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Subjective cognitive concerns and biomarker evidence of preclinical AD

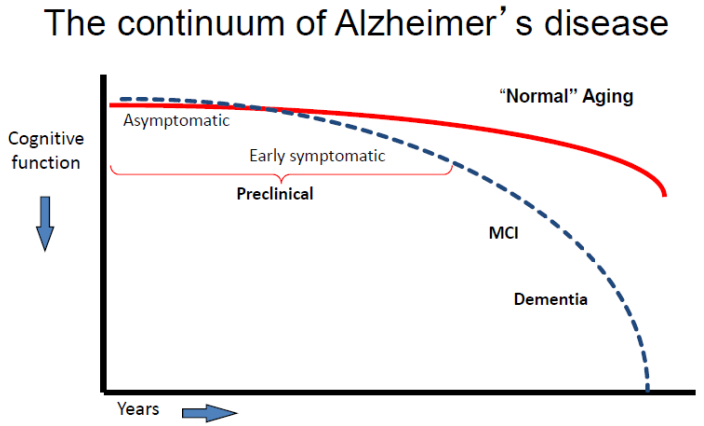
Rebecca E. Amariglio, PhD
Harvard Medical School

Departments of Neurology
Brigham and Women's Hospital
Massachusetts General Hospital

Background

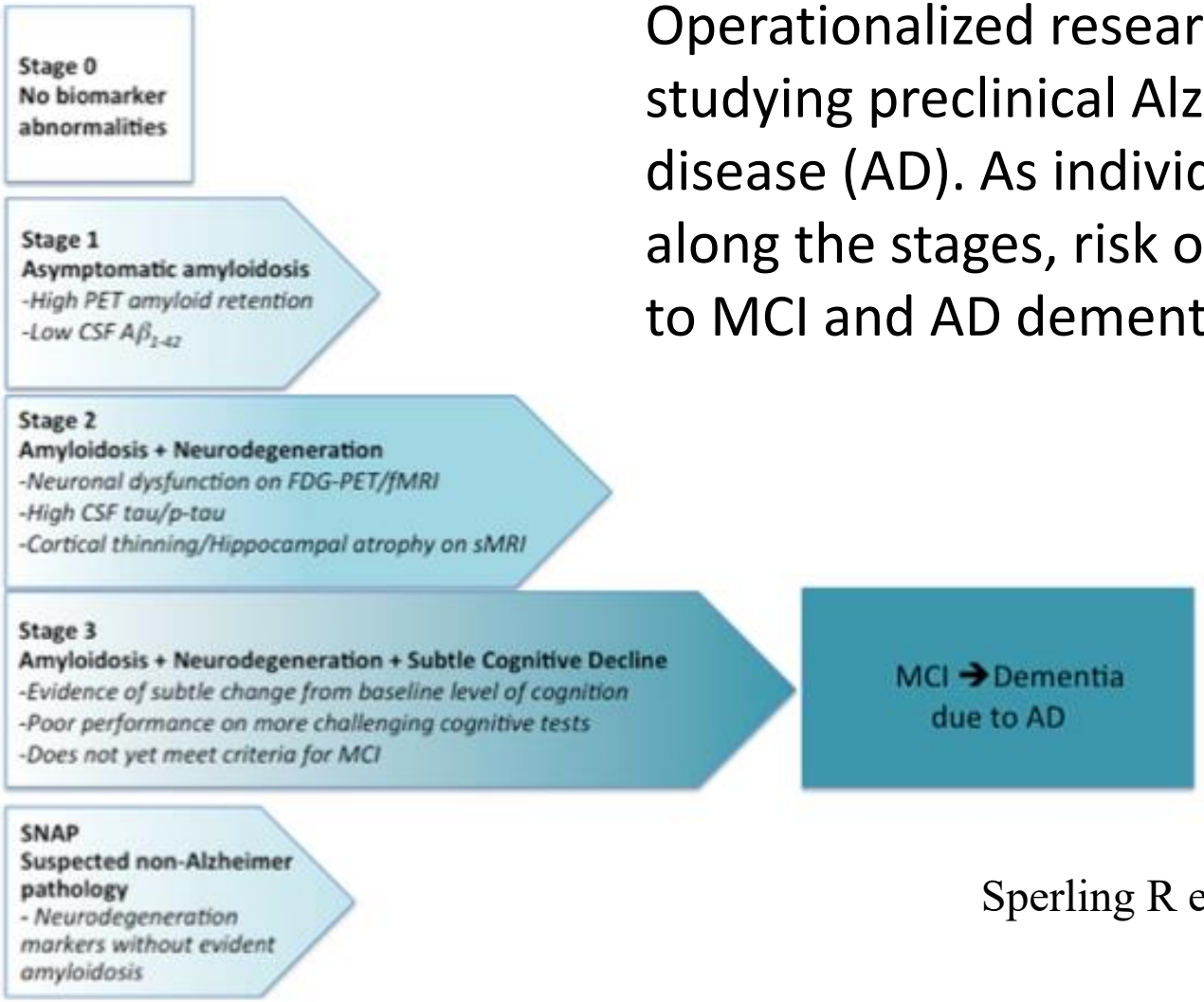
- Previously dismissed as a sign of the "worried well," emerging evidence suggests that subjective cognitive concerns (SCC) may serve as an early indicator of progression to Alzheimer's disease (AD).

