

Longitudinal Dynamics of Word List Recall: A Joint Modeling Comparison of CERAD and RBANS in Preclinical Alzheimer Disease

Authors and Affiliations

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Background

Autosomal Dominant Alzheimer's Disease (ADAD) provides a unique framework to examine disease progression prior to clinical impairment; however, traditional predictive models often overlook the prognostic value of time-varying trajectories both for clinical and laboratory disease-related phenomena, such as neuropsychological tests.

Previous studies have identified short term memory cognitive tasks as the earliest cognitive marker before clinical decline. Therefore, we employ the joint-modelling (JM) framework in order to explore further associations of cognitive biomarkers and the time-to-event outcome in ADAD for the *PSEN1*-E280A Colombian kindred.

Objective

To evaluate whether longitudinal trajectories of word list recall, assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Consortium to Establish a Registry for Alzheimer Disease (CERAD), could dynamically predict progression to mild cognitive impairment (MCI)

Methods

This secondary analysis of the API-ADAD Trial, focused on *PSEN1*-E280A carriers, cognitively unimpaired at baseline. JMs were developed to link longitudinal linear mixed-effects models of word recall performance, adjusted for education with a relative risk survival model for age at MCI onset. Clinical diagnosis was determined by a consensus panel and validated through external review based on the Albert and colleagues 2011 criteria. Lastly, we explored the prognostic accuracy and predictive error of such univariate JMs expressed as dynamic Area Under the Curve (AUC-ROC) and Brier scores.

Results

167 participants with a mean baseline age of 37.3 years (SD: 5.72). Over a mean 8-year follow-up, 53 participants (31.7%) progressed to MCI. Longitudinal decline in both tests strongly predicted clinical progression. For every one-point decrease in word recall, the hazard of progression increased by 23% for CERAD (HR: 1.23; 95% CI: 1.16–1.31) and 60% for RBANS (HR: 1.60; 95% CI: 1.34–2.10). Over a 10-year horizon, time-dependent ROC analysis demonstrated superior predictive discrimination for CERAD (AUC = 0.90) compared to RBANS (AUC = 0.87), with low global prediction error (Brier Score ≤ 0.14).

Conclusions

Longitudinal cognitive markers are dynamic predictors of ADAD progression. JM effectively quantifies individualized risk and facilitates the identification of individuals approaching clinical onset. Although both measures were associated with progression risk, CERAD Word Recall had superior predictive performance and longitudinal calibration, supporting further utility as a preferred cognitive biomarker for identifying high-risk individuals in early-stage ADAD.

Acknowledgments

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Results

Table 1: Baseline characteristics of *PSEN1* E280A Carriers

Variable	PSEN1 E280A Carriers (n=167)
Mean (SD)	
Median [Min, Max]	
Age (years)	37.3 (5.72)
Years of education	8.81 (4.06)
Female (%)	10.0 [0, 18.0]
MMSE total score	28.8 (1.38)
	29.0 [23.0, 30.0]
CERAD WL recall score	6.93 (2.12)
	7.00 [0, 10.0]
RBANS WL recall score	5.23 (3.05)
	6.00 [0, 10.0]

Table 2: Joint Model results (Longitudinal & Survival Submodels)

Model/Test	CERAD Word recall		RBANS Word recall	
Longitudinal submodel	β	95% CI	β	95% CI
Baseline age	0.0896	0.0235, 0.1537	-0.0947	-0.1772, -0.0166
Age at assessment (years)	-0.2184	-0.2739, -0.1603	-0.1857	-0.2368, -0.1307
Educational achievement (Years of education)	0.1854	0.1268, 0.2441	0.1445	0.0606, 0.2284
Model/Test	CERAD WL recall		RBANS WL recall	
Survival submodel	HR	95%CI	HR	95% CI
Baseline age	0.60	(0.50, 0.69)	0.62	(0.52, 0.71)
Years of education	1.02	(0.90, 1.16)	1.08	(0.93, 1.27)
Association (Alpha)				
CERAD Word recall*	0.81	(0.75, 0.85)		
RBANS Word recall*			0.62	(0.47-0.74)

