Cross-dataset Evaluation of Dementia Longitudinal Progression Prediction Models

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no cure, but early intervention can slow cognitive decline (1–3). Predicting AD progression is critical for timely treatment, caregiver planning, and optimizing clinical trial recruitment (4,5). Machine learning models leveraging multimodal biomarkers have shown promise in forecasting disease trajectory, but their generalizability across datasets remains an open question.

2. Substantial section

2.1 Related work

The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) challenge (6), involving 92 algorithms from 33 international teams, used multimodal biomarkers to predict clinical diagnosis, cognition, and ventricular volume up to five years into the future. The winning algorithm, FROG, utilized a Longitudinal-to-Cross-sectional (L2C) transformation, converting variable-length histories into fixed-length feature vectors by extracting key summary statistics (e.g., highest/lowest values, time since the highest/lowest values). This approach reformulates a longitudinal problem into a static prediction task, broadening the range of applicable machine learning models (e.g., XGBoost (7)) beyond conventional time-series approaches.

As far as we know, the L2C approach is relatively unique in the medical imaging community, where most methods fit models to entire longitudinal histories— either through parametric trajectory modeling, such as AD Course Map (AD_Map) (8), or dynamic state modeling, such as minimalRNN (9).

2.2 Method

While effective, FROG required separate models for different forecast windows and target variables, making it cumbersome. We propose L2C-FNN, a streamlined variant of FROG that replaces XGBoost with a single feedforward neural network (FNN), unifying prediction across all forecast windows and target variables.

TADPOLE evaluated models solely on the Alzheimer's Disease Neuroimaging Initiative (ADNI) (10,11) dataset, leaving cross-cohort generalizability untested. To address this, we trained models on the ADNI dataset and evaluated them on three independent cohorts—AIBL (N=402, Australia) (12), MACC (N=650, Singapore) (13), and OASIS (N=1260, North America) (14)—covering 2,312 participants and 13,200 timepoints across three continents.

ADNI participants were randomly divided into training, validation, and test sets (18:1:1) with 20 repetitions to ensure result stability (Figure 1). Care was taken to ensure non-overlapping test sets, covering the entirety of the ADNI cohort across the 20 data splits. Following TADPOLE convention, the first 50% of each participant's timepoints were used to predict the second 50%. Performance was evaluated through within- and cross-cohort comparisons. Model performance was evaluated using multiclass area under the operating curve (mAUC) (15) for clinical diagnosis, and Mean Absolute Error (MAE) for Mini-Mental State Examination (MMSE) and ventricle volume predictions.

Statistical significance was assessed using corrected resampled t-tests (16) for within-cohort evaluation and paired t-tests (17) for cross-cohort evaluation. Multiple comparisons were corrected with a false discovery rate of $q < 0.05$ (18). For more details, please refer to our preprint (19).

2.3 Results

2.3.1 Within-cohort comparisons

Figure 2 shows within-cohort clinical diagnosis prediction in ADNI. The three FROG variants: L2C-XGBw (original FROG), L2C-XGBnw, and L2C-FNN outperformed MinimalRNN, which in turn outperformed AD-Map. However, all models performed similarly for MMSE and ventricle volume prediction (Appendix Figure 1).

2.3.2 Cross-cohort comparisons

Figure 3 illustrates MMSE prediction errors across AIBL, MACC, and OASIS. L2C-FNN achieved the best overall performance, ranking first in AIBL and OASIS, while AD-Map performed slightly better in MACC. For ventricle volume prediction, overall L2C-FNN, L2C-XGBnw and AD-Map performed the best. The original FROG algorithm (L2C-XGBw) and MinimalRNN performed the worst (Appendix Figure 2). L2C-FNN also showed the best overall performance in clinical diagnosis prediction (Appendix Figure 3).

2.3.3 Long-term prediction trends

Figure 4 presents a yearly breakdown of cross-cohort MMSE prediction from Figure 3 up to year 6, showing a decline in accuracy across all models as the prediction horizon increased. However, L2C-FNN consistently matched or outperformed other methods, except in MACC, where AD-Map was statistically superior in years 0–1 and 1–2 (Table 1). Similar trends were observed for ventricle volume and clinical diagnosis (Appendix Figures 4–5). Statistical comparisons (Appendix Table 1) confirm that L2C-FNN generally maintained strong performance across all time horizons and datasets.

3. Conclusion

Our benchmarking study showed that L2C-FNN achieved the best overall cross-cohort performance and demonstrated robust long-term prediction capabilities for dementia progression.