- In particular, SCC may be most sensitive at the preclinical stage of AD, prior to the onset of clinical impairment on standardized cognitive measures



Sperling R et al *Alzheimer & Dementia* 2011

Staging Framework for Preclinical AD



Operationalized research criteria for studying preclinical Alzheimer's disease (AD). As individuals advance along the stages, risk of progressing to MCI and AD dementia increases.

Sperling R et al, *Neuron,* 2014

Subjective Cognitive Concerns and AD biomarkers

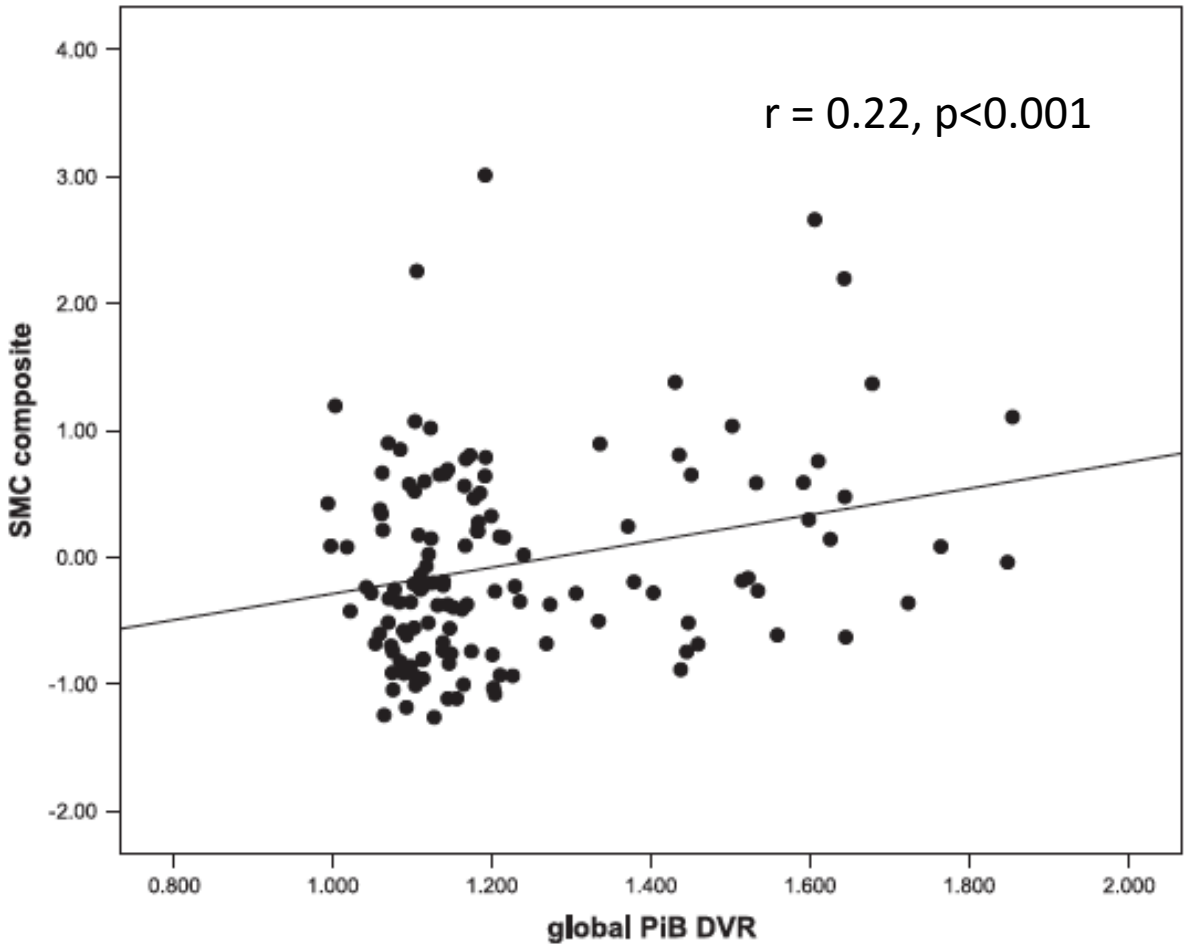
- If SCC herald initial changes due to AD, it would follow that greater SCC would be associated with greater evidence of Aβ and ND in individuals who are clinically normal

