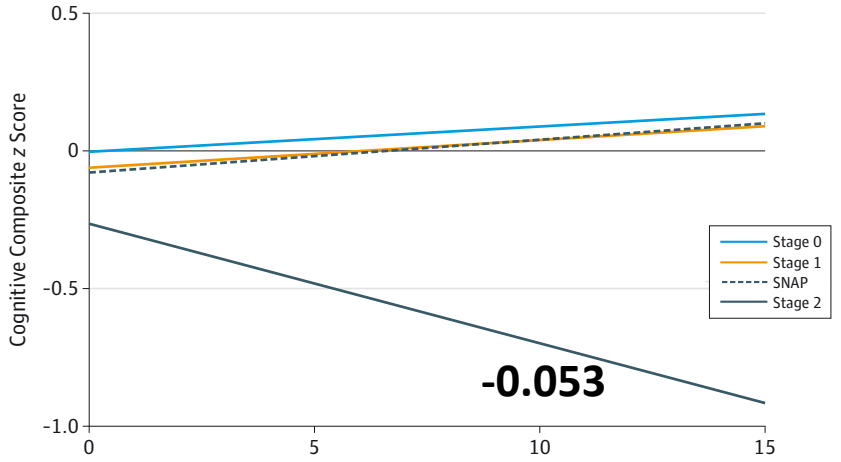
N=573
6 years
Age=73
ND=Hip Vol



Burnham 2016 Lancet Neurol

BIOCARD

N=222
11 years
Age=57
ND=CSF Tau



Soldan 2016 JAMA Neurol

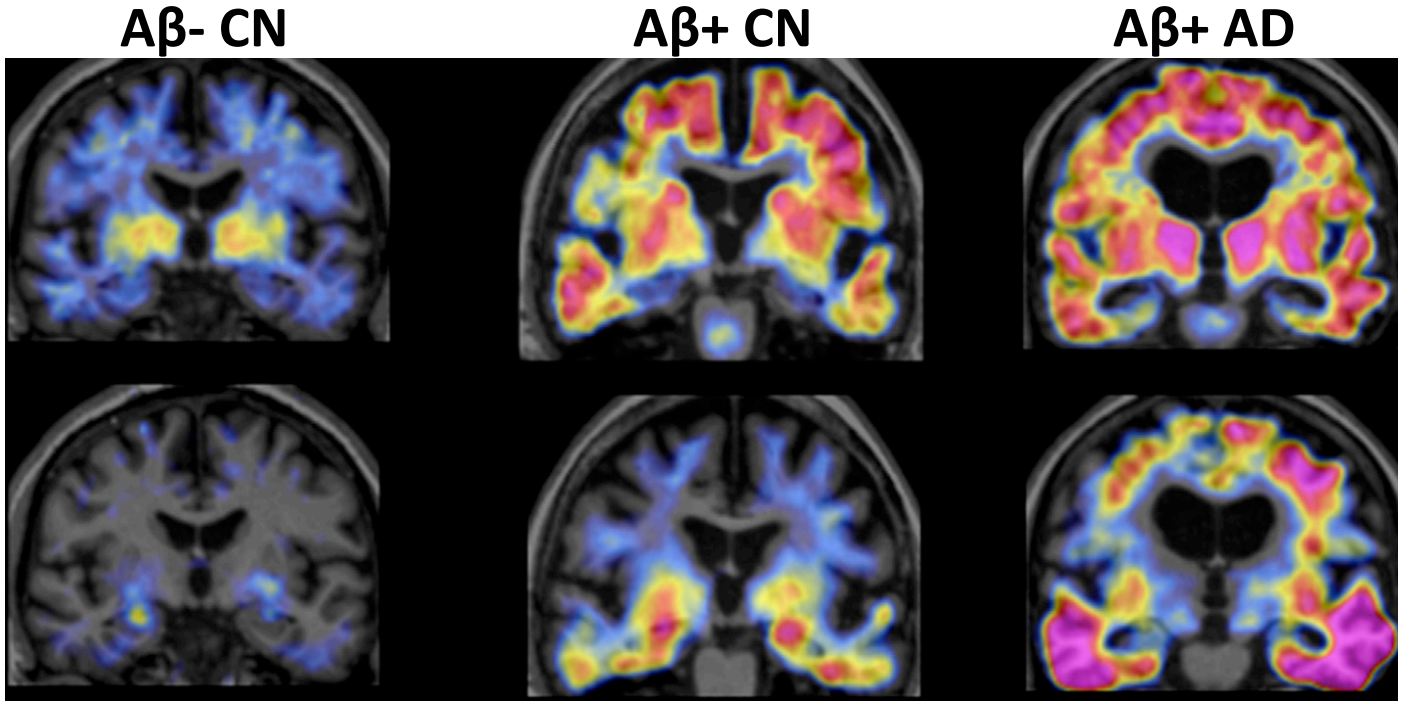
HABS: Multi-domain decline in Stage 2

		Stage 0 vs.		
		Stage 1 Aβ+/ND-	**Stage 2** Aβ+/ND+	**SNAP** Aβ-/ND+
	MMSE	0.61	-4.40**	-1.83
Memory	FC SRT(Free Recall)	-1.20	-5.17**	-0.88
	FC SRT (Total Recall)	-0.04	-5.96**	-0.42
	6-SRT Total Recall	-2.33	-5.11**	-2.47*
	6-SRT Delayed Recall	-2.51*	-6.21**	-2.72**
	6-SRT MC	-0.44	-1.81	-0.15
	Logical Memory II	-0.14	-4.41**	-2.88**
Language	Category Fluency	-3.06**	-4.76**	-2.81**
	Boston Naming Test	-1.72	-3.60**	-2.50*
Attention	Digits Forward	-0.59	-1.12	-0.73
	Digits Backward	0.26	-1.98	-0.98
	Trail Making Test A	-0.73	-1.55	-1.79
	Letter Number Sequencing	-0.44	-1.47	-1.11
Executive Functions	Trail Making Test B	-1.82	-2.56**	-1.87
	Letter Fluency (F-A-S)	-0.44	-2.57*	-1.25
	Digit Symbol	0.35	-3.70**	-1.56
Visuospatial	Visual Form Discrimination	-0.06	-0.58	1.15

