

Efficient Early Screening For Alzheimer’s Disease Using Cortical Diffusion MRI With Principal Component Analysis

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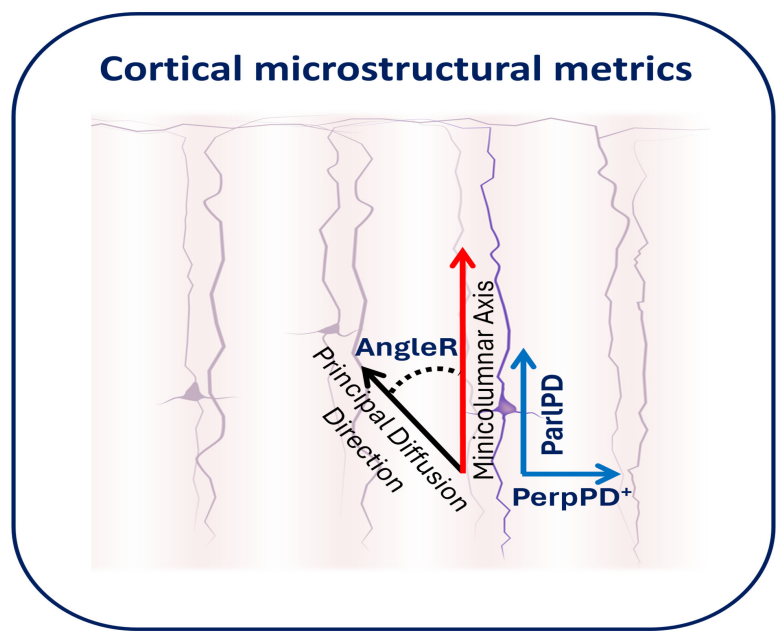
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AIM: Develop an MRI-based pre-test stratification tool for differentiating amyloid-positive AD from amyloid-negative clinically AD-like dementia before confirmatory biomarker testing. Evaluate the clinical utility of diffusion MRI-derived cortical microstructural signatures for MRI-based pre-test stratification in a real-world cohort.

INTRODUCTION

- To maximize the benefit of disease-modifying therapies such as lecanemab and donanemab, patients with mild cognitive impairment (MCI) and very mild dementia must be efficiently screened and accurately stratified before confirmatory amyloid biomarker testing. In routine memory-clinic practice, a substantial proportion of patients clinically suspected of having Alzheimer’s disease (AD) are ultimately found to be amyloid-negative (NonADD), highlighting the need for practical imaging biomarkers that can improve pre-test stratification while minimizing unnecessary biomarker testing.
- Magnetic resonance imaging (MRI) is routinely performed during the diagnostic evaluation of cognitive impairment and is mandatory before amyloid-targeted therapy to assess treatment safety. Unlike fluid biomarkers, MRI-derived biomarkers can therefore provide additional diagnostic information without increasing patient burden and are likely to complement plasma biomarkers such as p-tau217.
- Cortical thickness is widely used as an MRI biomarker but may lack sensitivity in the earliest stages of AD because it primarily reflects macroscopic cortical atrophy. Diffusion MRI-derived cortical microstructural features, analyzed using the Cortical Disarray Measurement (CDM), have recently been reported as sensitive markers of AD-related neurodegeneration^{1,2,3}.
- We hypothesized that integrating **regional cortical microstructural features quantified by CDM (AngleR, PerpPD⁺, and ParIPD)** using principal component analysis (PCA) would improve discrimination between amyloid-positive AD and amyloid-negative clinically AD-like dementia beyond conventional cortical thickness measurements.



Cortical microstructural metrics. This figure shows a cross-sectional image of diffusion-based metrics CDM (AngleR, PerpPD⁺, and ParIPD) for the three directional components of diffusion in cortical gray matter².