- Furthermore, SCC would be associated with advancing stages of preclinical AD, such that individuals with both Aβ and ND would show greater SCC than those with Aβ in isolation

Subjective Cognitive Concerns and Aβ

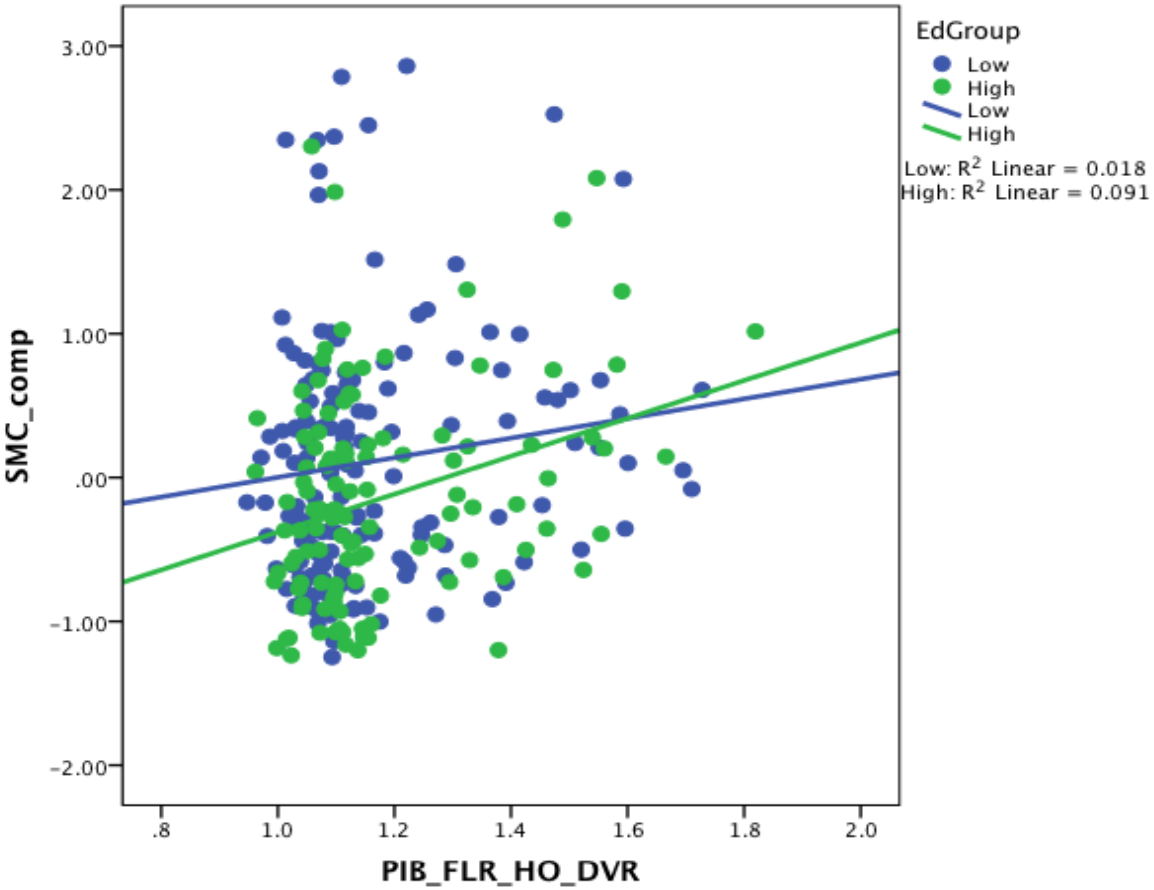
- We examined 131 CN older individuals from the Harvard Aging Brain Study who had amyloid imaging (PiB-PET)
- PiB PET imaging was measured using an aggregate of cortical regions vulnerable to amyloid deposition
- Participants were given several questionnaires about their subjective memory to create a composite
- Study partner was also given a questionnaire about subjective memory
- Participants were given an extensive cognitive battery