Papp in prep

Associations between Aβ, ND, & Tau PET

Tau PET Imaging in HABS

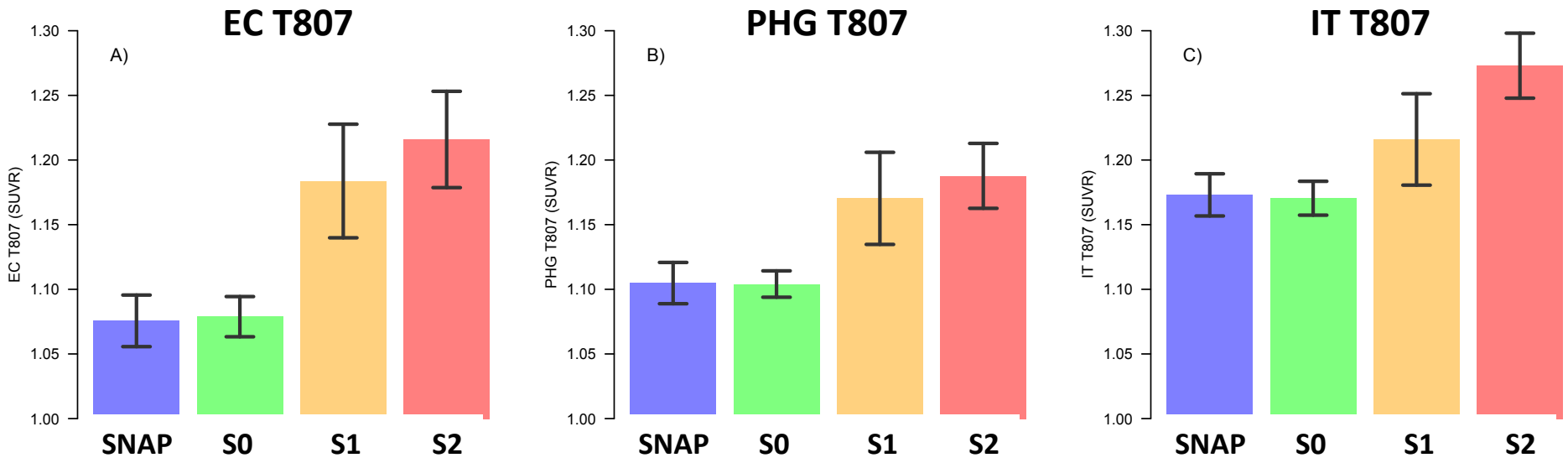


Sperling, Mormino, & Johnson, 2015 Neuron

HABS T807 Sample

	All	Aβ-	Aβ+
N	134	92	42
Age	76.2 (6.2)	75.3 (6.4)	78.3 (5.4)
