

An MRI-Based Marker of Braak Stage

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Introduction

Neurofibrillary tangles (NFTs) are a hallmark Alzheimer's disease (AD) pathology linked to neurodegeneration and cognitive decline^{1,2}. While tau-PET and blood tau assays support in-vivo detection, PET is costly and blood markers lack regional specificity. MRI is noninvasive and widely available, and it offers measures of not only neurodegeneration, but also cerebrovascular abnormalities, typically inaccessible to PET or blood markers. We developed an MRI-based classifier of Braak NFT staging using machine learning on ex-vivo MRI and neuropathology data from community-based older adults.

Methods

Data from four longitudinal cohort studies at the Rush Alzheimer's Disease Center (N=915) were utilized^{3,4}. Participants underwent ex-vivo MRI and neuropathological examination to determine Braak stage (0-VI) (Table 1).

We developed a two-level stacking ensemble to classify advanced NFT burden (Braak V-VI vs. 0-IV) using fractional anisotropy (FA) information from diffusion MRI and regional gray matter and white matter volumes. Modality-specific XGBoost models generated first-level risk scores, which were then combined using an L2-regularized

Table 1. Demographic, clinical and neuropathologic characteristics of the participants.

N	915
Age at death, years (SD)	90.6 (6.5)
Male, n (%)	254 (27.9)
Education, years (SD)	15.7 (3.5)
Antemortem clinical diagnosis, n (%)	
- No Cognitive Impairment	290 (31.7)
- Mild Cognitive Impairment	213 (23.3)
- Dementia ^a	412 (45.0)
Mini-mental State Examination (MMSE), mean (SD)	19.9 (9.6)
Race, n (%)	
- White	829 (90.6)
- Black or African American	64 (7.0)
- American Indian or Alaska Native	4 (0.4)
- Other/Unknown	18 (2.0)
AD-NC (NIA-AA), n (%)	
- Low AD neuropathologic change	187 (20.4)
- Intermediate AD neuropathologic change	376 (41.1)
- High AD neuropathologic change	242 (26.4)
Lewy bodies, n (%)	262 (28.6)
Gross infarcts, n (%)	369 (40.3)
Microscopic infarcts, n (%)	350 (38.3)
Atherosclerosis, n (%)	
- Mild	489 (53.4)
- Moderate	180 (19.7)
- Severe	45 (4.9)
Cerebral amyloid angiopathy, n (%)	
- Mild	389 (42.5)
- Moderate	224 (24.5)
- Severe	111 (12.1)
Arteriosclerosis, n (%)	
- Mild	345 (37.7)
- Moderate	184 (20.1)
- Severe	59 (6.4)
LATE-NC, n (%)	
- TDP-43 inclusions in amygdala only	159 (17.4)
- TDP-43 inclusions in amygdala and entorhinal cortex or hippocampus CA1	102 (11.2)
- TDP-43 inclusions in amygdala and entorhinal cortex or hippocampus CA1 and neocortex	249 (27.2)
Postmortem interval to fixation, hours (SD)	9.7 (7.4)
Postmortem interval to imaging, days (SD)	36.4 (16.0)
MRI Scanner, n (%)	
- 3T GE Signa, n (%)	73 (8.0)
- 3T Siemens Trio, n (%)	81 (8.9)
- 3T Philips Achieva, n (%)	287 (31.4)
- 3T Siemens Verio, n (%)	474 (51.8)

