

Diagnosis-Agnostic Representation Learning Reveals Stable Functional Connectivity Signatures of Alzheimer’s Disease from Resting-State fMRI

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Santiago V. Blas Laguzza¹, Hugo Aimar¹, Diego M. Mateos^{1,2}, Martin A. Belzunce³

¹Instituto de Matemática Aplicada del Litoral (IMAL-CONICET-UNL), CCT CONICET, Santa Fe, Argentina. ²Achucarro Basque Center For Neuroscience, Leioa, Vizcaya, Spain. ³Centro Universitario de Imágenes Médicas (CEUNIM), Instituto de Ciencias Físicas (ICIFI UNSAM-CONICET), Escuela de Ciencia y Tecnología, Universidad Nacional de San Martín (UNSAM), San Martín, Argentina.

A diagnosis-agnostic β -VAE achieved leakage-controlled CN–AD discrimination and identified a compact, cross-fold stable connectivity signature involving default-mode, control, limbic/orbitofrontal, sensorimotor, and cerebellar systems.

INTRODUCTIONMETHODSRESULTSCONCLUSIONS

Resting-state fMRI can reveal network alterations in Alzheimer’s disease, but connectivity-based classification is challenged by high dimensionality, acquisition heterogeneity, and unstable interpretation.

Objective: To evaluate a leakage-controlled latent-modelling framework for CN–AD classification and the identification of stable, anatomically interpretable connectivity signatures.

DATASET

Group	n	Age (y)	M / F
AD	97	74.4 ± 7.5	57 / 40
CN	300	73.1 ± 7.7	128 / 172
MCI	250	73.4 ± 8.0	135 / 115
Total	647	73.4 ± 7.8	320 / 327

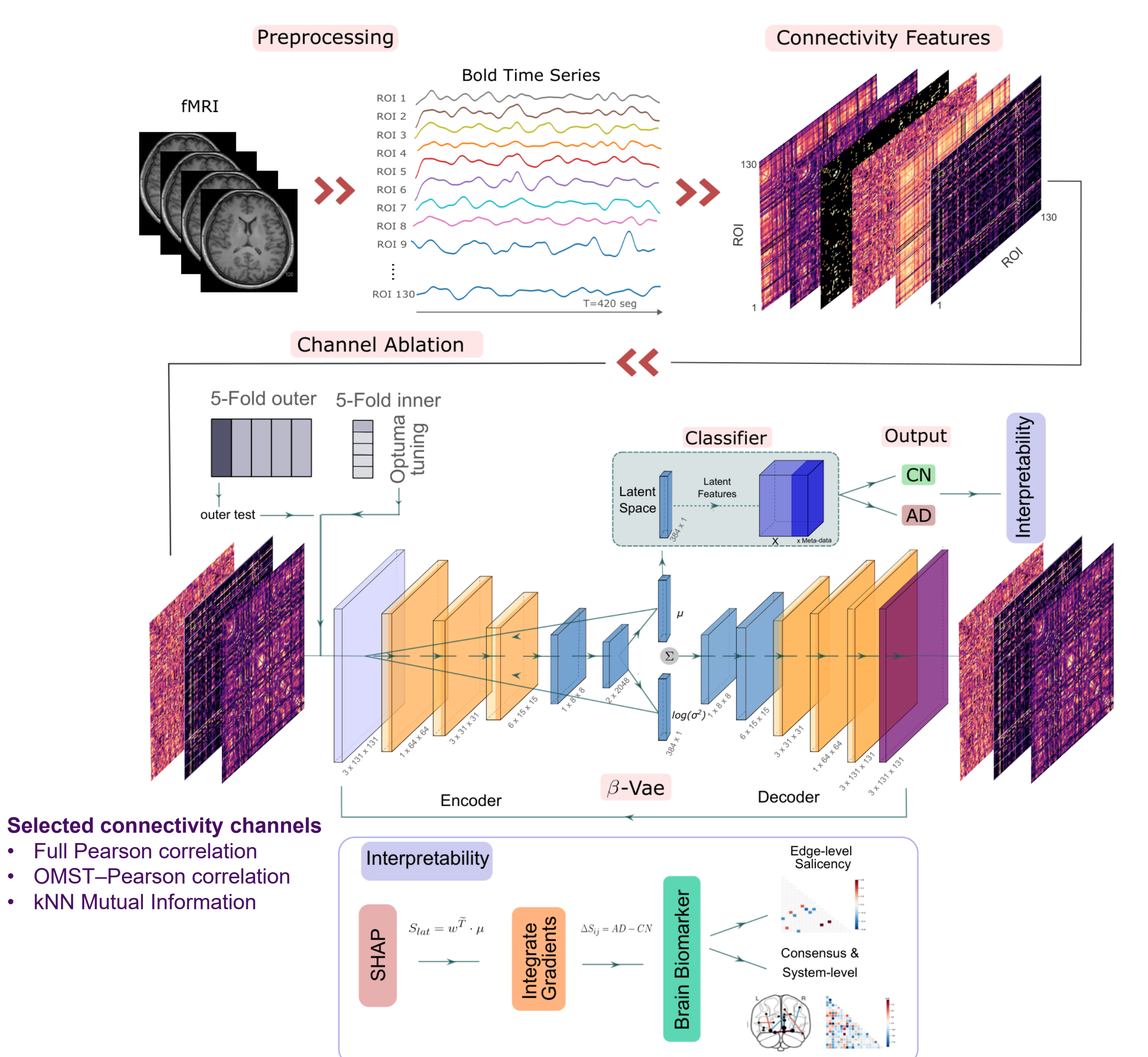
rs-fMRI acquisition (ADNI): 3T EPI · TR 3 s · TE 30 ms · 7–10 min (140/200 volumes) · Philips / Siemens / GE.