Increased SCC related to increased amyloid burden in CN



Amariglio et al., 2012 *Neuropsychologia*

Relationship between SCC and amyloid stronger in higher education group



Aghjayan et al., in preparation

Association between SCC, Aβ, and ND

- Dichotomized Aβ and ND (Mormino et al. 2014)
  - Aβ using PiB-PET
  - ND using both hippocampal volume and FDG-PET

- Resulted in 4 groups (Jack et al., 2012; Knopman et al., 2012)
  - Aβ-/ND- (Stage 0)
  - Aβ+/ND- (Stage 1)
  - Aβ+/ND+ (Stage 2)
  - Aβ-/ND+ (SNAP)

SCC and preclinical AD staging

		Group, mean (SD)			
Demographic variable	Total, mean SD (total n = 257)	Stage 0 (Aβ−/ND−) (total n = 122)	Stage 1 (Aβ+/ND−) (total n = 32)	Stage 2 (Aβ+/ND+) (total n = 36)	SNAP (Aβ−/ND+) (total n = 67)
Age, y	73.7 (6.1)	71.6 (5.7)	73.1 (4.96)	77.1 (6.38)	76.1 (5.67)
Female, %	57.6	63.1	59.4	61.1	44.8
Education, y	15.8 (3.0)	15.9 (3.0)	16.4 (2.7)	16.2 (2.8)	15.1 (3.3)
MMSE	29.0 (1.1)	29.2 (1.0)	28.8 (1.0)	28.7 (1.0)	28.9 (1.1)
GDS	2.9 (2.6)	2.6 (2.3)	2.4 (2.7)	3.6 (2.8)	3.3 (2.8)
Memory factor score	5.4 (2.1)	5.5 (2.2)	5.7 (2.3)	4.8 (1.8)	5.1 (2.1)
SCC composite, z score	0.0 (0.8)	−0.2 (0.7)	0.1 (0.9)	0.3 (0.7)	0.1 (0.8)
APOE ε4 carriers, %	27.8	16.2	62.1	56.3	18.5

