



Distinct Gray and White Matter Diffusion MRI Microstructural Factors Associated with Amyloid Burden



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Introduction

Objective: Understand how dMRI measures from multiple microstructural models cluster into latent factors in gray versus white matter, whether these factors capture distinct microstructural processes across tissue types, and how they relate to A β burden.

Diffusion MRI (dMRI) provides sensitive markers of brain microstructure including promising early biomarkers of Alzheimer's disease (AD), detecting alterations before macrostructural atrophy. Different dMRI models can probe distinct microstructural features. Although dMRI models are largely developed for white matter (WM), early AD pathology originates in cortical gray matter (GM), where they may capture different cellular and tissue-level processes. Here, we applied non-negative matrix factorization (NMF) to dMRI measures in GM and WM to compare how microstructural metrics cluster into latent factors and test their associations with amyloid burden in cognitively normal (CN) individuals.

Novel dMRI Models

Major methodological limitation of assessing dMRI in GM is that most dMRI protocols are single-shell dMRI acquisitions.

- **DTI:** most widely used single-shell dMRI model BUT cannot accurately measure sources of non-Gaussianity in complex GM microarchitecture (e.g., restricted diffusion, neurite dispersion, free water)
- **Multi-shell dMRI models:** address limitations but rarely available for analysis
- **News single-shell dMRI techniques:** NODDI-DTI [1] and MAP-AMURA [2] developed to mimic the sensitivity of multi-shell NODDI [3] and MAPMRI [4] models, but their sensitivity to AD is unknown

Model	Cortical MRI Measure	Description
FreeSurfer	CTH	Cortical Thickness
	FA	Fractional Anisotropy
	MD	Mean Diffusivity
DTI	AD	Axial Diffusivity
	RD	Radial Diffusivity
APAD	Apparent Propagator Anisotropy	Extension of DTI fractional anisotropy but based on the model-free, nonparametric ensemble average diffusion propagator
RTOP	Return-to-origin Probability	Probability that water molecules undergo zero net displacement (i.e., diffusion is restricted)
MAP-AMURA	RTAP	Return-to-axis Probability
	RTPP	Return-to-plane Probability
NODDI-DTI	ICVF	Intracellular Volume Fraction
	ODI	Orientation Dispersion Index
	Tau	An intermediate parameter in the Watson distribution coupling axonal packing and orientation coherence
FreeSurfer	FW	Freesurfer

**NOTE: Tau is a NODDI parameter, not Alzheimer's disease tau protein.

Datasets

T1-weighted brain MRI, dMRI, and amyloid-PET data were analyzed in 1,256 CN participants from five ADRD datasets

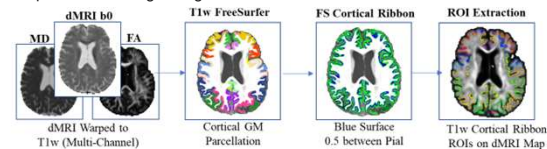
Study:	ADNI3/4 ¹	OASIS3 ²	HABS-HD ³	PREVENT-AD ⁴	HABS-MGH ⁵
Total (N)	164	71	977	24	29
Age (Mean [SD] yrs.)	71.4 [7.1]	68.7 [8.4]	64.5 [8.2]	65.6 [4.6]	71.2 [4.6]
Sex (N)					
Male	63	35	286	4	5
Edu (Mean [SD])	16.9 [2.3]	16.0 [2.4]	14.3 [3.7]	14.8 [3.6]	15.0 [2.3]
Race/Ethnicity					
Black (N)	10	9	337	0	8
Hispanic (N)	13	0	298	0	0
Other* (N)	13	0	14	0	0
A β -PET Tracer**	FBB/FBP	PIB/FBP	FBB	NAV	PIB
dMRI Protocols (N)	8	1	2	1	2

*"Other" includes Asian or American Indian/Alaskan

Methods

dMRI Processing

To extract cortical dMRI measures, preprocessed dMRI scalar maps were warped to T1w images segmented with FreeSurfer:



- 12 dMRI measures from 4 single shell models averaged in in 31 JHU WM regions and 34 cortical regions and the full cortex
- Measures harmonized across dMRI protocols using ComBat [10]