Female	75	51	24
Ed	15.9 (3.0)	15.7 (3.1)	16.2 (2.7)

Tau PET (T807) more specific for Aβ than ND markers



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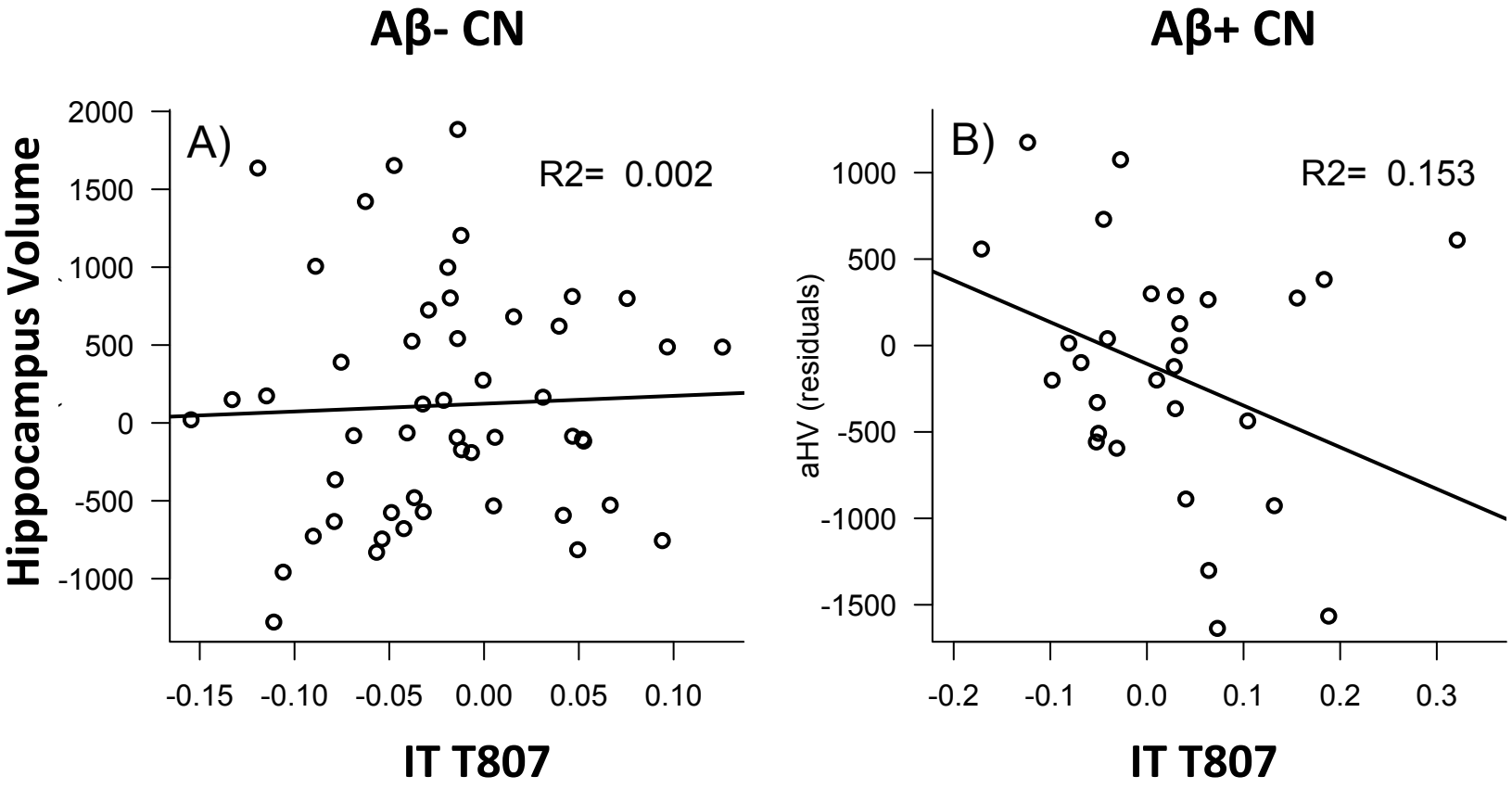
IT Tau associated with hippocampus volume only in Aβ+