*The main text reports the inverse of these values (e.g., $1/0.81=1.23$), which reflects the mathematically equivalent elevated risk per 1-point decrease in performance

Figure 1: Longitudinal Cognitive Decline trajectories

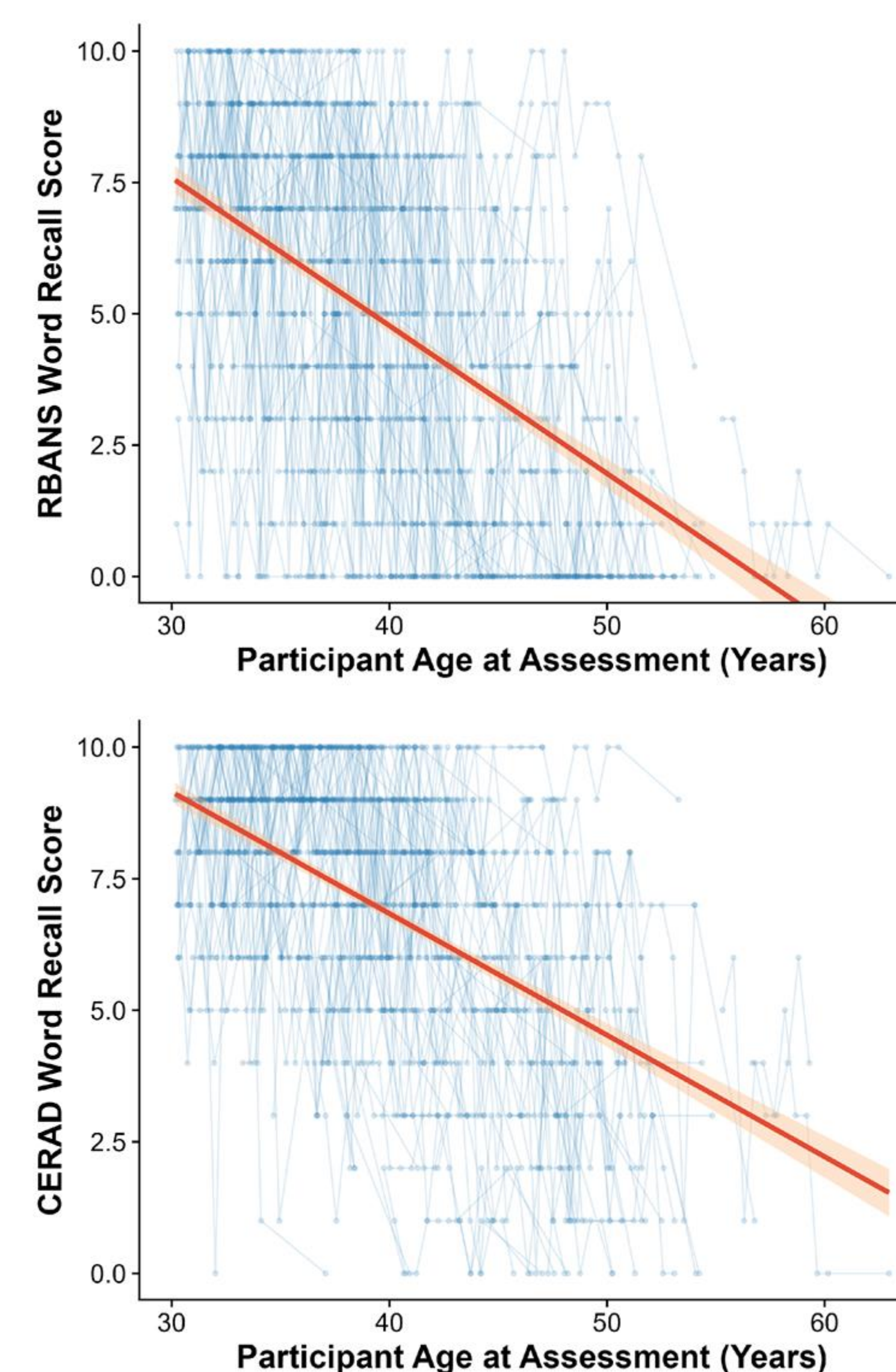
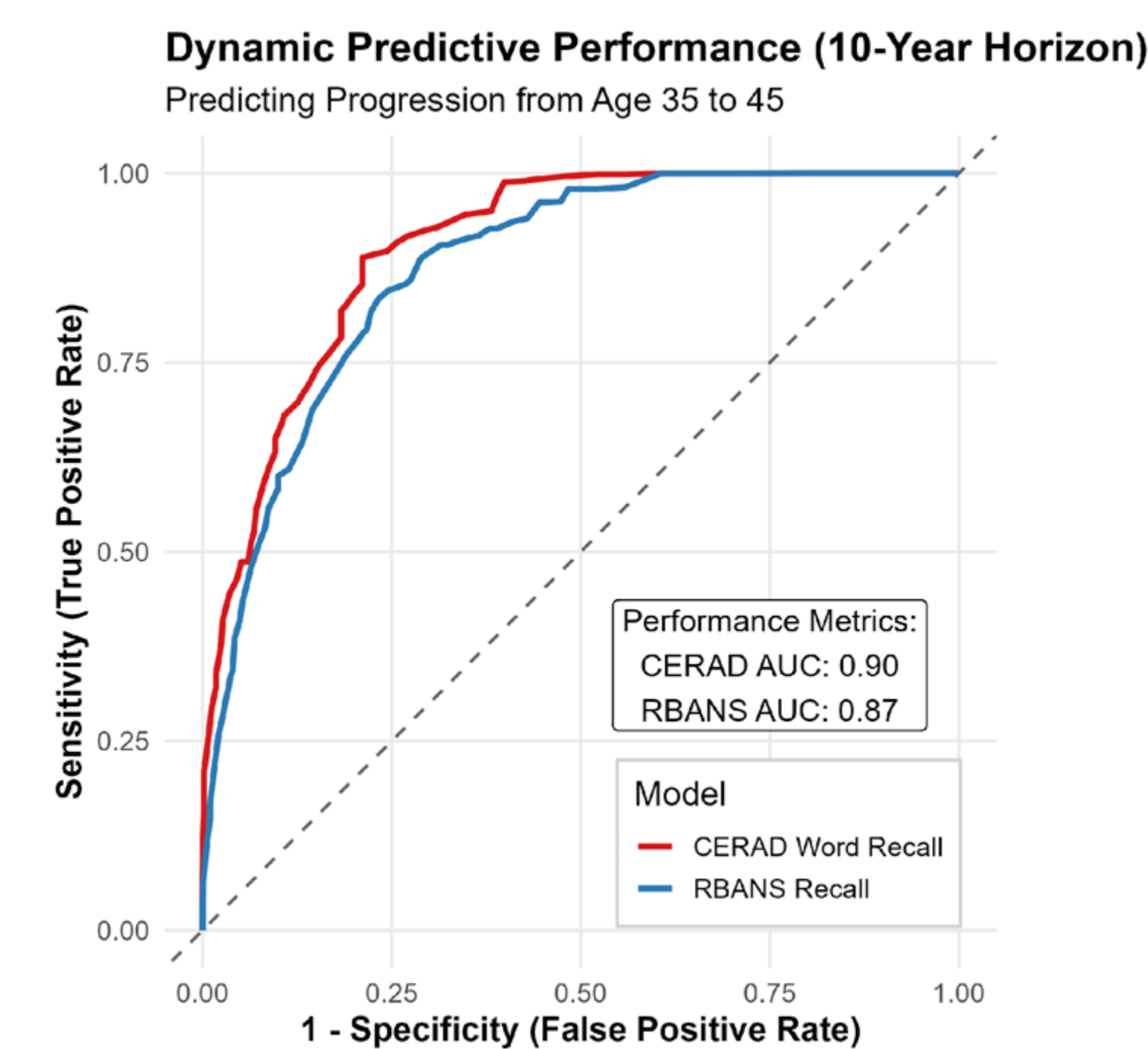


Figure 2: Comparative dynamic AUCs



References

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