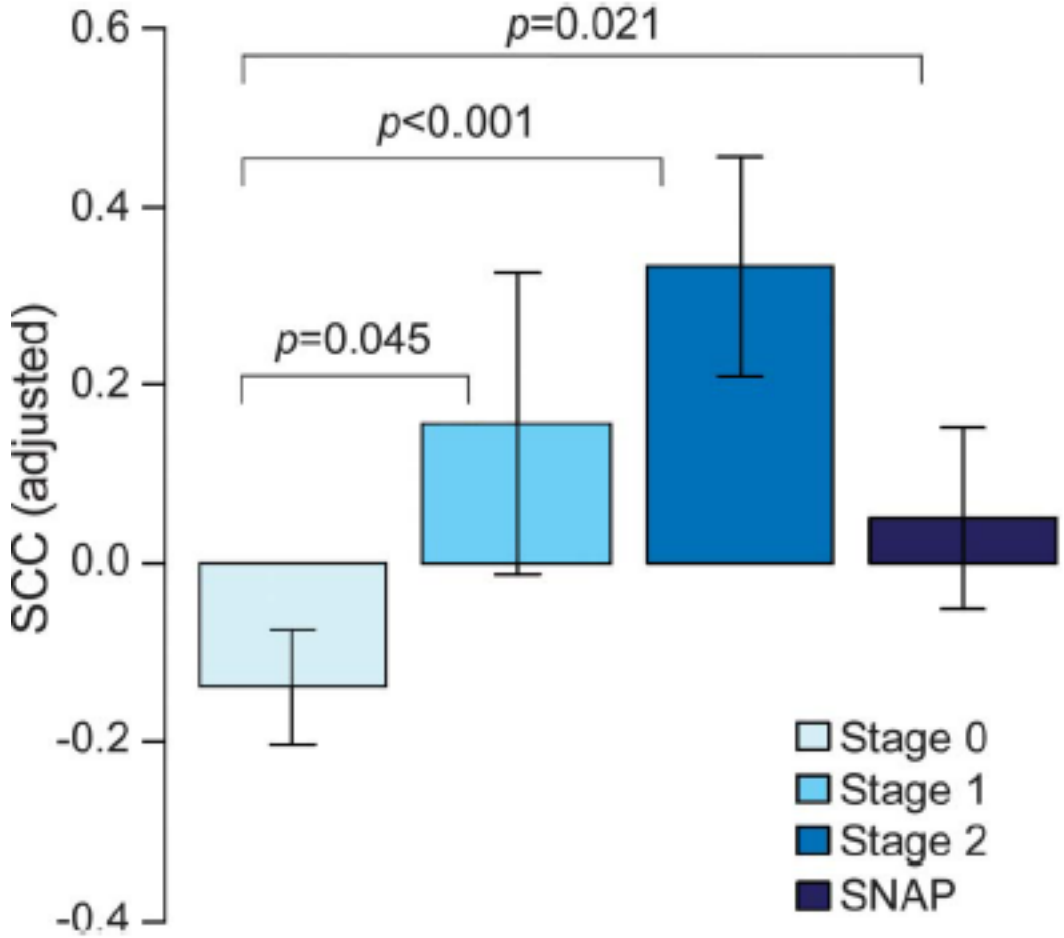
Amariglio et al. 2015 *Neurology*

Both Aβ+ and ND+ independently associated with increased SCC

	Estimate	Std. Error	P-value
ND group	**0.284**	**0.127**	**0.026**
Aβ group	**0.396**	**0.133**	**0.003**
Age	-0.007	0.010	0.503
Education	-0.016	0.020	0.433
Sex	-0.097	0.116	0.406