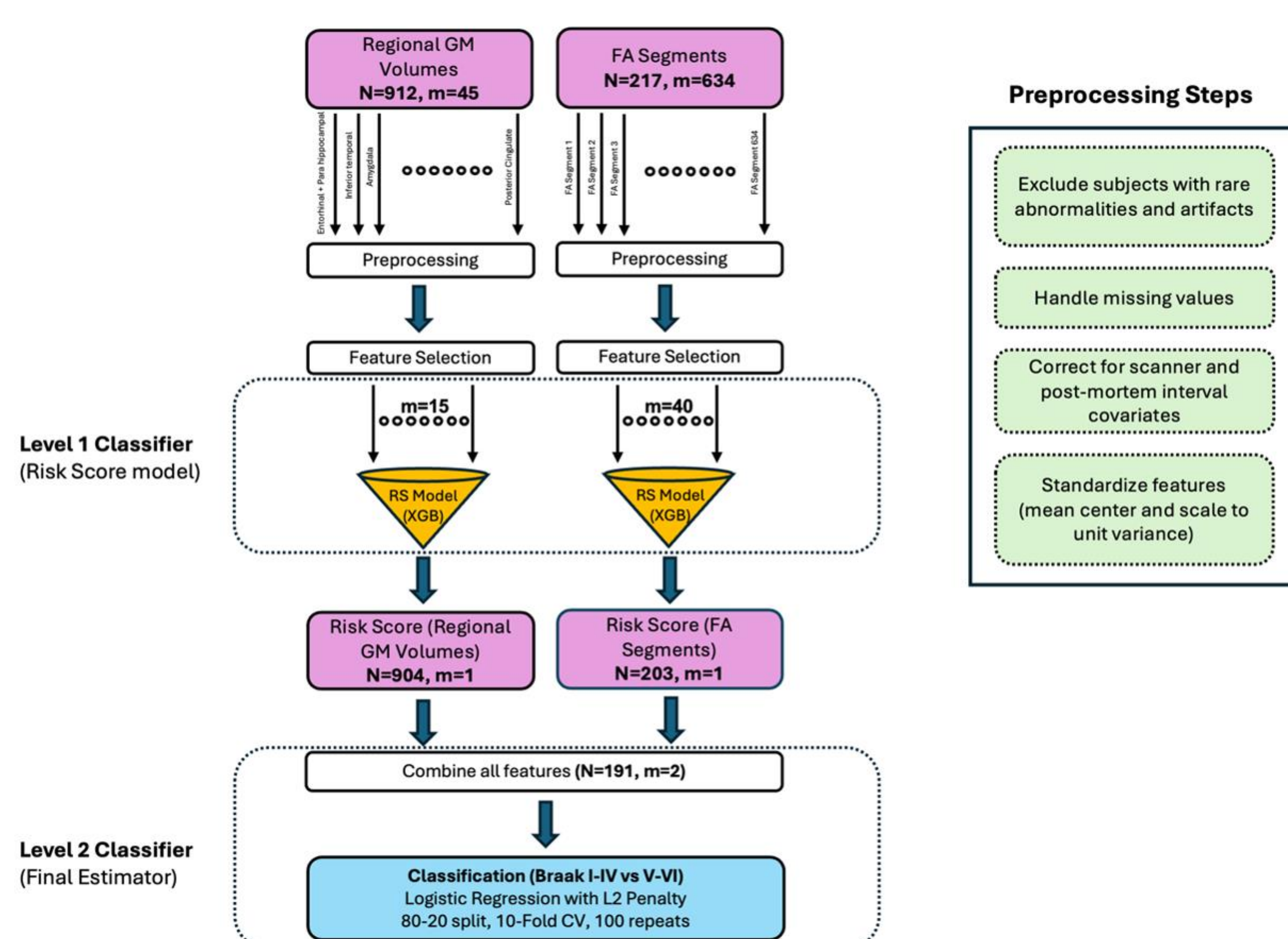


Fig 1: Schematic of the two-level stacking ensemble architecture. In the first level, base XGBoost classifiers generate cross-validated risk scores from ex-vivo MRI features. These scores serve as inputs for the second-level meta-learner (logistic regression), which integrates the data to produce the final classification of Braak NFT burden. RS, risk score; XGB, extreme gradient boosting or XGBoost; N, samples; m, features.

logistic regression meta-learner (Fig. 1). Performance was assessed with 100× repeated stratified shuffle-split cross-validation (80/20 per split), using mean ROC AUC as the primary metric (Fig. 2).