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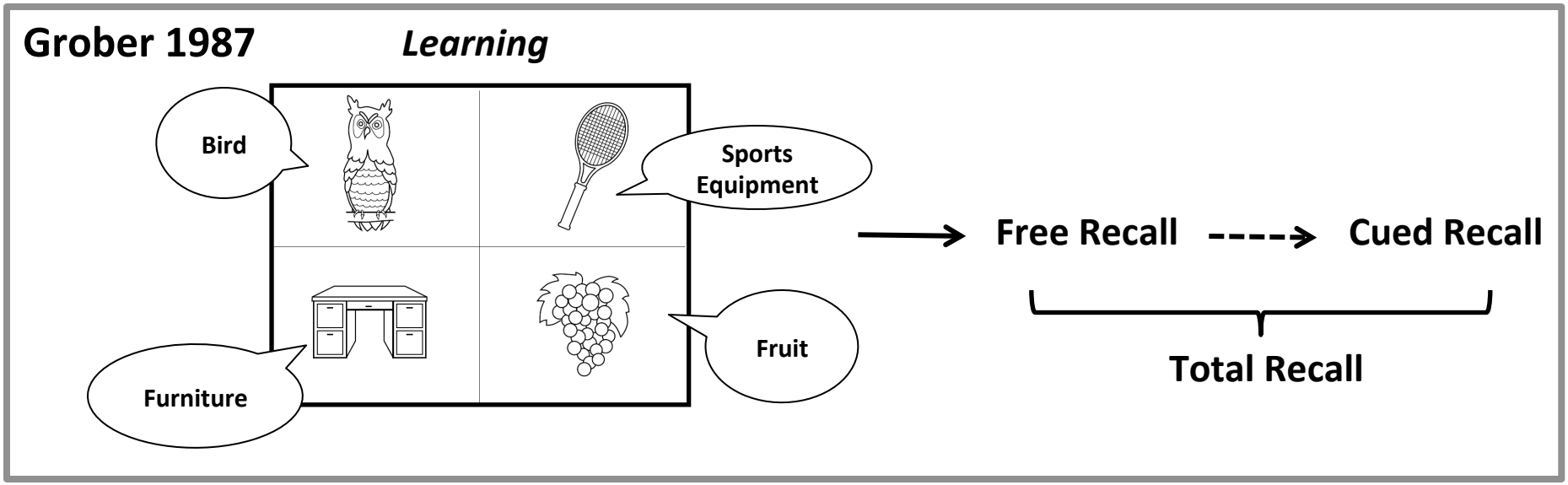
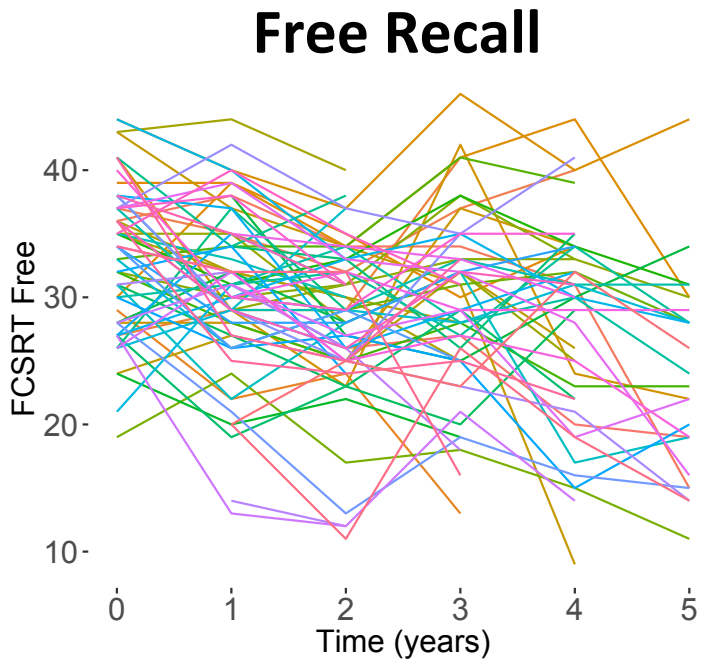
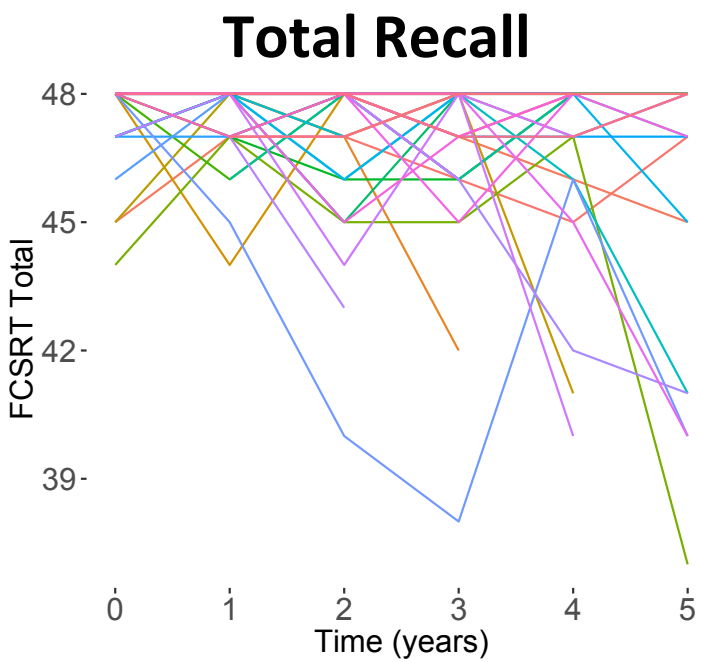
Evidence for early Aβ related cognitive changes