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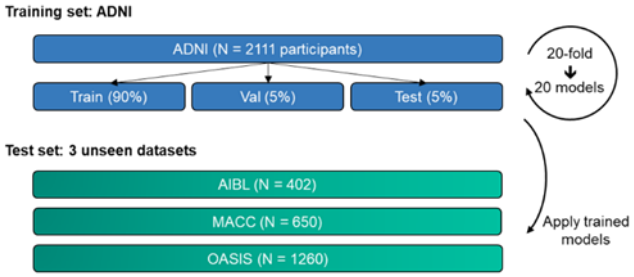
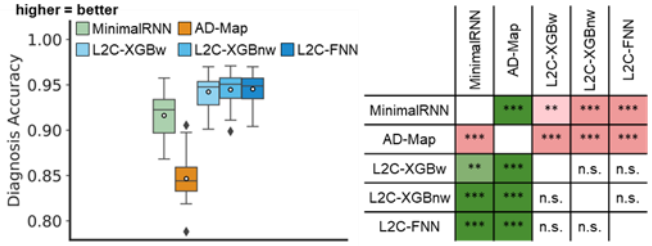
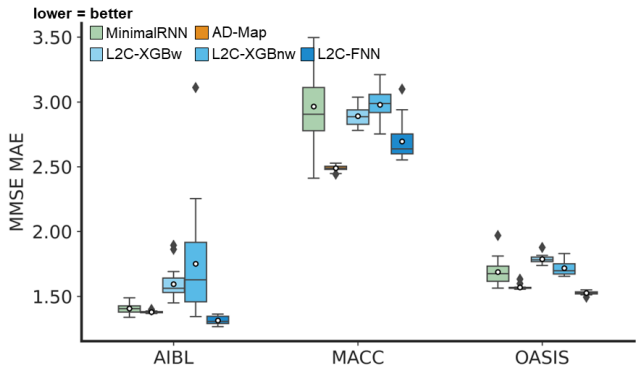


Fig. 1: Overview of model training on ADNI and evaluation on three external datasets.



	MinimalRNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		***	**	***	***
AD-Map	***		***	***	***
L2C-XGBw	**	***		n.s.	n.s.
L2C-XGBnw	***	***	n.s.		n.s.
L2C-FNN	***	***	n.s.	n.s.	

Fig.2: Within-cohort (ADNI) prediction performance for clinical diagnosis prediction. Left: Boxplots show variability across 20 test sets. Right: Statistical differences between models. '***' $p < 0.00001$, '**' $p < 0.001$. 'n.s.' indicates non-significant results ($p > 0.05$) or those not surviving FDR correction. Each row compares a model against all others; green indicates better performance, red worse.



AIBL MMSE	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		n.s.	**	***	*
AD-Map	n.s.		n.s.	**	n.s.
L2C-XGBw	**	n.s.		**	***
L2C-XGBnw	***	**	**		***
L2C-FNN	*	n.s.	***	***	

MACC MMSE	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		***	n.s.	n.s.	**
AD-Map	***		***	***	**
L2C-XGBw	n.s.	***		n.s.	**
L2C-XGBnw	n.s.	***	n.s.		***
L2C-FNN	**	**	**	***	

OASIS MMSE	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		**	*	n.s.	***
AD-Map	**		***	**	n.s.
L2C-XGBw	*	***		*	***
L2C-XGBnw	n.s.	**	*		***
L2C-FNN	***	n.s.	***	***	

Fig. 3: Cross-cohort MMSE prediction error (MAE) on three external datasets. Top: Boxplots show variability across 20 trained models. The x-axis denotes the test dataset. Bottom: Statistical differences between models. Each row compares a model against all others. Color and marker definitions follow Fig. 2.

