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# INTRODUCTION

Recent studies have implicated both resident microglia and infiltrating peripheral immune cells in the pathogenesis of Alzheimer's disease (AD), yet their contributions at different stages of the disease remain inadequately defined. Disease-associated microglia (DAM) are known to drive neuroinflammation and phagocytic responses to amyloid and tau pathology, potentially facilitating the infiltration of peripheral immune cells. However, the specific phenotypes of DAM across distinct stages of Alzheimer's disease neuropathological changes (ADNC) and in the brains of individuals exhibiting substantial amyloid and tau burden while maintaining preserved cognition (referred to as resilient brains) <sup>1,2</sup> remain largely uncharacterized.

## METHODS

Fifty-one post-mortem human brains were included and stratified into four groups: (1) demented Braak V–VI (DEM V–VI); (2) demented Braak III–IV (DEM III–IV); (3) non-demented Braak III–IV (resilient; RES III–IV); and (4) non-demented with absent or negligible ADNC. All brains included lacked significant coexisting synucleinopathy, TDP-43 pathology, cerebrovascular lesions, or other major comorbid neuropathologic conditions. Quantitative immunohistochemical analyses of amyloid plaque and phosphorylated Tau (pTau) burdens, DAM, and CD8+T cells were performed on entorhinal cortex sections using validated antibodies.

## CONCLUSIONS

These findings suggest that the disease-associated microglia (DAM) signature and peripheral immune cell infiltration are significantly elevated in the brains of demented individuals with Alzheimer's disease neuropathological changes (ADNC), starting from early pathological stages. In contrast, resilient individuals demonstrate minimal DAM signatures and reduced peripheral cell infiltration, resembling control brains without ADNC. Ongoing studies aim to further elucidate the effects of central and peripheral immune cells on cognitive function and the integrity of neuronal and synaptic structures.

## References:

1. Gómez-Isla, T. and M.P. Frosch, Lesions without symptoms: understanding resilience to Alzheimer disease neuropathological changes. *Nature Reviews Neurology*, 2022. **18**(6): p. 323-332.
2. Schneider, J.A., et al., The neuropathology of older persons with and without dementia from community versus clinic cohorts. *Journal of Alzheimer's Disease*, 2009. **18**(3): p. 691-701.