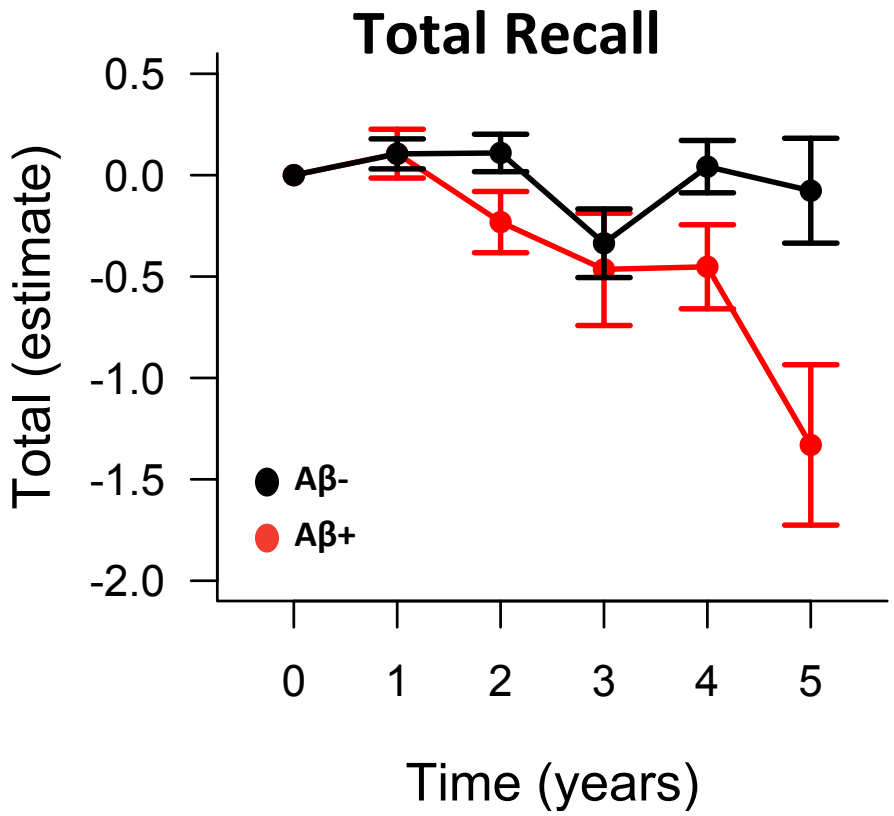
Free and Cued Selective Reminding Test (FCSRT)