METHODS

Study population: This real-world observational study included 51 participants recruited at NHO Niigata National Hospital. Patients with early symptomatic cognitive impairment (CDR 0.5–1.0) undergoing evaluation for amyloid-targeted therapy between January 2024 and November 2025 were consecutively enrolled. Following confirmatory amyloid biomarker assessment using amyloid PET or CSF Aβ42/Aβ40, patients were classified as either amyloid-positive Alzheimer’s disease (AD; n = 31) or amyloid-negative clinically AD-like dementia (NonADD; n = 10) (jRCT1031240123). Cognitively normal controls (CDR = 0; n = 10) were obtained from a previously approved pilot study (jRCT1032210367) (**Table 1**).

MRI-derived features: All participants underwent MRI (1.5T Philips Ingenia), including 32-direction diffusion tensor imaging (DTI) and 3D T1-weighted imaging. Regional cortical thickness and three cortical disarray measurement (CDM) parameters (AngleR, PerpPD⁺, and ParIPD) were quantified using the Desikan–Killiany atlas (34 cortical regions per hemisphere), yielding **204 CDM-derived features per participant**. Group comparisons are shown for whole-brain averages for cortical thickness and cortical microstructural measures derived from Cortical Disarray Measurement (CDM), including PerpPD⁺, ParIPD, and AngleR. Data are presented as individual participant values (gray dots) with group means and standard deviations (black markers and error bars). ANOVA followed by pairwise testing with the Benjamini–Hochberg false discovery rate (q-FDR) correction. Compared with Control: ++ q < 0.01, + q < 0.05. Compared with NonADD: † q < 0.05 (**Figure 1**).

Regional effect-size analysis: Regional cortical surface maps were generated to visualize the spatial distribution of group differences across cortical thickness and cortical microstructural parameters derived from cortical diffusion MRI. Z-score–normalized regional measurements were calculated for cortical thickness and the cortical disarray measurement (CDM) parameters AngleR, PerpPD⁺, and ParIPD. For each cortical region defined by the Desikan–Killiany atlas, Hedges’ g effect sizes were computed for three pairwise comparisons: AD vs. Control, NonADD vs. Control, and NonADD vs. AD. Effect sizes were projected onto cortical surfaces using FreeSurfer for visualization (**Figure 2**).

Feature integration and Statistical analysis: Regional features were standardized using control-derived Z scores and integrated using principal component analysis (PCA). Three feature models were evaluated: (1) cortical thickness, (2) combined CDM + cortical thickness, and (3) CDM alone. The first three principal components (PC1–PC3) were retained for subsequent analyses. Regional group differences were quantified using Hedges’ g effect sizes. PCA-derived feature models were evaluated using multivariate analysis of variance (MANOVA) and one-way ANOVA (**Table 2**).

Classification performance of PCA-derived MRI classifiers: Three PCA-based feature models were compared using one-vs-rest (OvR) logistic regression with leave-one-out cross-validation (LOOCV): (A) cortical thickness alone, (B) combined CDM and cortical thickness, and (C) CDM alone. The table summarizes OvR AUCs, macro-averaged AUCs, optimal probability thresholds, and Youden’s J statistics for each model. The CDM model achieved the highest overall classification performance (macro-AUC = 0.739) and was therefore selected for constructing the final MRI classifiers (**Table 3, Figure 3**). The ROC curves show the performance of the final CDM model for discrimination of Control (AUC = 0.856), AD (AUC = 0.639), and NonADD (AUC = 0.722) (**Figure 3**). Based on these results, two sequential MRI classifiers (MRI classifier 1 and MRI classifier 2) were incorporated into the proposed MRI-based workflow for pre-test stratification before confirmatory amyloid biomarker testing (**Table 4**).

Proposed MRI-based clinical workflow: Based on the optimized MRI classifiers, a practical MRI-based clinical workflow was proposed to support pre-test stratification before confirmatory amyloid biomarker testing in patients being evaluated for amyloid-targeted therapy (**Figure 4**).