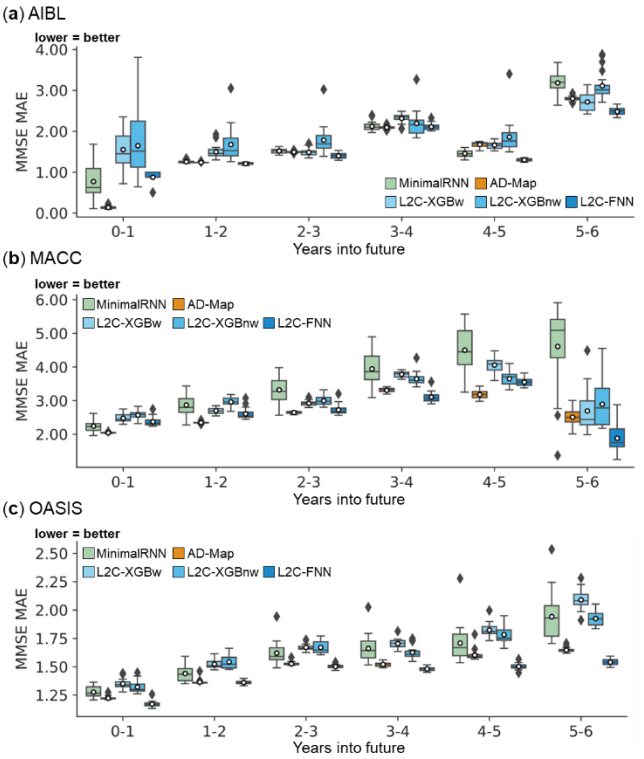


Fig. 4: Cross-cohort MMSE prediction performance (Fig. 3) broken down into yearly intervals up to 6 years.

	AIBL						MACC						OASIS					
MMSE	0-1	1-2	2-3	3-4	4-5	5-6	0-1	1-2	2-3	3-4	4-5	5-6	0-1	1-2	2-3	3-4	4-5	5-6
L2C-FNN vs MinimalRNN	ns	ns	ns	ns	ns	ns	ns	**	***	**	ns	ns	**	*	**	**	**	***
L2C-FNN vs AD-Map	ns	ns	ns	ns	*	ns	***	**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
L2C-FNN vs L2C-XGBw	*	***	ns	ns	*	ns	ns	ns	ns	**	ns	ns	***	***	**	***	***	***
L2C-FNN vs L2C-XGBnw	ns	***	*	ns	**	ns	*	***	*	**	ns	ns	***	**	**	*	**	***

Table 1: Statistical significance between L2C-FNN and other approaches for cross-cohort MMSE prediction performance (Fig. 3) broken down into yearly intervals up to 6 years into the future. Color and marker definitions follow Fig. 2.

Acknowledgments

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Data were provided in part by OASIS-3: Longitudinal Multimodal Neuroimaging: Principal Investigators: T. Benzinger, D. Marcus, J. Morris; NIH P30 AG066444, P50 AG00561, P30 NS09857781, P01 AG026276, P01 AG003991, R01 AG043434, UL1 TR000448, R01 EB009352. AV-45 doses were provided by Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly.

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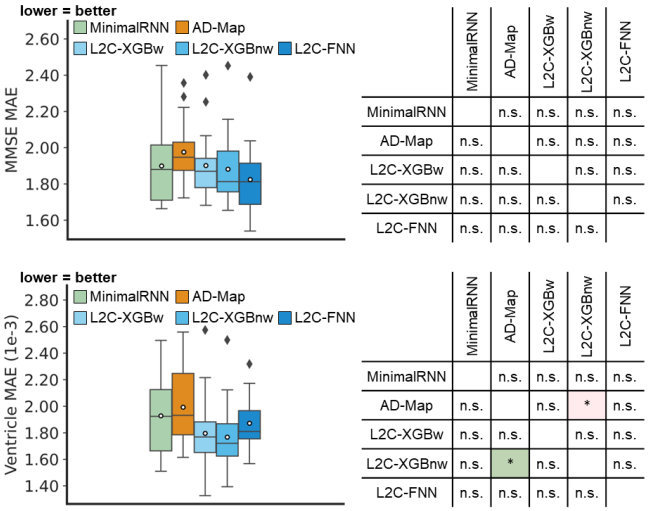
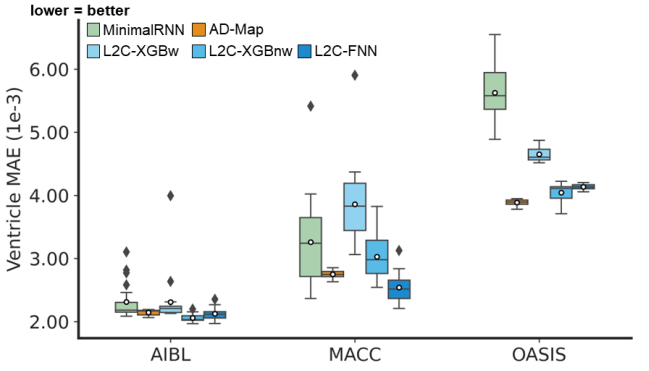
Appendix. Supplementary figures and tables



	MinimalRNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		n.s.	n.s.	n.s.	n.s.
AD-Map	n.s.		n.s.	n.s.	n.s.
L2C-XGBw	n.s.	n.s.		n.s.	n.s.
L2C-XGBnw	n.s.	n.s.	n.s.		n.s.
L2C-FNN	n.s.	n.s.	n.s.	n.s.	

	MinimalRNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		n.s.	n.s.	n.s.	n.s.
AD-Map	n.s.		n.s.	*	n.s.
L2C-XGBw	n.s.	n.s.		n.s.	n.s.
L2C-XGBnw	n.s.	*	n.s.		n.s.
L2C-FNN	n.s.	n.s.	n.s.	n.s.	

Appendix Fig. 1: Within-cohort (ADNI) prediction performance. Left: Boxplots show variability across 20 test sets for MMSE (top) and ventricle volume (bottom) predictions. Right: Statistical differences between models for MMSE (top) and ventricle volume (bottom). Color and marker definitions follow Fig. 2.



AIBL Ventricle	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		n.s.	n.s.	*	*
AD-Map	n.s.		n.s.	n.s.	n.s.
L2C-XGBw	n.s.	n.s.		*	n.s.
L2C-XGBnw	*	n.s.	*		n.s.
L2C-FNN	*	n.s.	n.s.	n.s.	

MACC Ventricle	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		**	***	*	***
AD-Map	**		***	n.s.	n.s.
L2C-XGBw	***	***		***	***
L2C-XGBnw	*	n.s.	***		***
L2C-FNN	***	n.s.	***	***	

OASIS Ventricle	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		***	*	***	***
AD-Map	***		***	n.s.	n.s.
L2C-XGBw	*	***		***	***
L2C-XGBnw	***	n.s.	***		n.s.
L2C-FNN	***	n.s.	***	n.s.	

Appendix Fig. 2: Cross-cohort ventricle volume prediction error (MAE) on three external datasets. Top: Boxplots show variability across 20 trained models. The x-axis denotes the

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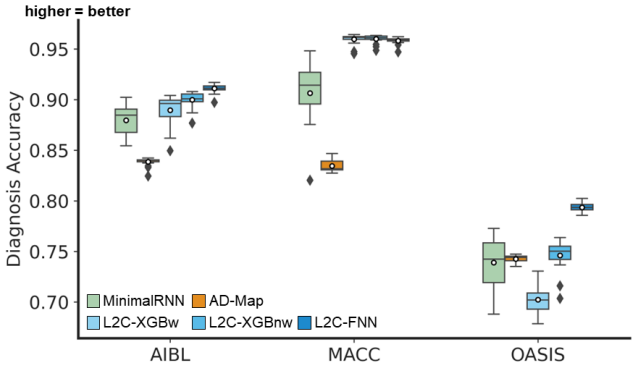
test dataset. Bottom: Statistical differences between models. Each row compares a model against all others. Color and marker definitions follow Fig. 2.

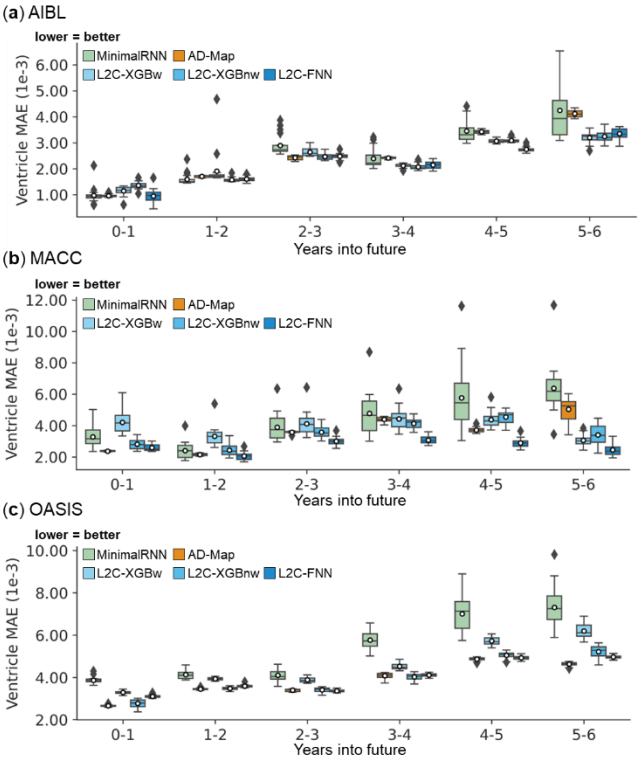


AIBL Diagnosis	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		n.s.	n.s.	n.s.	n.s.
AD-Map	n.s.		*	*	**
L2C-XGBw	n.s.	*		n.s.	n.s.
L2C-XGBnw	n.s.	*	n.s.		n.s.
L2C-FNN	n.s.	**	n.s.	n.s.	