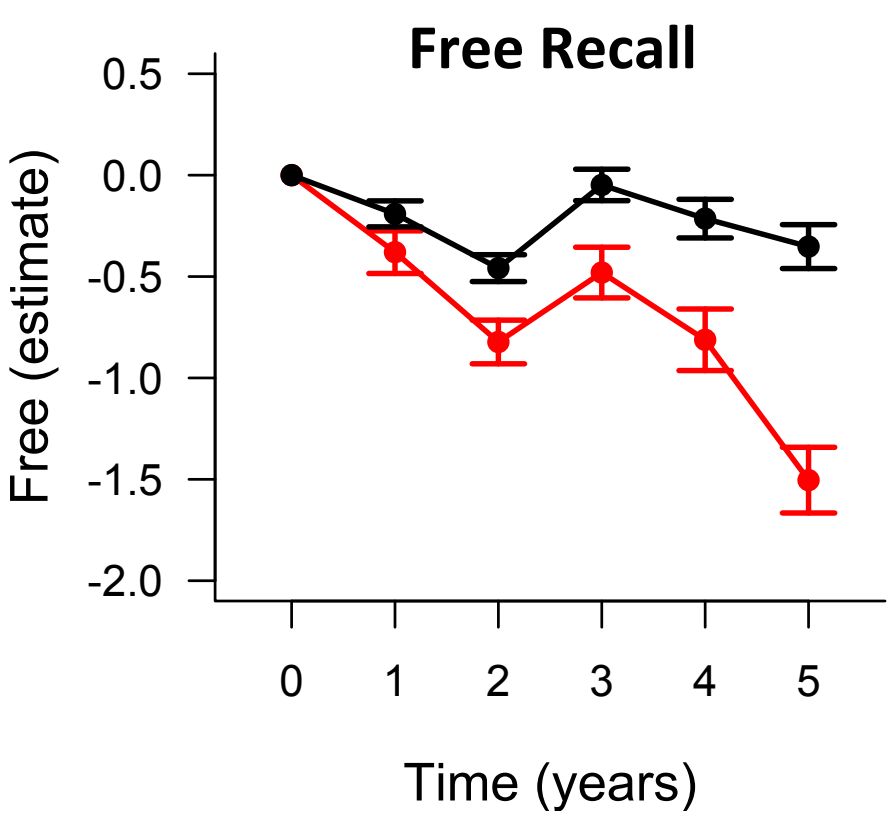






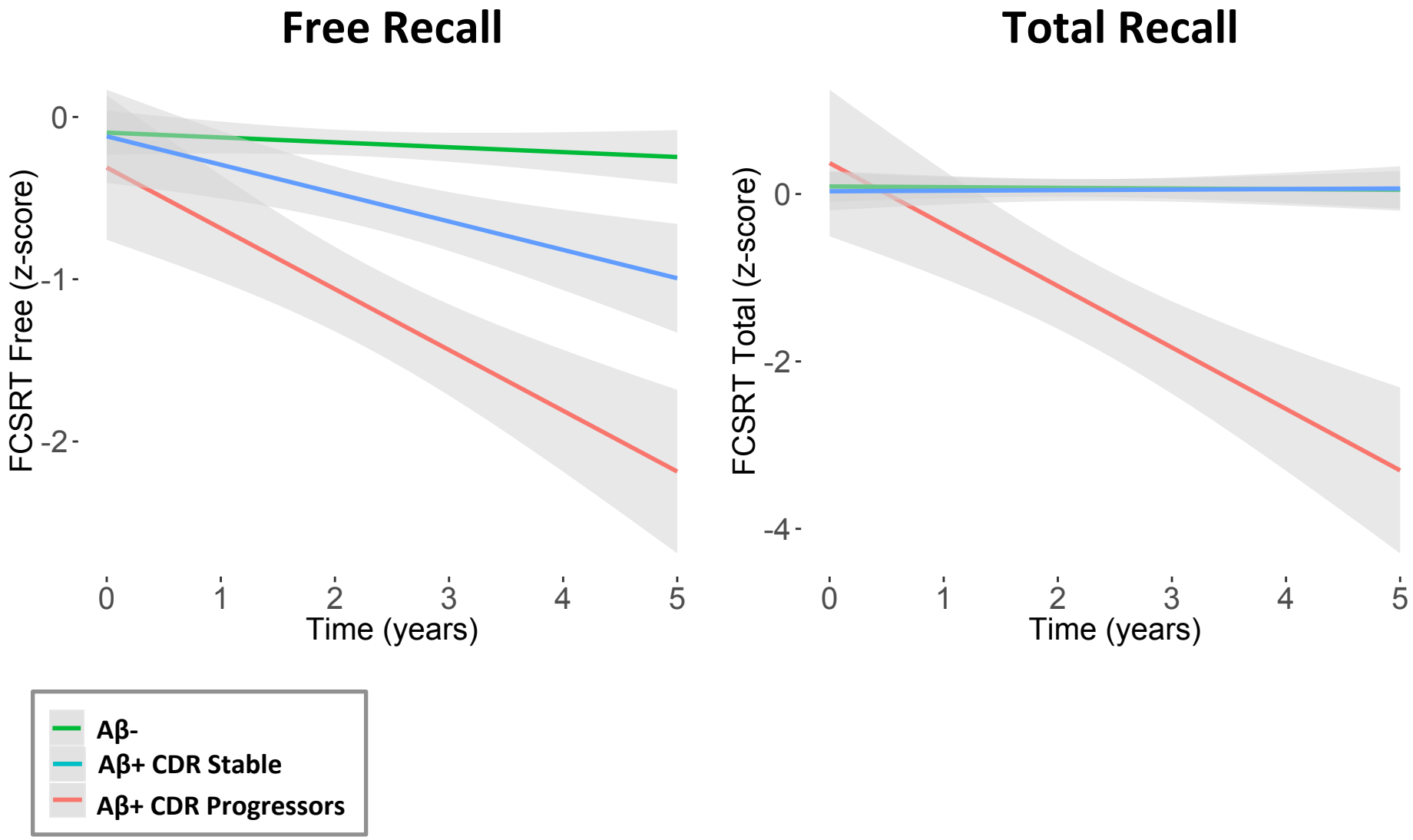
Aβ group difference emerges earlier for Free Recall





Papp Under Review

Aβ related change among CDR stable subgroup



Summary

- **Biomarker staging criteria enables direct comparisons across studies and provides framework for prevention trials.**

