

Heterogeneous Spatial Relationships between Fibrinogen, Amyloid, and Tau in the Frontal Cortex of Alzheimer's Disease Patients

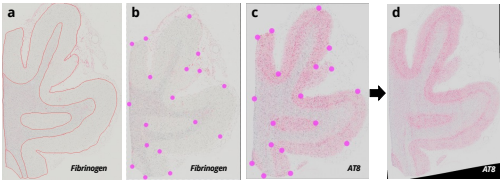
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Introduction

- Alzheimer's Disease (AD) is characterized by amyloid and tau pathology, neuroinflammation, and blood-brain barrier (BBB) compromise.
- Fibrinogen (FIB), a plasma glycoprotein with roles in coagulation and inflammation, does not normally permeate the BBB.³
- FIB can be observed diffusely extending into the brain from some vasculature in AD patients, correlating with disease severity.^{5,6}
- Previous studies have shown that FIB interacts directly with both amyloid and tau proteins, suggesting a link between vascular dysfunction and AD pathology accumulation.^{1,7}
- In this study, we assessed the spatial overlap between FIB, amyloid, and tau in the frontal cortex of post-mortem human AD patients.

Methods

Whole Slide Image (WSI) ROI Segmentation & Warping



Tiling & Quantification

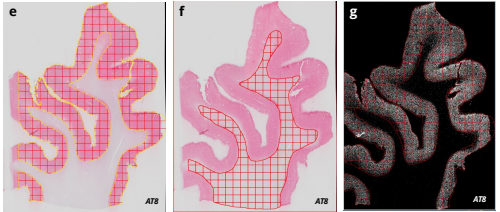


Figure 2 (below): Demographic table.

Characteristic	APOE4- N = 6 ¹	APOE4+ N = 9 ¹
PMI (hours)	14 (13)	16 (14)
Sex		
F	2 (33%)	5 (56%)
M	4 (67%)	4 (44%)
Age	87 (6)	84 (8)
ADNC Status		
High	2 (33%)	2 (22%)
Intermediate	3 (50%)	4 (44%)
Unknown	1 (17%)	3 (33%)

¹ Mean (SD); n (%)

Results

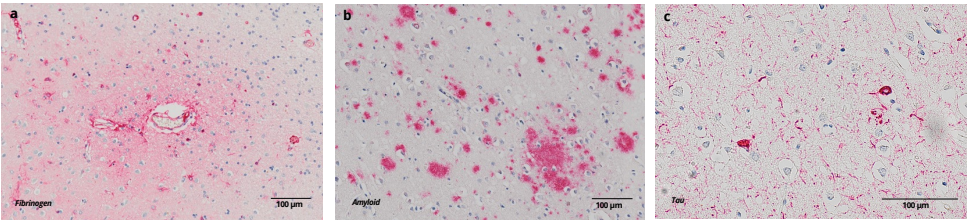


Figure 3: Frontal lobe WSIs showing distribution of (a) fibrinogen (FIB), (b) amyloid plaques (4G8), and (c) tau tangles (AT8).

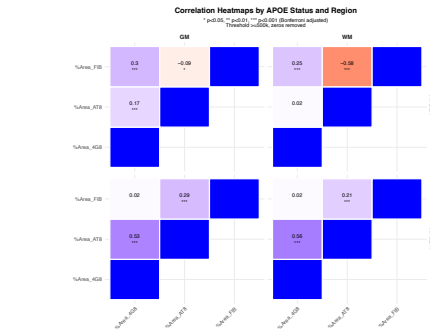


Figure 4: Heatmaps show pairwise Spearman correlation coefficients (r) among pathology markers in GM and WM, excluding zero values, and stratified by APOE4 status. Color intensity reflects correlation strength and direction (red = negative, blue = positive; range -1 to 1). Values displayed within tiles indicate correlation coefficients with Bonferroni-adjusted significance levels (* p < 0.05, ** p < 0.01, *** p < 0.001).

Mean stain density by tissue subregion (%)				
Subregion	4G8	AT8	FIB	
GM	6.67 ± 8.44	8.39 ± 15.42	1.61 ± 5.62	
WM	0.67 ± 2.14	1.39 ± 3.07	1.05 ± 4.46	

Figure 5: Summary table of mean percent area of each stain by tissue region (GM, WM).

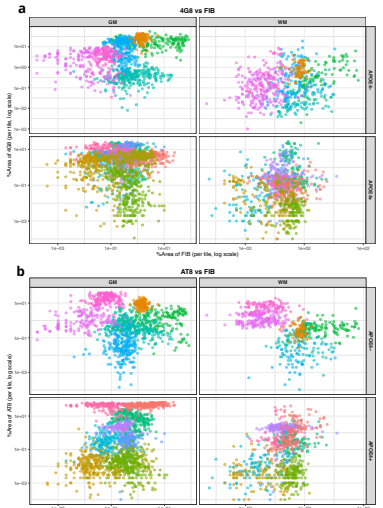


Figure 6: Log-scaled percent area of FIB is plotted against percent area of (a) 4G8 and (b) AT8 across all sampled tiles of each subject. Panels are organized by brain region (GM, WM) and APOE4 status. Each point represents a single tile, colored by subject.

Discussion

In this small cohort study, we quantitatively analyzed the spatial relationships between fibrinogen, amyloid, and tau pathology within the frontal cortex of AD patients. While amyloid and tau were typically positively correlated in gray matter, their relationships with fibrinogen varied by APOE4 status. In gray matter, fibrinogen positively correlated with amyloid (non-carriers) or tau (carriers), but not both. In white matter, fibrinogen correlated positively with amyloid and negatively with tau in non-carriers, versus positively with tau in carriers. APOE4 status appears to partially modify the relationship between these pathologies in both gray matter and white matter, which suggests larger cohort studies are warranted to examine the heterogeneity among AD patient populations.

Acknowledgements and References

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