Statistics

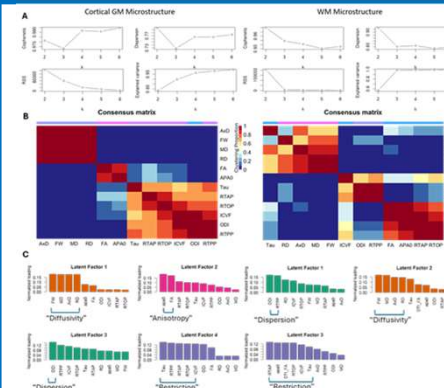
- NMF [11] was applied separately to GM and WM subject-by-region-by-measure matrices to derive latent factors capturing shared variance across dMRI metrics
- Associations between resulting factors and amyloid-PET centiloids were tested using linear models adjusting for age, sex, education, and race/ethnicity.
- Quadratic amyloid terms were also tested to assess nonlinear effects on microstructure.
- For comparison with dMRI factors, cortical thickness (CTH) associations were also evaluated.
- FDR procedure corrected for multiple comparisons across 35 cortical regions ($q=0.05$)

References & Funding

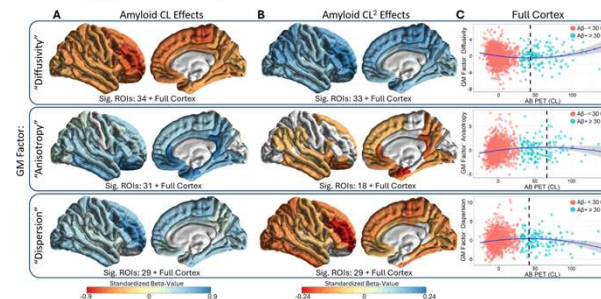
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Funding: AARG-23-1149996, R01AG058854, RF1AG057892, R01AG059874, R01AG087513, U01AG068057, RF1NS136995, S10OD032285

Results



Latent dMRI microstructural factors in GM and WM. NMF was performed separately in gray and white matter using 50 iterations across multiple ranks. (A) The optimal number of latent factors was determined based on consensus stability metrics across ranks (k=2-6) (i.e., high cophenetic correlation and dispersion and minimal gains in explained variance), yielding four components in GM and three in WM. (B) GM and WM showed similar latent structures, but tissue-specific clustering indicates that identical dMRI measures reflect different microstructural properties. (C) The bottom panel illustrates ordered dMRI measures contributing most strongly to each latent factor. Measures contributing to multiple factors are highlighted only under their primary factor of contribution, revealing distinct microstructural signatures for each latent factor. The names of the latent factors are given based on the top measures contributing to each factor e.g., "Anisotropy" for the FA and APA0. We note that there is an overlap between factors, particularly "Restriction" and "Dispersion". GM and WM each exhibited three latent microstructural factors related to extracellular diffusivity, dispersion, or restriction. However, in GM, anisotropy formed a distinct fourth factor, whereas in WM, anisotropy clustered with restriction



Biphasic relationship between amyloid and GM microstructure. Significant quadratic associations were detected between A β CL and three of the four GM latent microstructural factors, whereas only one quadratic WM diffusivity association was detected in the hippocampal cingulum and no associations were detected with CTH. Regional effect sizes are shown for significant (A) linear and (B) squared A β CL terms ($P_{adj}<0.05$). ANOVA model comparisons indicated significantly improved fit for quadratic relative to linear models across all significant regional associations, with the exception of anisotropy in the banks of the superior temporal sulcus, caudal anterior cingulate, caudal middle frontal, lateral occipital, paracentral, superior parietal, and transverse temporal gyri; dispersion in the entorhinal cortex; and diffusivity in the transverse temporal gyrus. (C) Quadratic associations between GM factors in the full cortex show early decreases in diffusivity and concurrent increases in dispersion and anisotropy, followed by increased diffusivity and decreased dispersion and anisotropy at higher amyloid levels. For reference, A β - and A β + groups are indicated (defined by a cut point of CL=30), and a dotted vertical line marks the estimated peak CL value for each curve.

Conclusions

- GM and WM show distinct latent microstructural factors.
- Amyloid burden was more consistently associated with GM dMRI factors than WM factors or CTH, suggesting greater sensitivity of cortical microstructure to early pathology.
- The observed biphasic relationships may reflect early amyloid-related inflammatory processes (e.g., microglial activation or cellular hypertrophy) marked by reduced diffusivity and increased anisotropy or dispersion, with the opposite pattern emerging at higher amyloid levels, consistent with neurite loss and neurodegeneration.