## ACKNOWLEDGEMENTS

## RESULTS

## Assessment of Amyloid Plaque and Tau Pathology in the Entorhinal Cortex (EC) Across Braak Stages

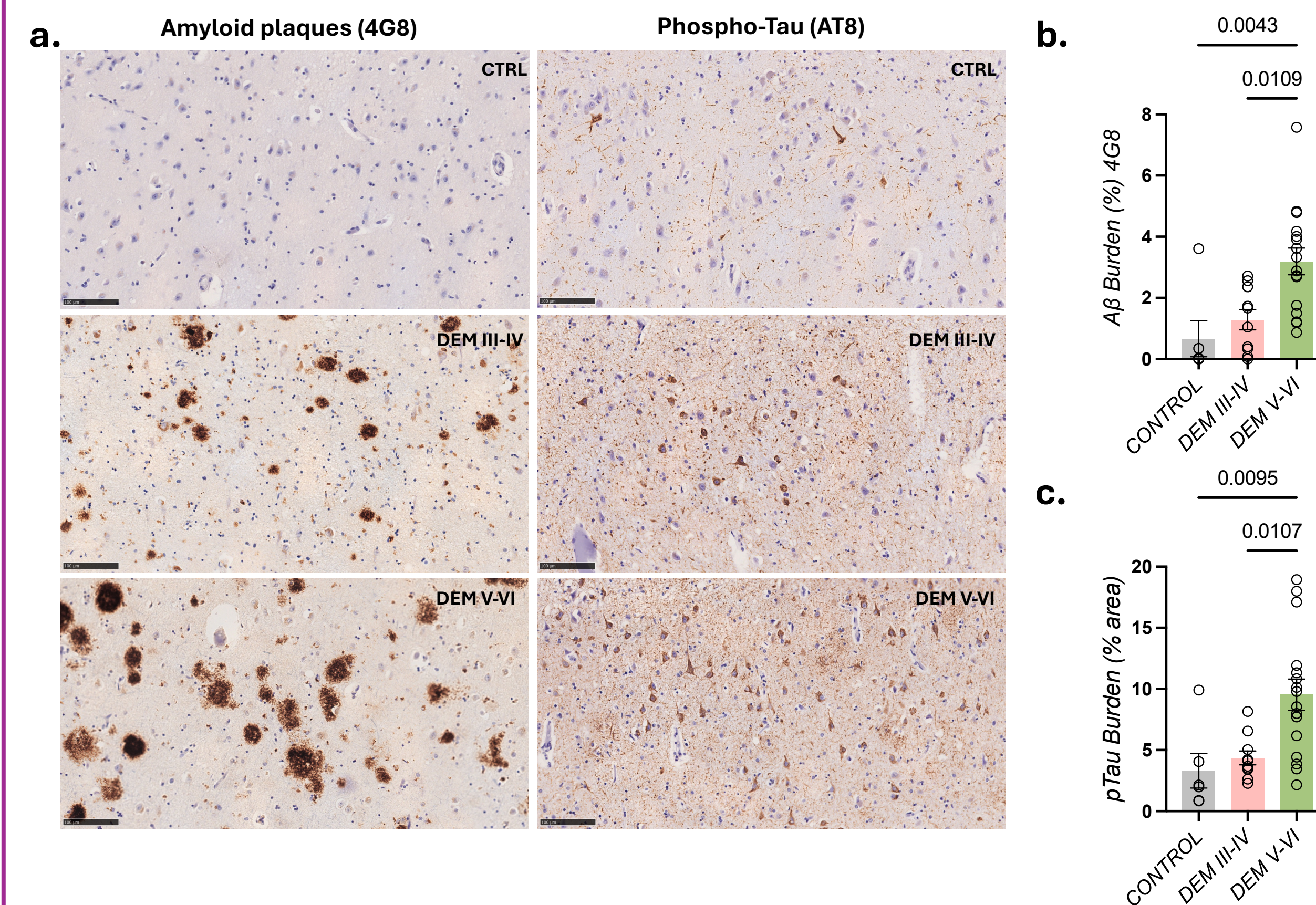


**Fig. 1:** Representative (a) images and datasets obtained from 4G8 and AT8 antibody staining reveal an increase in (b) amyloid plaque burden and (c) hyperphosphorylated Tau levels in the entorhinal cortex (EC) associated with higher Braak staging. Scale bar = 100  $\mu$ m.

