Associations of Episodic Memory Measures with Alzheimer's Disease Biomarkers in Clinically Unimpaired Participants: AHEAD3-45 Screening Data

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Background

- Sensitive and scalable cognitive measures are needed to detect subtle cognitive dysfunction associated with Alzheimer's disease (AD) pathology before the onset of clinical impairment.
- The International Shopping List Test (ISLT) is a digital verbal learning and memory measure with software-controlled administration, while the Free and Cued Selective Reminding Test (FCSRT) is an established examiner-administered measure of episodic memory.
- Although both measures assess episodic memory, data characterizing their relationships with multimodal AD biomarkers in clinically unimpaired individuals are limited.

The aim of this study was to examine associations of ISLT and FCSRT episodic memory performance with plasma and PET biomarkers of AD pathology in clinically unimpaired participants screened for AHEAD3-45.

Methods

AD Biomarkers

- Plasma p-tau217
- Continuous amyloid PET burden
- Early Tau PET composite
- Middle Tau PET composite

Statistical Analyses

- Pearson correlations examined associations among cognitive measures and between cognitive performance and AD biomarkers
- Tau PET analyses were conducted in the subset with available Tau PET data
- False discovery rate (FDR) adjustment was applied for multiple comparisons.

Methods

Sample

Cross-sectional screening data were analyzed from 3,698 AHEAD3-45 participants with a Clinical Dementia Rating (CDR) Global score of 0 and available cognitive and plasma biomarker data. Amyloid PET was available for 3,347 participants and Tau PET for 1,272 participants.

Participant Characteristics

	Overall (N = 3,698)
Age, years	68.7 (6.1)
Education, years	16.2 (3.1)
Female	2,408 (65%)
APOE ε4 carrier	2,232 (60%)
MMSE	29.0 (1.1)

Values are mean (SD) or n (%).

Cognitive Measures

International Shopping List Test (ISLT)

The ISLT is a verbal list-learning test using a 12-item shopping list, with 3 learning trials followed by a 10-minute delayed recall trial. Outcomes included:

- ***Immediate Recall:*** total words correctly recalled across the 3 learning trials
- ***Delayed Recall:*** total words correctly recalled following the 10-minute delay

Free and Cued Selective Reminding Test (FCSRT)

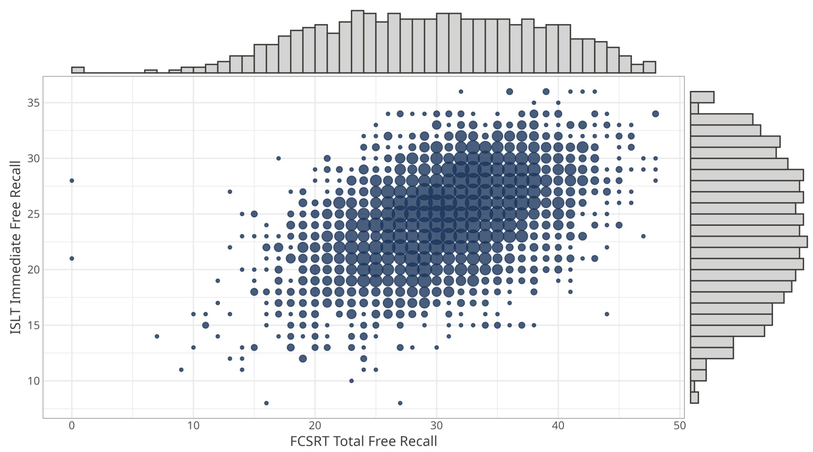
The FCSRT uses 16 items presented across four 4-item study sheets, with controlled learning through identification and immediate cued recall of each item. This is followed by 3 recall trials incorporating free recall, cued recall, and selective reminding. The outcome examined was:

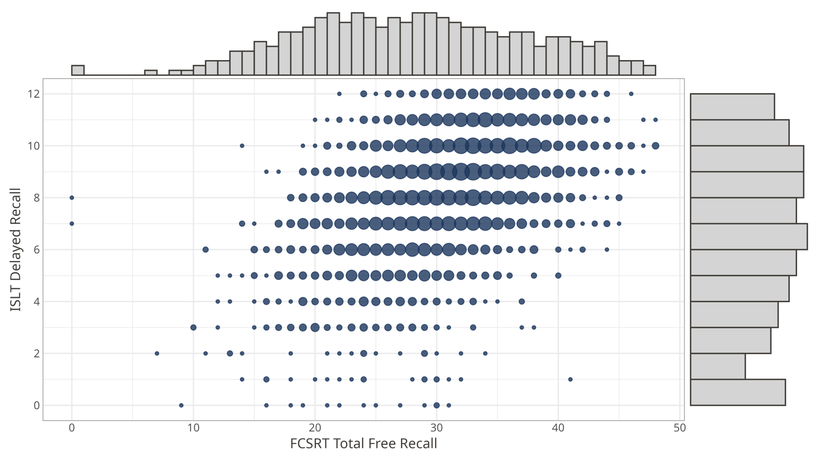
- ***Total Free Recall:*** total freely recalled items across the 3 recall trials

Results

Relationship Between Cognitive Measures

FCSRT Total Free Recall was moderately correlated with ISLT Immediate (r = .49) and Delayed Recall (r = .47; both FDR-adjusted $p < .001$).





Results

Associations with AD Biomarkers

Correlations between cognitive outcomes and biomarkers

	Cognitive Outcome	Confidence interval	p-value[1]	95% CI
Plasma p-tau217	FCSRT Total Free Recall		< .001	[−0.153, −0.091]
	ISLT Immediate		< .001	[−0.182, −0.120]
	ISLT Delayed Recall		< .001	[−0.194, −0.132]
Amyloid PET	FCSRT Total Free Recall		< .001	[−0.134, −0.068]
	ISLT Immediate		< .001	[−0.160, −0.094]
	ISLT Delayed Recall		< .001	[−0.192, −0.127]
Early Tau PET	FCSRT Total Free Recall		0.012	[−0.123, −0.015]
	ISLT Immediate		< .001	[−0.147, −0.040]
	ISLT Delayed Recall		< .001	[−0.211, −0.105]
Middle Tau PET	FCSRT Total Free Recall		0.154	[−0.093, 0.015]
	ISLT Immediate		0.011	[−0.124, −0.016]
	ISLT Delayed Recall		< .001	[−0.181, −0.074]

[1] p-values are unadjusted; see text for FDR-adjusted significance.

Greater AD biomarker burden was associated with poorer episodic memory performance, although associations were small. Associations were generally similar across cognitive measures, with **ISLT Delayed Recall showing a qualitative pattern of slightly stronger associations across biomarker modalities**, particularly for Tau PET.

All were FDR-adjusted $p < .05$ except FCSRT with Middle Tau PET

Conclusion

In clinically unimpaired participants, ISLT performance showed associations with multimodal AD biomarkers comparable to the established FCSRT, supporting its potential as a scalable episodic memory measure for preclinical AD trials.

- The ISLT's brief, standardized, software-controlled administration and reduced reliance on specialized rater expertise and training may offer practical advantages for large-scale preclinical AD trials.
- The qualitative pattern of stronger associations for ISLT Delayed Recall supports further investigation of specific memory components that may be more sensitive to early AD pathology.

Disclosures

Disclosures: All authors are employees of Cogstate. Cogstate is contracted to provide central monitoring, rater training, and related services for the AHEAD3-45 study.

Acknowledgments/Funding: Data used in this analysis were obtained from the Alzheimer's Clinical Trial Consortium AHEAD3-45 study, which is supported by the National Institute on Aging/NIH, Eisai Inc., Alzheimer's Association, GHR Foundation, and additional philanthropic donors.