RESULTS

Table 1. Baseline demographic characteristics of the study participants

	Control(n=10)	NonADD(n=10)	AD (n=31)
mean±SD	mean±SD	mean±SD	mean±SD
AGE	72.7±5.7 [58.6, 76.7]	80.7±4 [77.8, 83.5]	78.3±6.8 [75.8, 80.8]
Male, n (%)	6 (60)	4 (40)	6 (19.4)
MMSE (0–30)	28.4±1.3 [27.4, 29.4]	25.9±2.0 [24.5, 27.3]	24.8±2.8 [23.8, 25.8]
Delayed recall (1–5)	3.0 [3, 3]	1.9±0.7 [1.4, 2.4]	1.6±1.2 [1.1, 2.0]
CDR-SB			
0, n (%)	10 (100)	0 (0)	0 (0)
0.5, n (%)	0 (0)	10 (100)	24 (77.5)
1, n (%)	0 (0)	0 (0)	7 (22.5)
CDR-SB (0–18)	0±0 [0, 0]	1.8±1 [1.1, 2.5]	2.7±1.4 [2.2, 3.2]
MDL (0–8)	8±0 [8, 8]	6±1.7 [4.8, 7.2]	6.9±1.4 [6.4, 7.4]
CSF Aβ42/40 ¹	N/A	33.1±7 [24.4, 44.8]	95.3±15.7 [72.3, 118.3]
CSF Aβ42/40 ²	N/A	0.107±0.003 [0.103, 0.111]	0.048±0.008 [0.046, 0.052]
Amyloid PET positive ³ , n (%)	N/A	5 (50)	9 (29)

Figure 1. Group differences in cortical thickness and cortical microstructural parameters

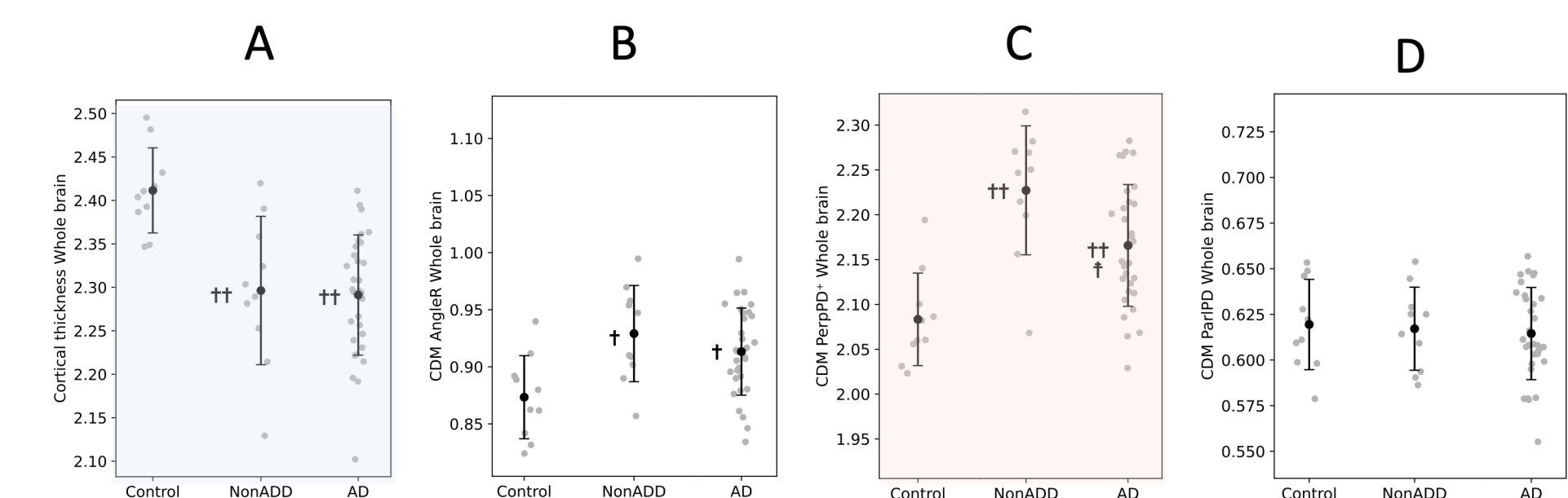


Figure 2. Cortical surface maps of regional effect sizes across cortical thickness (A) and cortical microstructural parameters (B: AngleR, C: PerpPD⁺, D: ParIPD)