Results

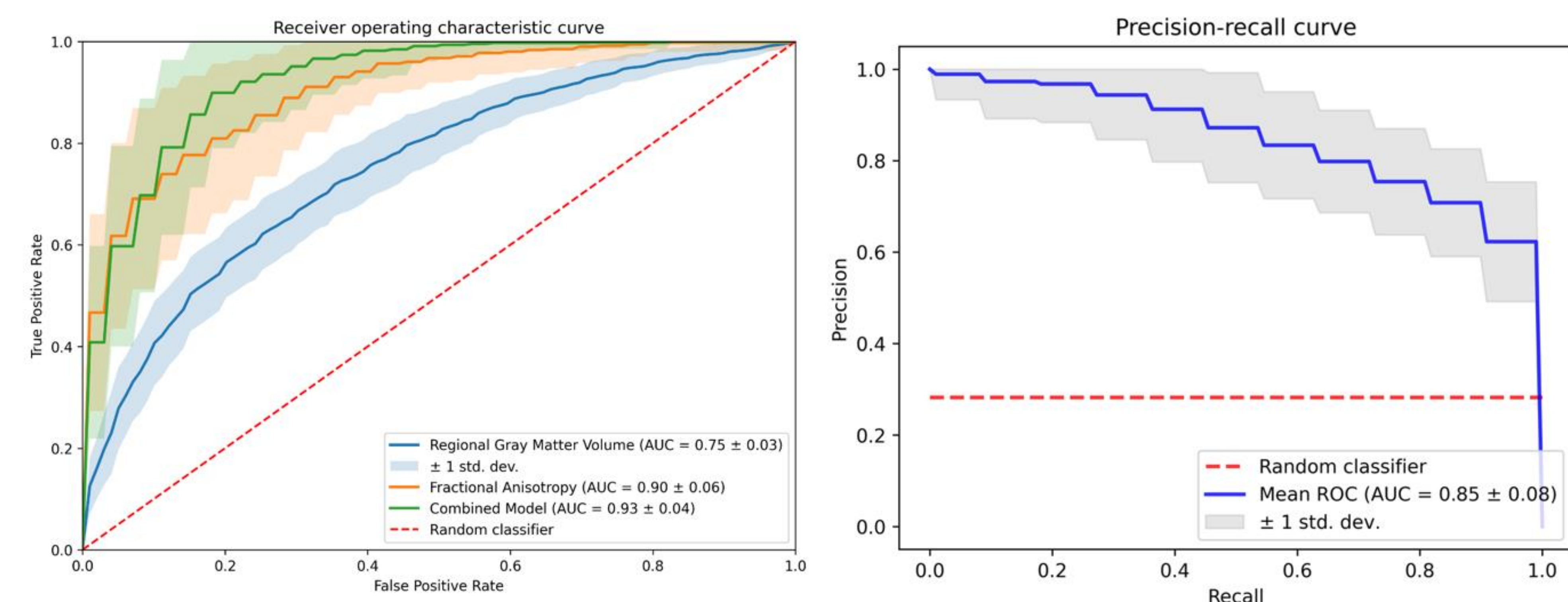


Fig. 2: ROC (left) and precision-recall (right) performance for classifying Braak V-VI vs 0-IV across 100× repeated stratified shuffle-split cross validation. The combined stacking model outperforms single modalities.

Conclusion

We present an MRI-based marker of Braak NFT staging trained on ex-vivo MRI and pathology data from community-based older adults. Our marker distinguishes Braak V-VI with high AUC = 0.93, outperforming prior in-vivo MRI-pathology models (AUC = 0.69; V-VI vs 0-II)⁵. Pending independent validation, this novel, noninvasive MRI marker may enable in-vivo detection of NFTs while the same and other MRI data from the same MRI scanning session may allow assessment of other neurodegenerative and cerebrovascular abnormalities.

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