Amariglio et al. 2015 *Neurology*

SCC is associated with advancing stages of preclinical AD

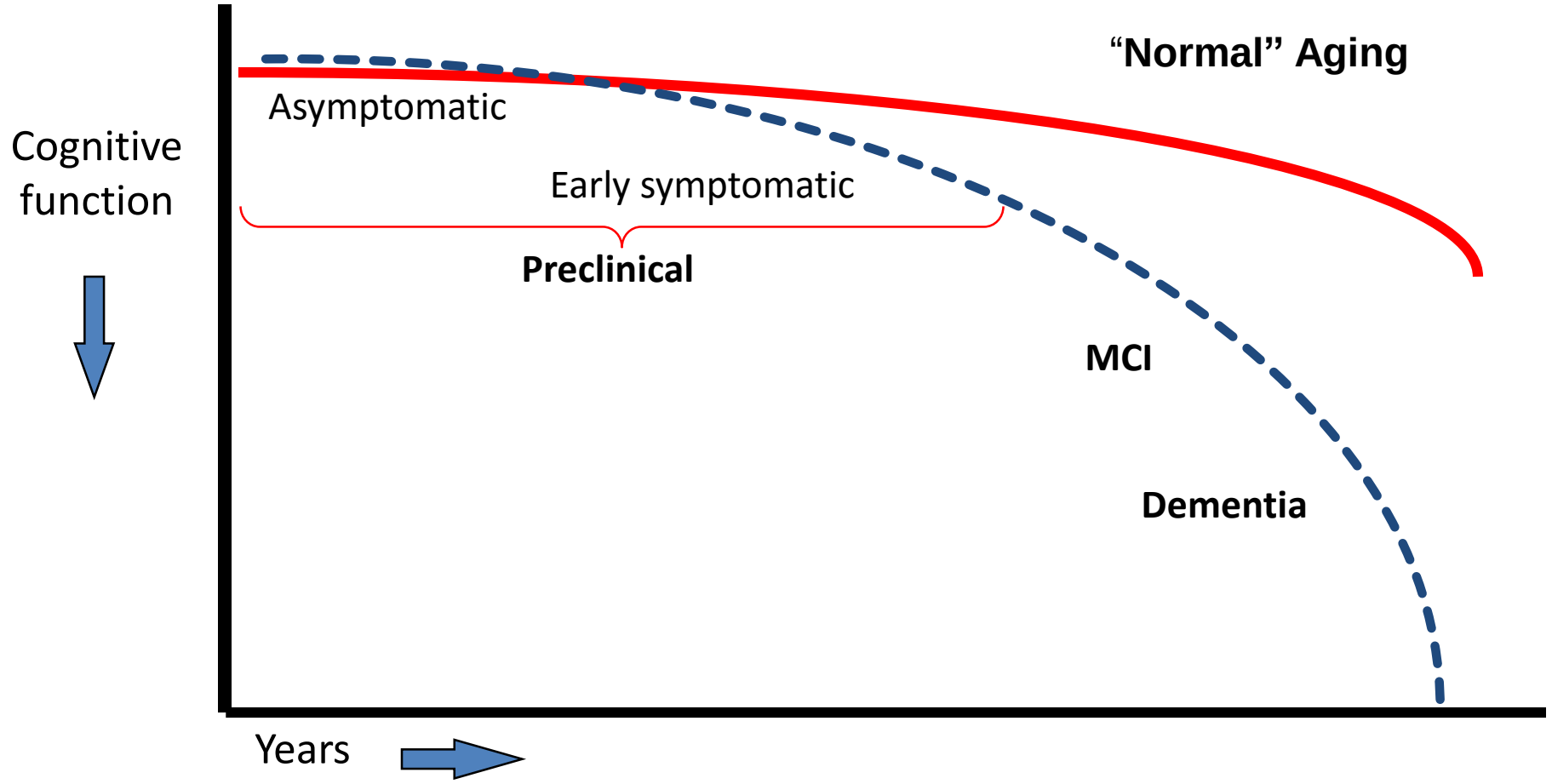


Amariglio et al. 2015 *Neurology*

Conclusions

- Greater self-reported subjective cognitive concerns is related independently to both Aβ and ND in clinically normal older individuals
- Evidence of both Aβ and ND is associated with greater subjective cognitive concerns than Aβ in isolation
- Additional variables, such as education, may modify the relationship between SCC and AD biomarkers