## Differential Immune Cell Activation in the Entorhinal Cortex (EC) Across Braak Stages

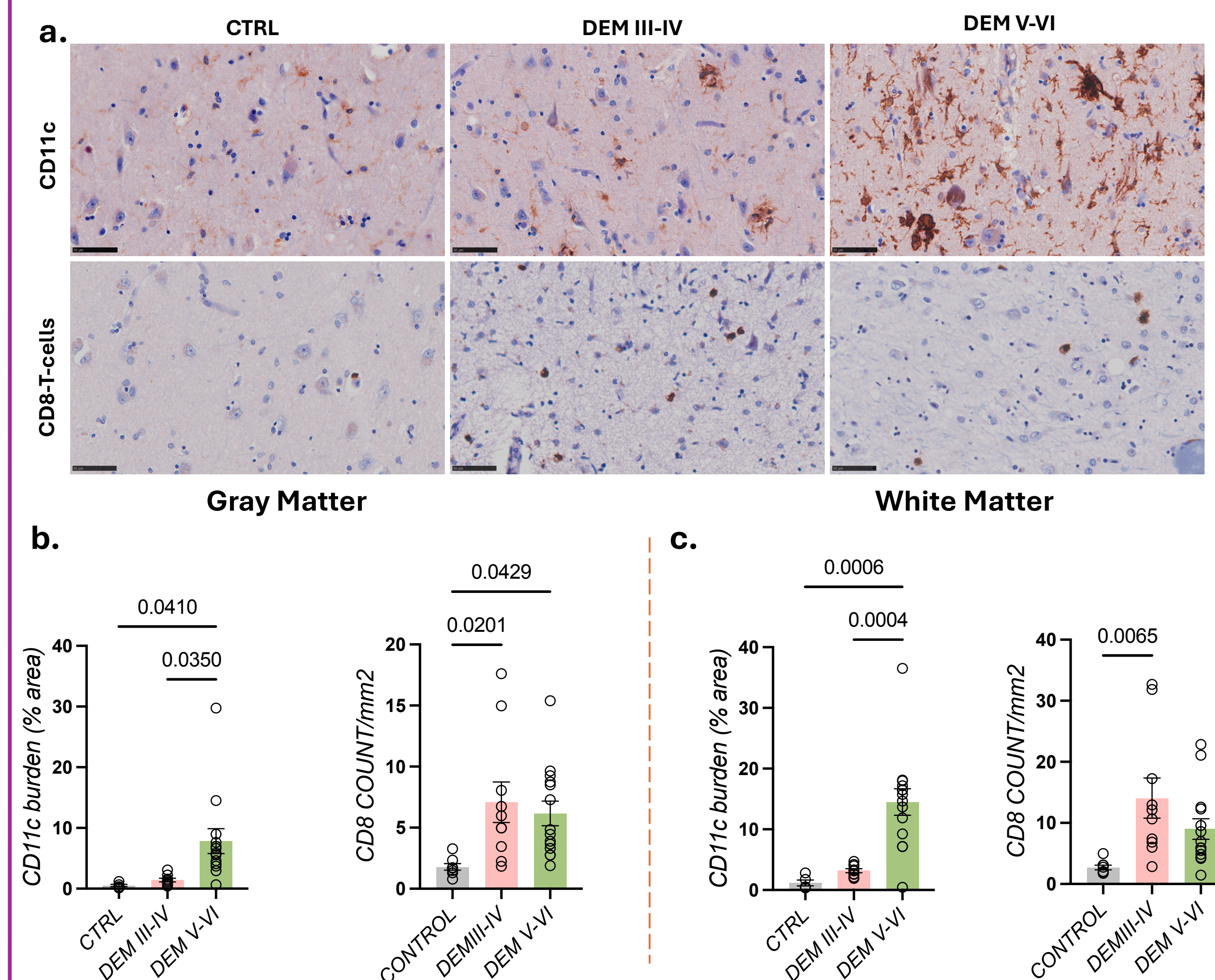


**Fig. 2:** Representative (a) images and datasets of CD11c and CD8 positive immunostaining in control and demented AD cases (Braak III-IV and V-VI). CD11c burden is significantly increased in the entorhinal cortex (EC) gray matter of demented AD cases (Braak V-VI) compared to controls. CD8 positive T-cell counts are elevated in both Braak stage III-IV and V-VI demented AD cases compared to controls, indicating early and persistent T-cell activation in the EC. Similar trends are observed in the entorhinal white matter. Scale bar = 50  $\mu$ m.