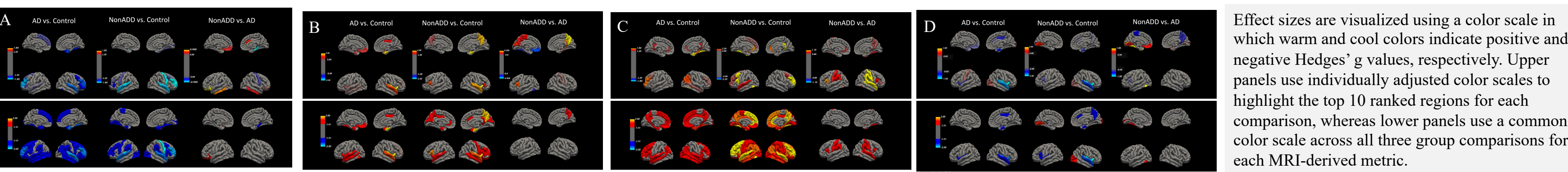
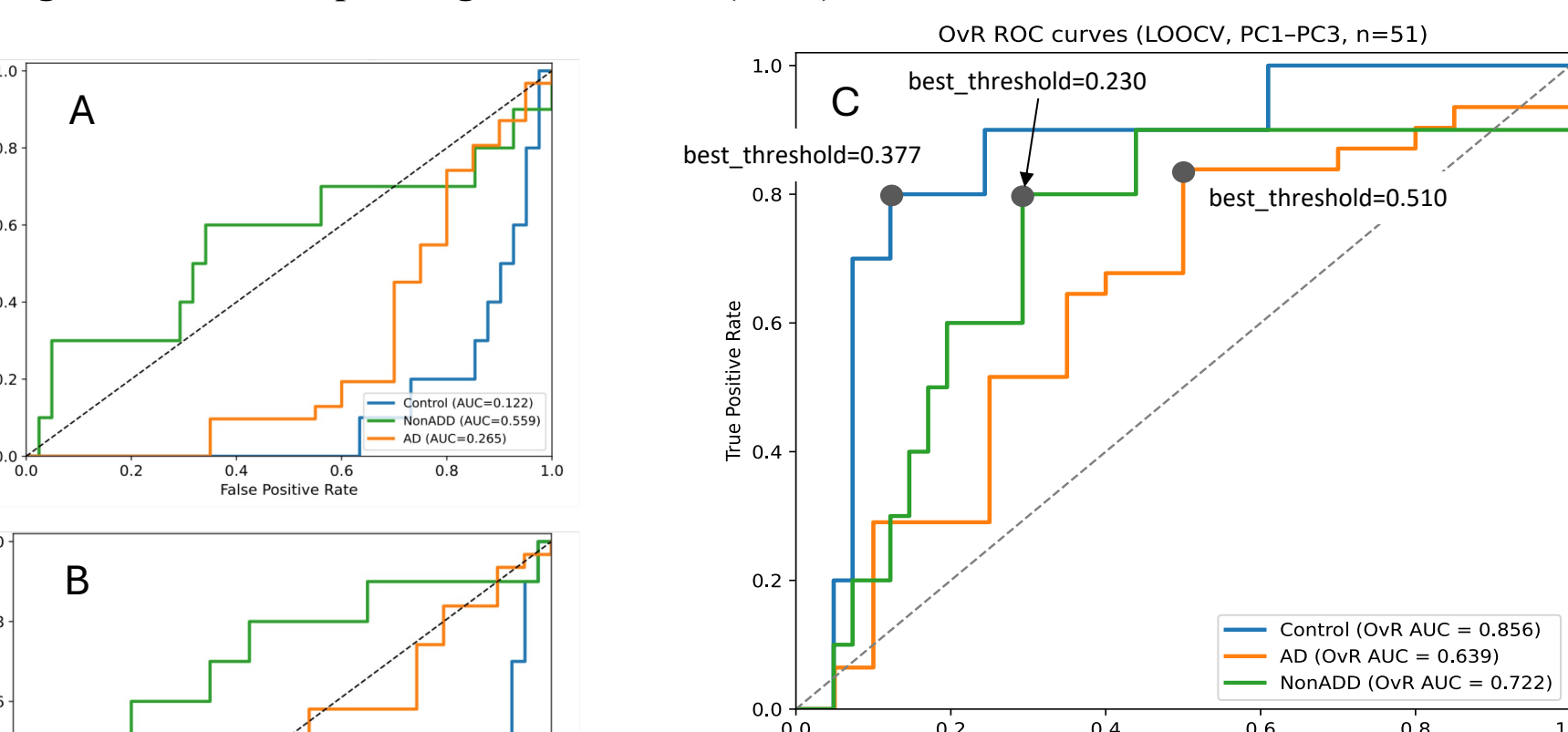


