

White Matter Microstructure Changes Differently in Aging and Alzheimer's Disease Cohort

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ABSTRACT

BACKGROUND AND OBJECTIVE

White matter (WM) microstructural degradation occurs in both normal aging and Alzheimer's disease (AD). However, closer examination reveals distinct patterns: AD exhibits more temporally and spatially localized WM changes than normal aging, particularly in tau-positive individuals. This localization may reflect tau's dependence on neural connectivity for aggregation. We hypothesized that these pattern differences allow WM microstructure, measured through multi-shell dMRI, to serve as a biomarker to distinguish AD-related pathology from normal aging.

METHODS

- WM microstructure was analyzed using SuStaln across three cohorts: the population-based Mayo Clinic Study of Aging (MCSA¹) and two AD-enriched cohorts (Mayo ADRC² and ADNI3³).
- MCSA and Mayo ADRC were combined as the training dataset (Mayo dataset; n = 1,640), while ADNI3 served as the external validation dataset (n = 323).
- Participants were required to have available NODDI, tau PET, and amyloid PET imaging. Individuals with non-AD neurodegenerative diseases were excluded.
- NDI and FWF measures from 55 WM regions were screened for monotonic trends across cognitive stages.
- Regional NDI and FWF measures meeting the selection criteria were z-scored relative to the unimpaired group and entered the SuStaln model⁴.
- Occlusion saliency analysis was subsequently performed to evaluate the relative importance of individual WM features.

Table 1: Characteristics of the Study Cohort

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Characteristic	Mayo Dataset		ADNI3, n = 329
	MCSA, n = 1,548	Mayo ADRC, n = 86	
Demographics and cognition			
Age, y	70.3 (13.0)	75.7 (6.0)	72.8 (8.1)
Males, %	50.70%	53.40%	44.40%
APOE e4, %	23.80%	65.10%	29.16%
Education, y	15.3 (2.47)	16.0 (2.75)	16.2 (2.54)
MMSE	28.2 (1.89)	21.0 (5.36)	27.9 (2.93)
Trail Making Test Part B, Seconds	86.2 (56.6)	194 (92.4)	N/A
MCI, (n,%)	148 (9.56%)	6 (6.98%)	117, (35.56%)
Dementia (n,%)	66 (4.26%)	34 (39.53%)	31, (9.42%)
Imaging markers			
PiB SUVR	1.60 (0.43)	2.45 (0.49)	N/A
Amyloid Centiloid	--- N/A ---		31.5 (42.9)
Amyloid Positivity ¹ (n,%)	502 (32.43%)	82 (95.34%)	97 (30.22%)
Tau SUVR	1.20 (0.12)	1.81 (0.47)	1.30 (0.29)
ERC Tau SUVR	1.13 (0.16)	1.65 (0.29)	N/A
Tau Positivity ² (n,%)	239 (15.44%)	73 (84.89%)	50 (15.20%)
WMH / TIV, %	0.7 (0.8)	1.32 (1.13)	0.81 (0.85)
WMH Positivity ³ (n,%)	243 (15.70%)	15 (17.44%)	62 (18.84%)

¹: Amyloid positivity was defined as amyloid PET standardized uptake value ratio (SUVR) >1.52 or Centiloid >25.
²: Tau positivity was defined as tau PET SUVR >1.29.
³: WMH positivity was defined as WMH volume normalized to total intracranial volume (WMH/TIV) >1.3%.
Abbreviations: MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; WMH, white matter hyperintensities; TIV, total intracranial volume.

