

Distinct Microglia-Plaque Spatial Relationships in Individuals Resilient to Alzheimer's Disease

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Background and Significance

- Some older adults have Alzheimer's pathology but remain cognitively intact—a phenomenon called resilience¹.
- These resilient individuals may have unique neuroimmune responses, particularly involving microglia².
- Microglia cluster around amyloid beta plaques, but their role in cognitive resilience is not yet well understood³.

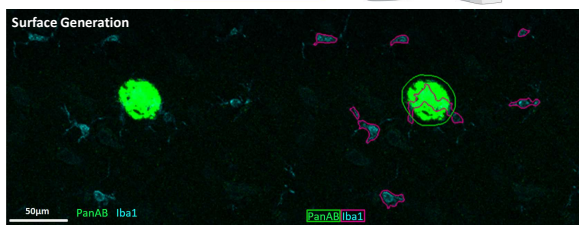
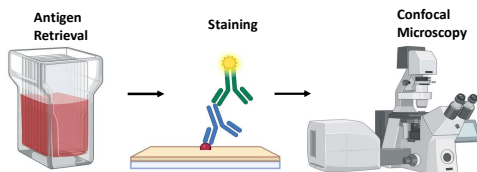


Hypothesis: Cognitively resilient individuals with Alzheimer's pathology will exhibit distinct microglia-A β colocalization patterns compared to symptomatic individuals

Methods

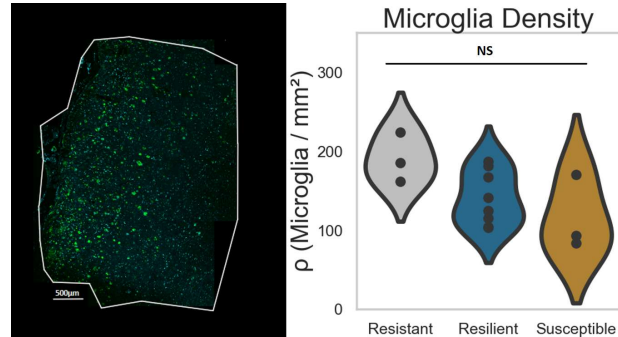
Group	Males	Females	Mean Age	Mean Cognitive Score (MMSE)	Total
Resistant	2	1	85	28	3
Resilient	5	3	91	26	8
Susceptible	2	1	80	18	3

1. 15 μ m-thick dorsolateral prefrontal cortical slices were stained for Iba1⁺ microglia and Pan-A β ⁺ plaques
2. Immunofluorescence mosaics were acquired via stitching of confocal microscopy images
3. Surfaces characterizing the shape and area of microglia and plaques were generated using machine learning-based segmentation in IMARIS
4. Spatial overlap and proximity metrics were extracted. Spatial analysis was performed in Python to compare microglia-A β colocalization across groups



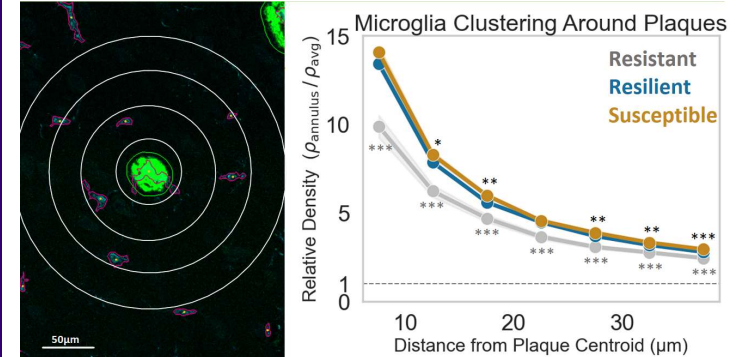
Results: Microglia Density

No difference in average microglial density across whole cortical slices



Whole cortical slice area was approximated in Python with a convex polygon based on microglia centroid coordinates (left, white). Slice-wide average microglial density was assessed by measuring microglia centroids per unit area. There was no significant difference between groups (Kruskal-Wallis, $p=0.118$).

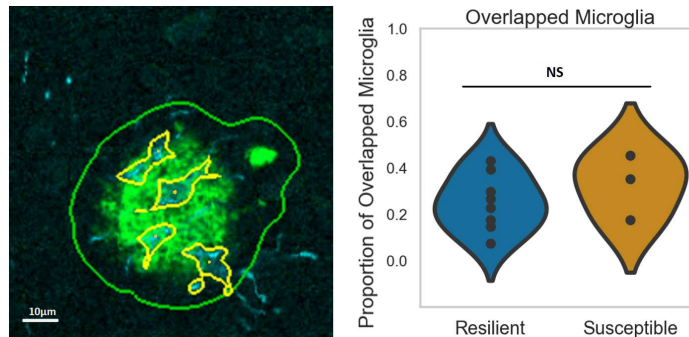
Microglia clustering is different between groups



Microglial clustering around plaques was assessed by comparing local density in concentric regions around plaque centroids to the slice-wide average. Resilient and Susceptible individuals showed significantly increased density compared to Resistant individuals at proximal distances. Resilient individuals showed decreased density compared to Susceptible individuals (Crossed t-test, * $p<0.05$, ** $p<0.005$, *** $p<0.0005$. Grey = Resistant-Resilient and Resistant-Susceptible; black = Resilient-Susceptible).

Results: Microglia-A β Overlap

No difference in Microglia-A β surface overlap in individuals with pathology



Microglia clustering profiles were compared between Resilient and susceptible individuals by measuring the proportion of Iba1⁺ microglia surfaces overlapping with Pan-A β ⁺ plaque surfaces. There was no significant difference between groups (Mann-Whitney U-test, $p=0.497$).

Conclusions and Future Work

- Whole-slice microglial density (centroids per unit area) did not significantly differ across groups, suggesting global microglia abundance may not distinguish cognitive phenotypes in Alzheimer's pathology.
- Resilient individuals had lower plaque-proximal microglial density than Susceptible ones, suggesting that resilience is associated with decreased microglial clustering in distal plaque areas.
- No significant difference in Iba1⁺ microglia overlapping with Pan-A β ⁺ plaques between Resilient and Susceptible groups, suggesting clustering or direct contact may not differ across these phenotypes.
- Future studies could pair spatial transcriptomics with single-nucleus RNA sequencing to test whether resilience is associated with distinct TREM2- and SPP1-linked activation states near A β plaques or phosphorylated tau.

References and Acknowledgements

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