A machine learning enrichment strategy for presymptomatic cohorts in Alzheimer's disease clinical trials

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Background

It is challenging for Alzheimer's disease trials to enroll presymptomatic individuals who are likely to decline cognitively.

Setup

Baseline T1 images from ADNI [1], AIBL [2], NACC [3], and OASIS-3 [4] were segmented into tissue classes. A clustering algorithm on images from AIBL identified subtypes of gray matter distribution. Features were generated from these subtypes. These subtype features and baseline scores of MMSE, CDR-SB, FAQ, APOE4 carriership, education, age, and sex were used to train a machine learning prognostic pipeline to classify individuals who received a diagnosis of MCI within 48 months of follow-up (progressors) and those who remained cognitively stable in ADNI, NACC, and OASIS-3.

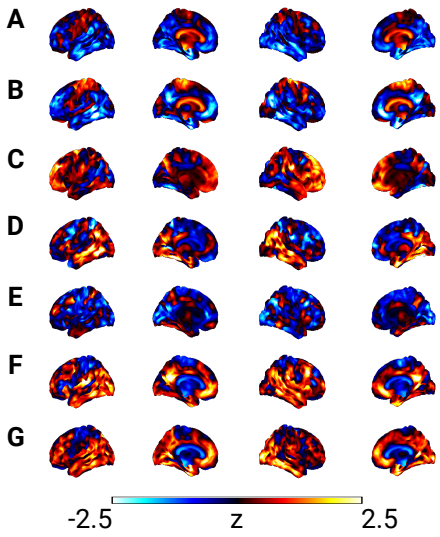

Figure 1. Maps of subtypes of gray matter distribution in the AIBL dataset. Each map was normalized by its mean and standard deviation across the voxels.

Results: Model performance

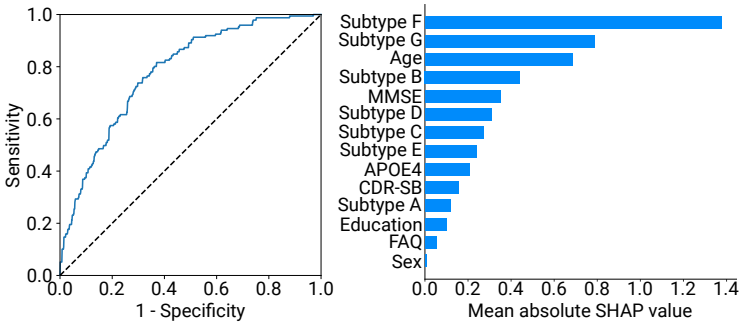

Figure 2. Left: ROC curve of the stable vs progressors classifier trained and cross-validated in ADNI, NACC, and OASIS-3. The model achieved a mean AUC of 78.0, sensitivity of 71.2, specificity of 71.6, and accuracy of 71.7. **Right:** Impact of each feature on the model output.

Results: Population analysis

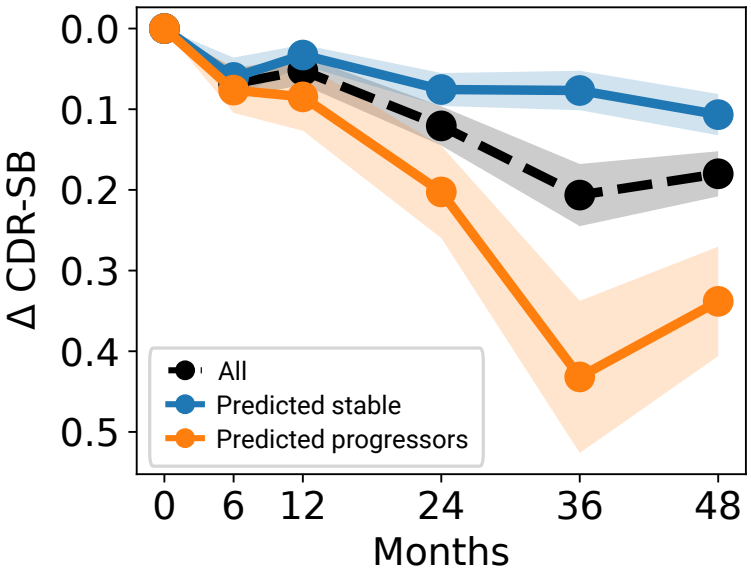

Figure 3. Cognitive trajectories of the predicted classes in ADNI, NACC, and OASIS-3 as measured by the CDR-SB.

Table 1. Baseline characteristics of the predicted classes

	All	Predicted stable	Predicted progressors
N	855	545	310
Age (mean ± std)	69.2 ±9.6	65.2 ±8.8	76.2 ±6.5
Female (%)	58.4	62.2	51.9
APOE4 (%)	31.6	28.2	37.7
Education (mean ± std)	16.1 ±2.7	16.6 ±2.4	15.2 ±3.1
CDR-SB (mean ± std)	0.07 ±0.3	0.02 ±0.1	0.17 ± 0.5
MMSE (mean ± std)	29.0 ±1.3	29.4 ±0.7	28.1 ±1.7
FAQ (mean ± std)	0.31 ±1.3	0.11 ±0.5	0.66 ±2.1
Amyloid positive (%) *	31.5	29.1	44.3
True progressors (%)	17.7	7.7	35.4

* Amyloid positive on either CSF or PET out of 301 individuals who had these measures

Conclusion

A machine learning tool can identify presymptomatic individuals with impending cognitive impairment from a single baseline time point. This tool can enhance trial enrollment by targeting individuals who are at the highest risk of cognitive decline.

Data were provided by [1] Alzheimer's Disease Neuroimaging Initiative (ADNI), adni.loni.usc.edu; [2] Australian Imaging Biomarkers and Lifestyle Study of Ageing, aibl.csiro.au; [3] National Alzheimer's Coordinating Center, naccdata.org, NIA/NIH Grant U24 AG072122 and NIA-funded ADRCs; [4] Open Access Series of Imaging Studies, oasis-brains.org, NIH P50 AG00561, P30 NS09857781, P01 AG026276, P01 AG003991, R01 AG043434, UL1 TR000448, R01 EB009352.