Figure 1: Regional WM microstructural changes associated with cognitive changes

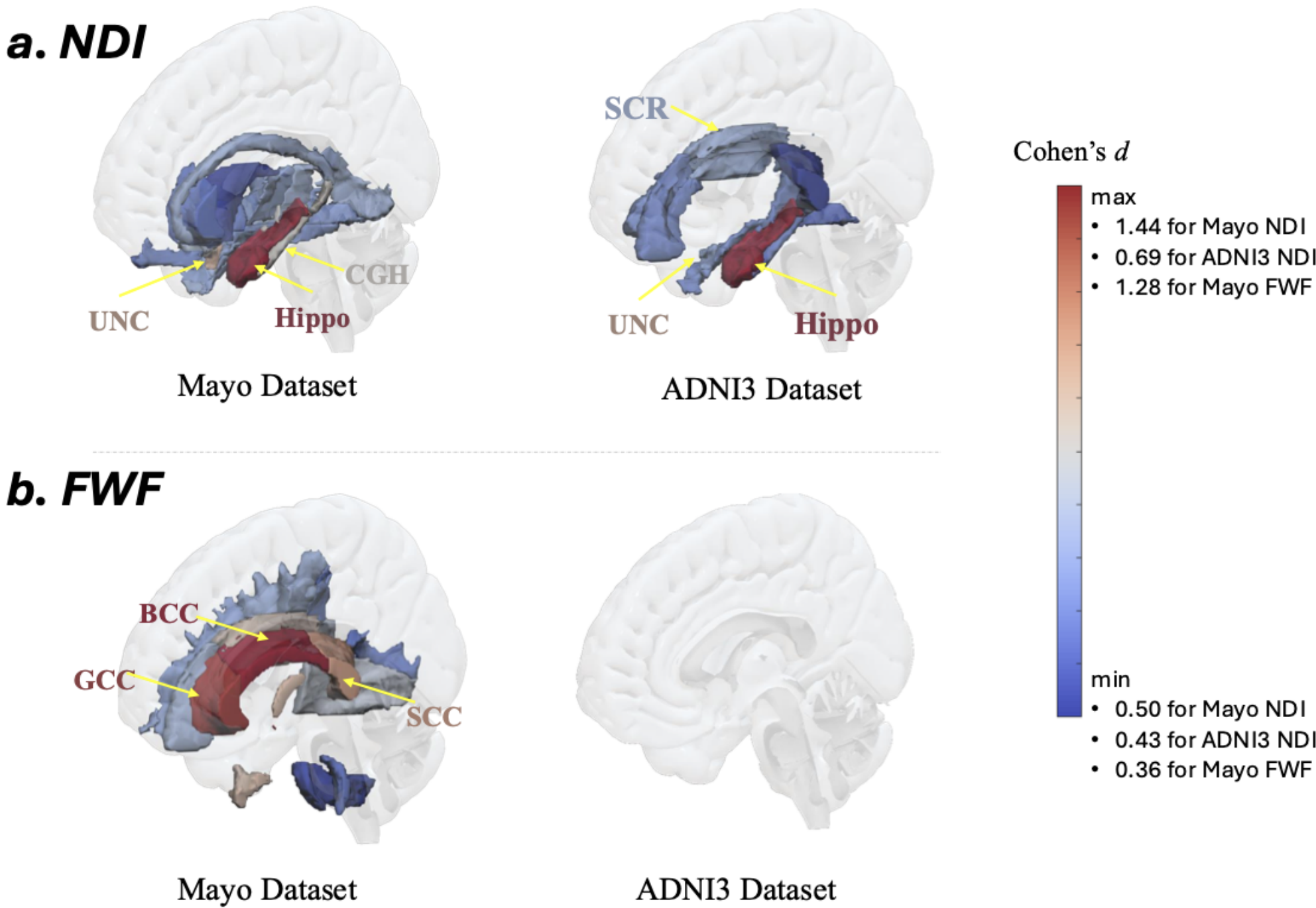


Figure 1. Selected white-matter ROIs showing monotonic trends and statistical significance across three cognitive groups: cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia. Based on the Mayo dataset, (a) neurite density index (NDI) had 16 regions and (b) free-water fraction (FWF) had 15 regions that met the selection criteria. The NDI regions (a) exhibited a *medial temporal-to-frontal* pattern of group differences between CU and cognitively impaired individuals (MCI + dementia), with the largest effects observed in hippocampal WM, the uncinate fasciculus (UNC), and the cingulum adjoining the hippocampus (CGH). This spatial pattern showed similar results in the ADNI3 cohort. In contrast, FWF regions (b) showed a *medial temporal-to-lateral* pattern, predominantly involving the corpus callosum, including the body, genu, and splenium (BCC, GCC, SCC). However, no regional FWF measures met the selection criteria in the ADNI3 cohort.

Figure 2: Two spatiotemporal trajectories identified based on WM microstructural changes