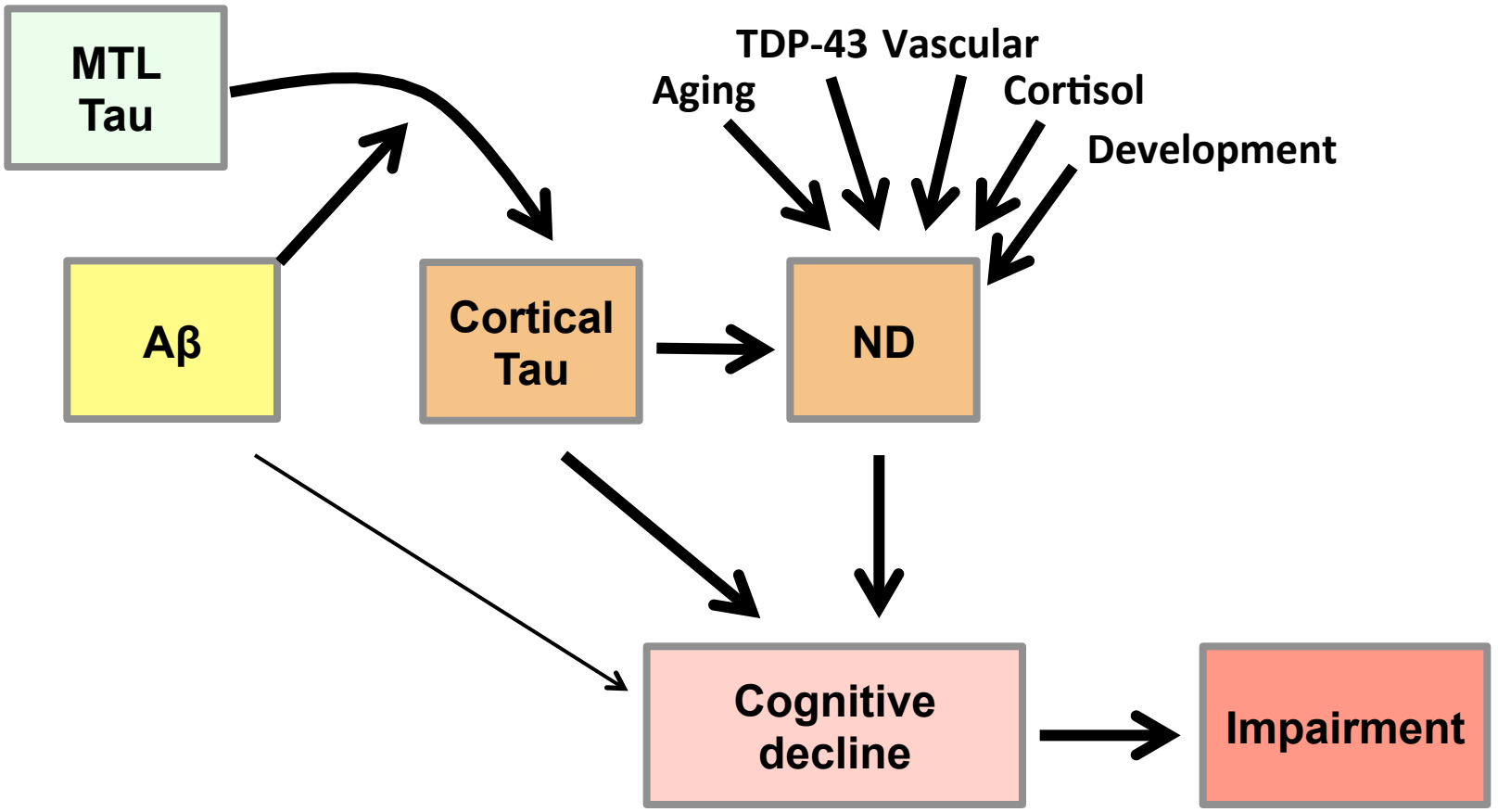
- **Greatest decline in NIA-AA Stage 2 (both functional and cognitive)**

- **Inconsistent patterns of decline for NIA-AA Stage 1 and SNAP**

Summary Cont.

- **Commonly used NIA-AA ND markers not aligned with Tau PET**
  - **Tau PET more specific for Aβ; ND markers influenced by multiple etiologies**
  - **Among Aβ+, ND may be more likely to be Tau related (but still doesn't rule out other etiologies)**

- **Although Aβ effects on decline are largely mediated/ exacerbated by ND and Tau, early Aβ associated with subtle cognitive changes**
  - **Ability to measure will depend on sensitive tests (not necessarily tests that are honed to predict progression to MCI/AD dementia)**


MTL
Tau
Aβ
Cortical
Tau
ND
TDP-43
Vascular
Aging
Cortisol
Development
Cognitive
decline
Impairment

Harvard Aging Brain Study

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