Preprocessing: DPARSF with motion correction, MNI normalisation, 4-mm smoothing, 0.01–0.10 Hz band-pass, nuisance regression.

Parcellation: AAL3 → 131 ROIs, Yeo-17 ordered, 140 z-scored timepoints.

External validation: OASIS, N=180 (90 CN / 90 AD), TR 2.5 s, 164 volumes.

A convolutional β -variational autoencoder learns a compact, diagnosis-agnostic latent embedding of multichannel functional connectivity (3 selected channels). Latent means with age and sex feed a strictly nested 5×5 cross-validated classifier. SHAP and Integrated Gradients map fold-stable signal back to connectivity edges.



Classification performance

L2 Logistic Regression applied to the 384 dimensions β -VAE latent features, together with age and sex, provided the strongest CN/AD discrimination, well above the 24.4% AD-prevalence baseline (N = 397; 97 AD / 300 CN).

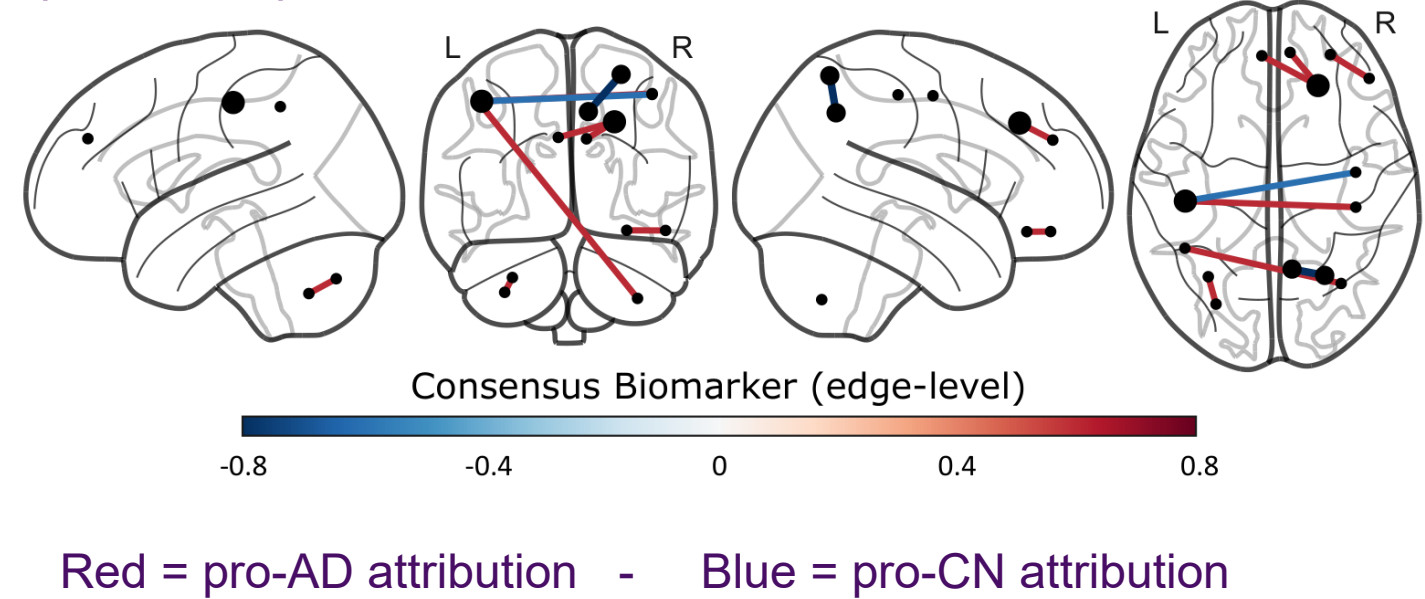
Classification Model	ROC-AUC	PR-AUC	Bal. Acc.
LogReg (L2)	0.795	0.624	0.698
LogReg (EN)	0.788	0.612	0.730
Random Forest	0.785	0.562	0.712

External OASIS evaluation: ROC–AUC 0.648; PR–AUC 0.668. PR baseline = 0.50.

Interpretability

SHAP + Integrated Gradients + cross-fold consensus: a compact **8-edge signature** (6 pro-AD, 2 pro-CN) spanning default-mode, control, dorsal-attention, limbic and somatomotor systems.

Top edge: Parietal_Sup_R – Precuneus_R (pro-CN).



- The diagnosis-agnostic β -VAE supported leakage-controlled CN–AD classification under strictly nested cross-validation.
- SHAP and Integrated Gradients identified a compact, fold-stable 8-edge signature spanning distributed functional systems.
- Reduced site-holdout and OASIS performance shows that harmonisation, domain adaptation, and further multi-cohort validation remain necessary.

REFERENCES

• Dennis & Thompson, *Neuropsychol Rev*, 2014.

• Ibrahim et al., *Hum Brain Mapp*, 2020.

• Chamakuri & Janapana, *Med Nov Technol Devices*, 2025.

CONTACT

Martín A. Belzunce, Ph.D.
mbelzunce@unsam.edu.ar