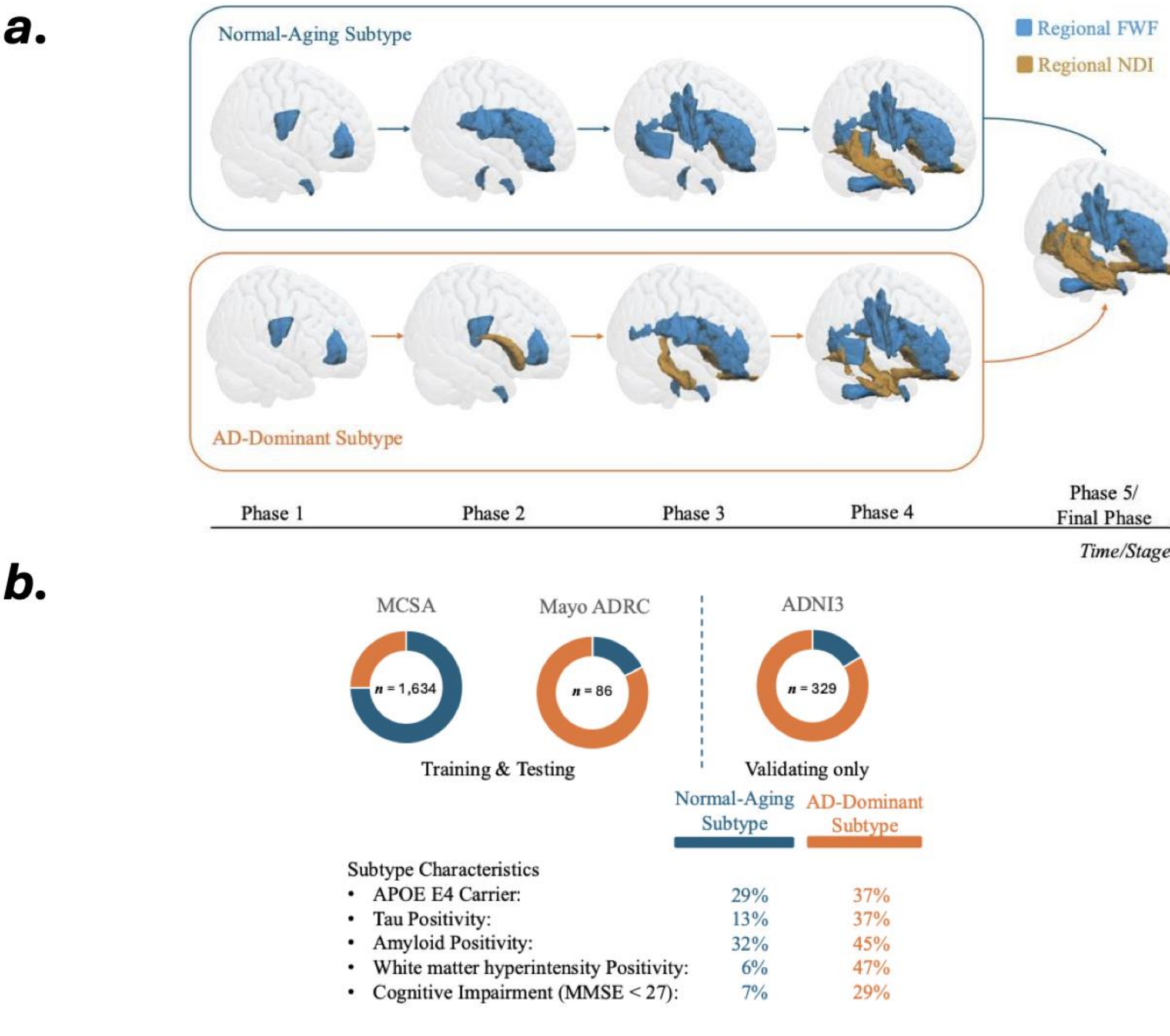


Figure 2. Two subtypes were identified (a), along with their subtype assignments across cohorts (b). **Normal-Aging subtype** exhibited an *FWF-leading* trajectory: the first three phases were characterized exclusively by FWF alterations, followed by progressive NDI decline in Phases 4 and 5. Aging-dominant subtype was predominantly observed in the aging cohort (MCSA) and was associated with a lower burden of AD-related pathology. In contrast, **AD-Dominant Subtype** showed more synchronized changes in FWF and NDI. This subtype displayed relatively slower progression in early stages but markedly accelerated deterioration in later stages compared with Aging-Dominant Subtype. AD-Related Subtype predominated in the AD-enriched cohorts (Mayo ADRC and ADNI3) and was associated with higher AD pathological burden.

RESULT

- In the Mayo dataset, 16 regional NDIs and 15 regional FWFs met the monotonicity criteria, highlighting WM pathways extending from the medial temporal lobe to the anterior frontal lobe.
- The qualifying FWF markers showed a broader and widespread distribution, with prominent involvement of medial and deep WM regions extending along anterior-posterior pathways.
- ADNI3 showed a similar regional NDI pattern but no FWF regions that met the monotonicity criteria.
- SuStaln identified two stable WM microstructural subtypes: Normal-aging subtype and AD-Dominant subtype.
- Normal-aging subtype was predominant in the aging cohort, comprising 76% of MCSA participants, and was characterized by early FWF abnormalities preceding NDI decline.
- AD-Dominant subtype was enriched in AD cohorts, comprising 83% of Mayo ADRC and 84% of ADNI3 participants, and showed concurrent worsening of NDI and FWF.
- AD-Dominant subtype was associated with greater AD-related pathology, i.e., amyloid positivity, tau positivity, white matter hyperintensity positivity, and poorer cognitive performance. These differences stayed statistically significant even after correcting for age.

- Saliency analysis indicated strong model reliance on free-water measures: all 10 highest-ranked features were FWF regions.

DISCUSSION

- This study demonstrated that WM microstructural integrity follows distinct alteration patterns associated with normal aging and AD.
- The Normal-aging subtype showed early free-water alterations, whereas the AD-Dominant subtype showed concurrent NDI and FWF deterioration accompanied by greater AD pathological burden and poorer cognition.
- The high diagnostic weighting of FWF features highlights the potential importance of free-water measures for characterizing heterogeneous AD progression trajectories.

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