The continuum of Alzheimer's disease

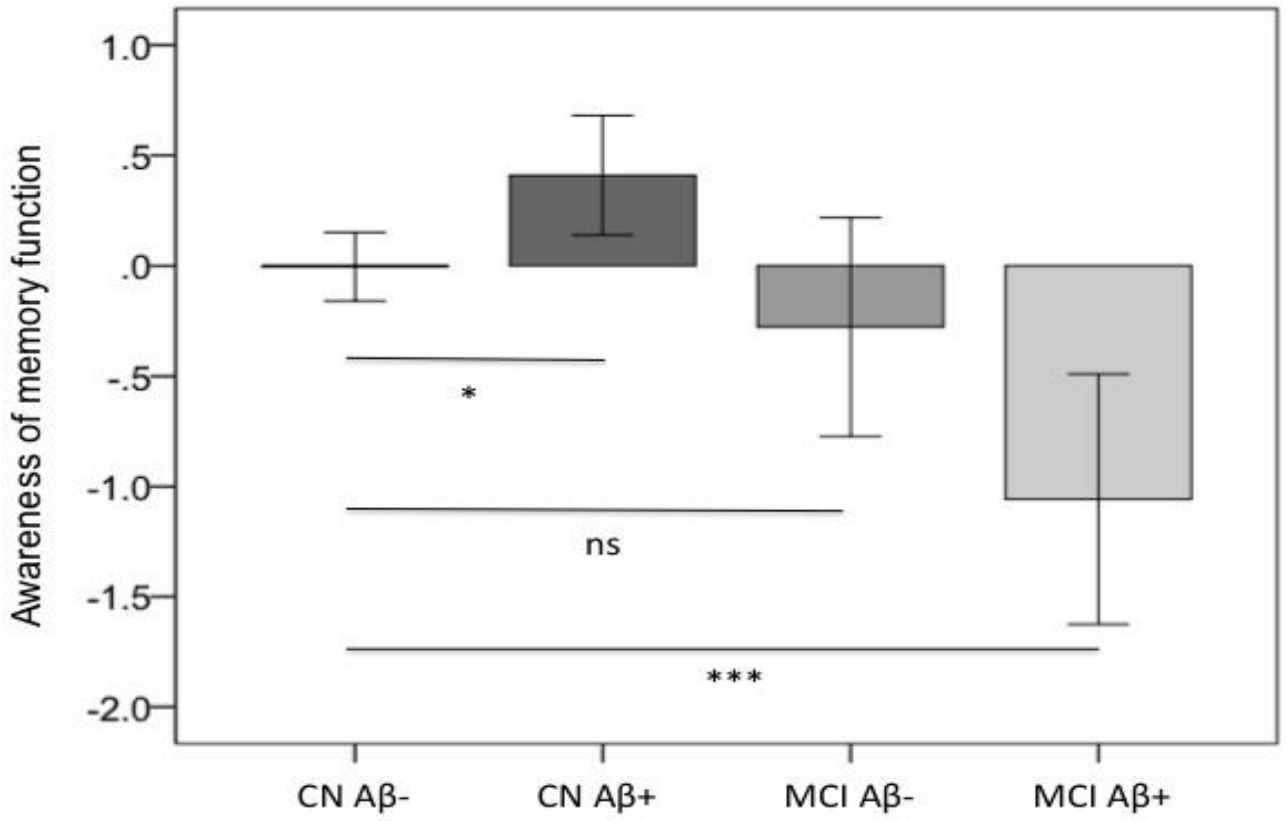


Sperling R et al *Alzheimer & Dementia* 2011

Preclinical and MCI groups

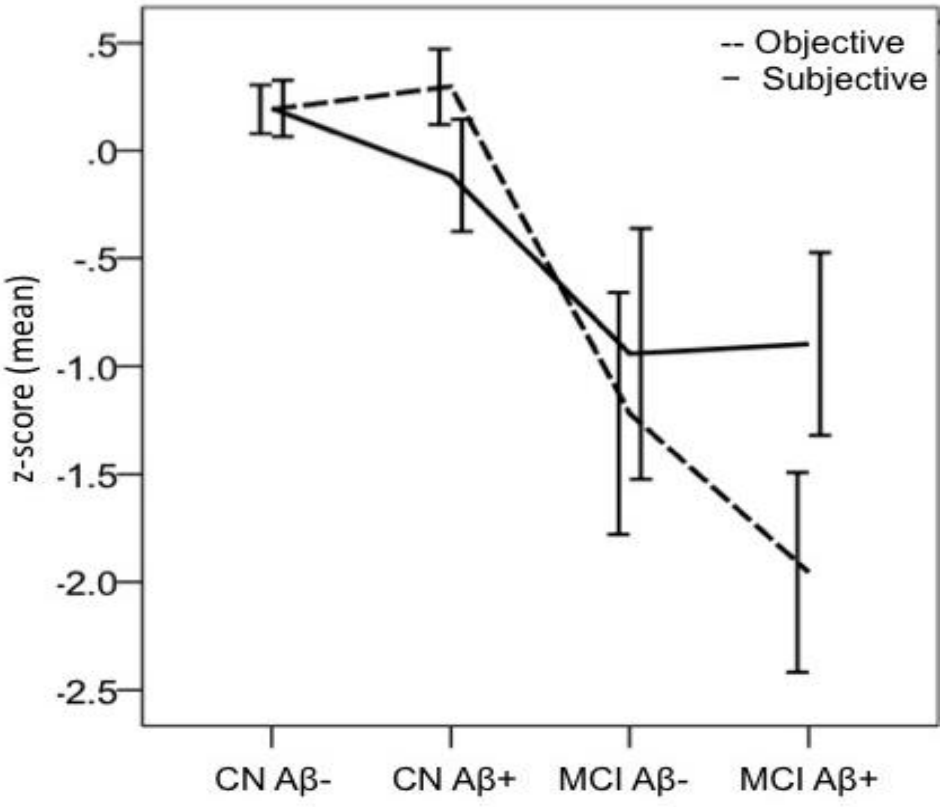
	Total	Cognitively normal		Mild Cognitive Impairment	
		Aβ -	Aβ +	Aβ -	Aβ +
N	286	191	62	13	20
Age, y	73.3 (6.4)	72.7 (6.1)	75.0 (6.2)	74.4 (7.5)	72.2 (8.4)
Female, %	56.7	59.1	59.7	53.8	25.0
Education, y	15.8 (3.1)	15.5 (3.1)	16.3 (2.8)	14.7 (3.8)	16.9 (2.4)
MMSE	28.7 (1.5)	29.0 (1.1)	28.8 (1.0)	27.9 (1.3)	25.7 (2.7)
AMNART	120.4 (9.7)	120.0 (9.6)	122.4 (8.4)*	115.9 (15.9)	120.3 (7.8)
GDS total	1.4 (1.5)	1 .2 (1.3)	1.2 (1.3)	4.2 (2.9)	1.6 (1.7)
Subjective, score 1-7	5.2 (0.9)	5.3 (0.9)	4.9 (0.9)	4.1 (0.9)	4.2 (0.9)
Objective, score 0-25	12.6 (4.4)	13.5 (3.5)	13.9 (3.0)	7.3 (3.9)	4.1 (4.3)

Self-awareness along preclinical/prodromal AD



Vannini et al., in review

Subjective vs. objective memory along preclinical/prodromal AD



Vannini et al., in review

Conclusions

- During the preclinical stage Aβ+ individuals may demonstrate greater cognitive concerns, despite normal memory performance
- At the stage of MCI, individuals demonstrate a discrepancy between objective memory performance and subjective report, particularly in Aβ+ individuals

Importance

- SCC may be one approach in identifying individuals at greater risk for progression to MCI and AD dementia
- More practically, findings may help to identify subjects appropriate for secondary prevention trials
- SCD may also serve as outcome measures in drug trials that are looking to demonstrate clinical benefit
- SCD should not be dismissed and may become particularly important as treatments become available

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