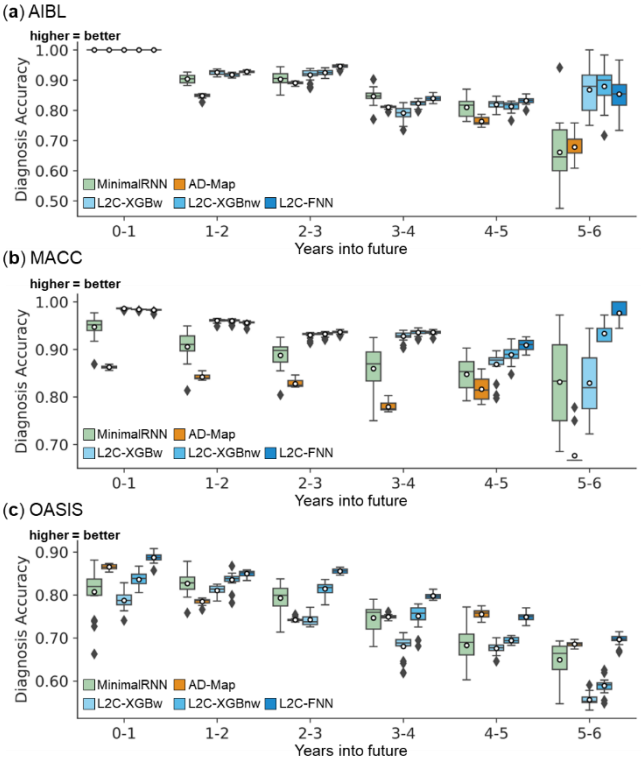
MACC Diagnosis	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		**	*	*	*
AD-Map	**		**	**	**
L2C-XGBw	*	**		n.s.	n.s.
L2C-XGBnw	*	**	n.s.		n.s.
L2C-FNN	*	**	n.s.	n.s.	

OASIS Diagnosis	Minimal RNN	AD-Map	L2C-XGBw	L2C-XGBnw	L2C-FNN
MinimalRNN		n.s.	**	n.s.	n.s.
AD-Map	n.s.		n.s.	n.s.	*
L2C-XGBw	**	n.s.		**	**
L2C-XGBnw	n.s.	n.s.	**		**
L2C-FNN	n.s.	*	**	**	

Appendix Fig. 3: Cross-cohort ventricle clinical diagnosis prediction accuracy (mAUC) on three external datasets. Top: Boxplots show variability across 20 trained models. The x-axis denotes the test dataset. Bottom: Statistical differences between models. Each row compares a model against all others. Color and marker definitions follow Fig. 2.



Appendix Fig. 4: Cross-cohort ventricle volume prediction performance (Appendix Fig. 2) broken down into yearly intervals up to 6 years.



Appendix Fig. 5: Cross-cohort clinical diagnosis prediction performance (Appendix Fig. 3) broken down into yearly intervals up to 6 years.

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	AIBL						MACC						OASIS					
Ventricle	0-1	1-2	2-3	3-4	4-5	5-6	0-1	1-2	2-3	3-4	4-5	5-6	0-1	1-2	2-3	3-4	4-5	5-6
L2C-FNN vs MinimalRNN	ns	ns	*	ns	***	ns	**	**	**	**	*	ns	*	ns	ns	*	ns	**
L2C-FNN vs AD-Map	ns	ns	ns	ns	*	ns	ns	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	ns
L2C-FNN vs L2C-XGBw	ns	**	ns	ns	ns	ns	***	***	***	***	*	ns	ns	ns	*	ns	ns	**
L2C-FNN vs L2C-XGBnw	*	ns	ns	ns	ns	ns	ns	***	**	***	*	ns	ns	ns	ns	ns	ns	ns
Diagnosis	0-1	1-2	2-3	3-4	4-5	5-6	0-1	1-2	2-3	3-4	4-5	5-6	0-1	1-2	2-3	3-4	4-5	5-6
L2C-FNN vs MinimalRNN	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
L2C-FNN vs AD-Map	ns	**	ns	ns	ns	ns	**	**	**	**	ns	ns	ns	ns	**	ns	ns	ns
L2C-FNN vs L2C-XGBw	ns	ns	**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	*	**	ns	**
L2C-FNN vs L2C-XGBnw	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	ns	ns	**	ns	ns	ns	ns	*

Appendix Table 1: Statistical significance between L2C-FNN and other approaches for cross-cohort ventricle volume (Appendix Fig. 2) and clinical diagnosis (Appendix Fig. 3) prediction performance broken down into yearly intervals up to 6 years into the future. Color and marker definitions follow Fig. 2.