Table 2. Principal component analysis (PCA) results and multivariate group comparisons across feature models

Model	Thickness model (A)	CDM+Thickness model (B)	CDM model (C)
Explained variance ratio of PC1–3			
PC1	0.5028	0.3780	0.3977
PC2	0.3218	0.2366	0.2416
PC3	0.1100	0.0798	0.0972
MANOVA Wilks’ λ	0.54, F(6,92) = 5.53, p = 6.3 × 10 ^{−4}	0.56, F(6,92) = 5.29, p = 1 × 10 ^{−4}	0.59, F(6,92) = 4.62, p = 3.8 × 10 ^{−4}
ANOVA			
PC1	F(2,48) = 11.47, p = 8.5 × 10 ^{−3} , η ² = 0.323	F(2,48) = 14.78, p = 9.9 × 10 ^{−3} , η ² = 0.381	F(2,48) = 14.61, p = 1.1 × 10 ^{−3} , η ² = 0.378
PC2	F(2,48) = 2.69, p = 0.078, η ² = 0.101	F(2,48) = 0.07, p = 0.937, η ² = 0.003	F(2,48) = 0.31, p = 0.733, η ² = 0.013
PC3	F(2,48) = 2.23, p = 0.118, η ² = 0.085	F(2,48) = 2.23, p = 0.119, η ² = 0.085	F(2,48) = 0.66, p = 0.521, η ² = 0.027

Figure 3. Receiver operating characteristic (ROC) curves of PCA-derived discriminant models



Receiver operating characteristic (ROC) curves illustrating the classification performance of PCA-derived discriminant models across three feature models. (A) Cortical thickness model, (B) Combined CDM + cortical thickness model, (C) CDM-only model. Curves represent one-vs-rest (OvR) classification performance for the Control, AD, and NonADD groups. Classification was evaluated using leave-one-out cross-validation (LOOCV). The diagonal dashed line indicates chance-level performance (AUC = 0.5).

Table 3. Cross-validated classification performance of PCA-derived discriminant models

Model	Thickness model (A)			CDM+Thickness model (B)			CDM model (C)		
Classification Scheme (One-vs-Rest)	Control	AD	NonADD	Control	AD	NonADD	Control	AD	NonADD
AUC	0.122	0.265	0.559	0.146	0.373	0.656	0.856	0.639	0.722
Macro-averaged AUC		0.315			0.392			0.739	
Optimal Threshold	0.057	0.002	0.242	0.171	0.009	0.269	0.376	0.510	0.230
Youden's J	0.024	0.018	0.259	0.024	0.039	0.381	0.678	0.339	0.507

Table 4. Final MRI classifiers for pre-test stratification before confirmatory amyloid biomarker testing

	Model	Positive class	b ₀	b ₁	b ₂	b ₃	Optimal probability threshold
MRI classifier1:	Control OvR	Control	-2.244314	-0.266710	0.012882	-0.160800	0.376854
MRI classifier2:	NonADD OvR	NonADD	-1.859465	0.182755	-0.076221	0.000325	0.230334
	AD OvR	AD	0.451853	0.025112	0.035790	0.075458	0.509566

CONCLUSIONS

- Diffusion MRI-derived CDM features improved discrimination between AD and clinically AD-like amyloid-negative cases (NonADD). The CDM model outperformed the cortical thickness model.
- The proposed MRI-based workflow may facilitate pre-test stratification before confirmatory amyloid biomarker testing.

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Score: $s = b_0 + b_1PC_1 + b_2PC_2 + b_3PC_3$
Probability from scikit learn tool: $p = \frac{1}{1 + e^{-s}}$