## Comparison of Amyloid Plaque and Tau Pathology in the Entorhinal Cortex (EC) of Resilient and Demented AD

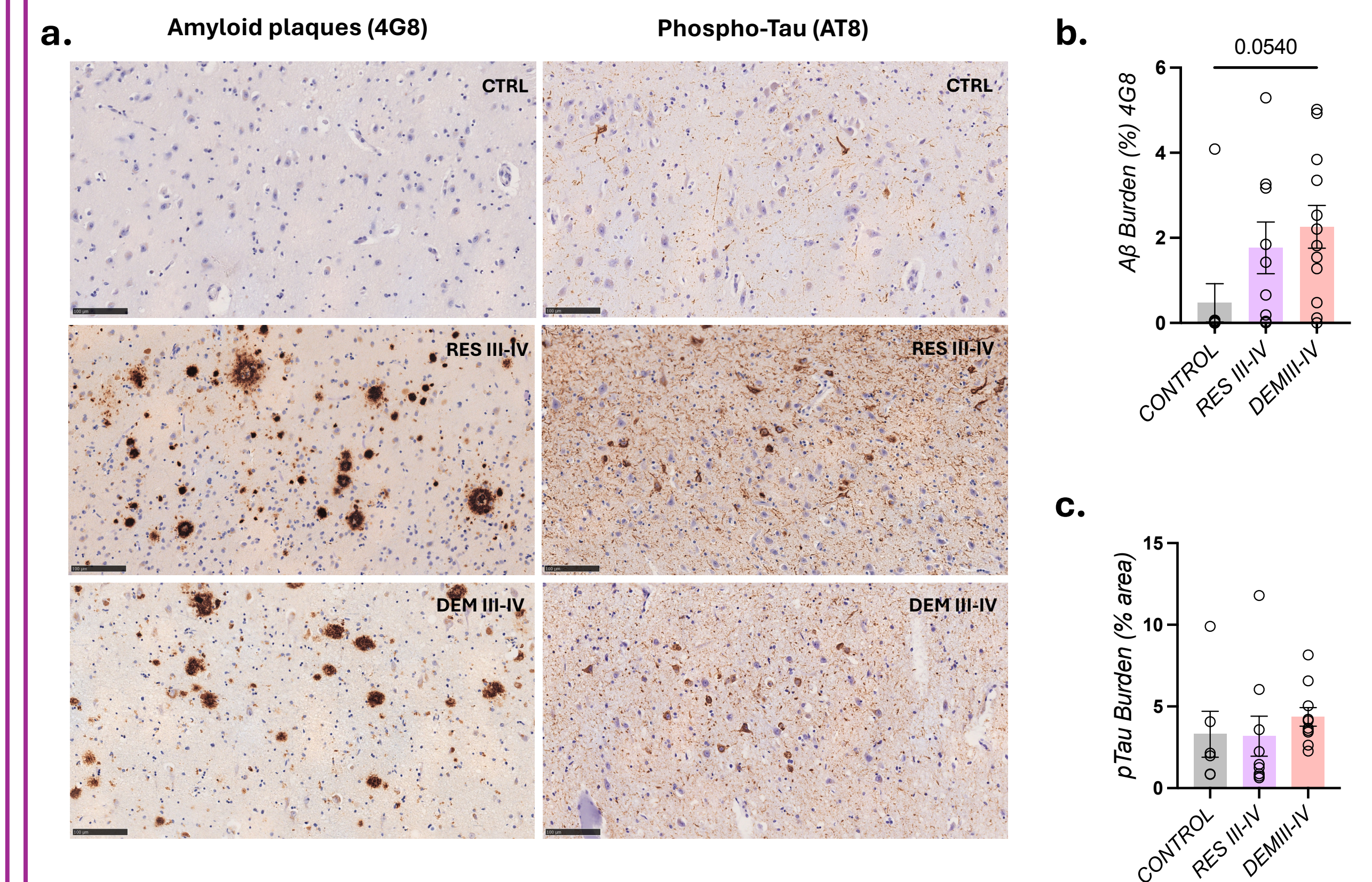


**Fig. 3:** Representative (a) images and datasets obtained from 4G8 and AT8 antibody staining reveal no significant differences in (b) amyloid plaque burden and (c) hyperphosphorylated tau levels in the entorhinal cortex (EC) between resilient and demented AD cases. Scale bar = 100  $\mu$ m.

### Reduced Inflammatory Markers in the Entorhinal Cortex (EC) of Resilient Cases Compared to Demented AD

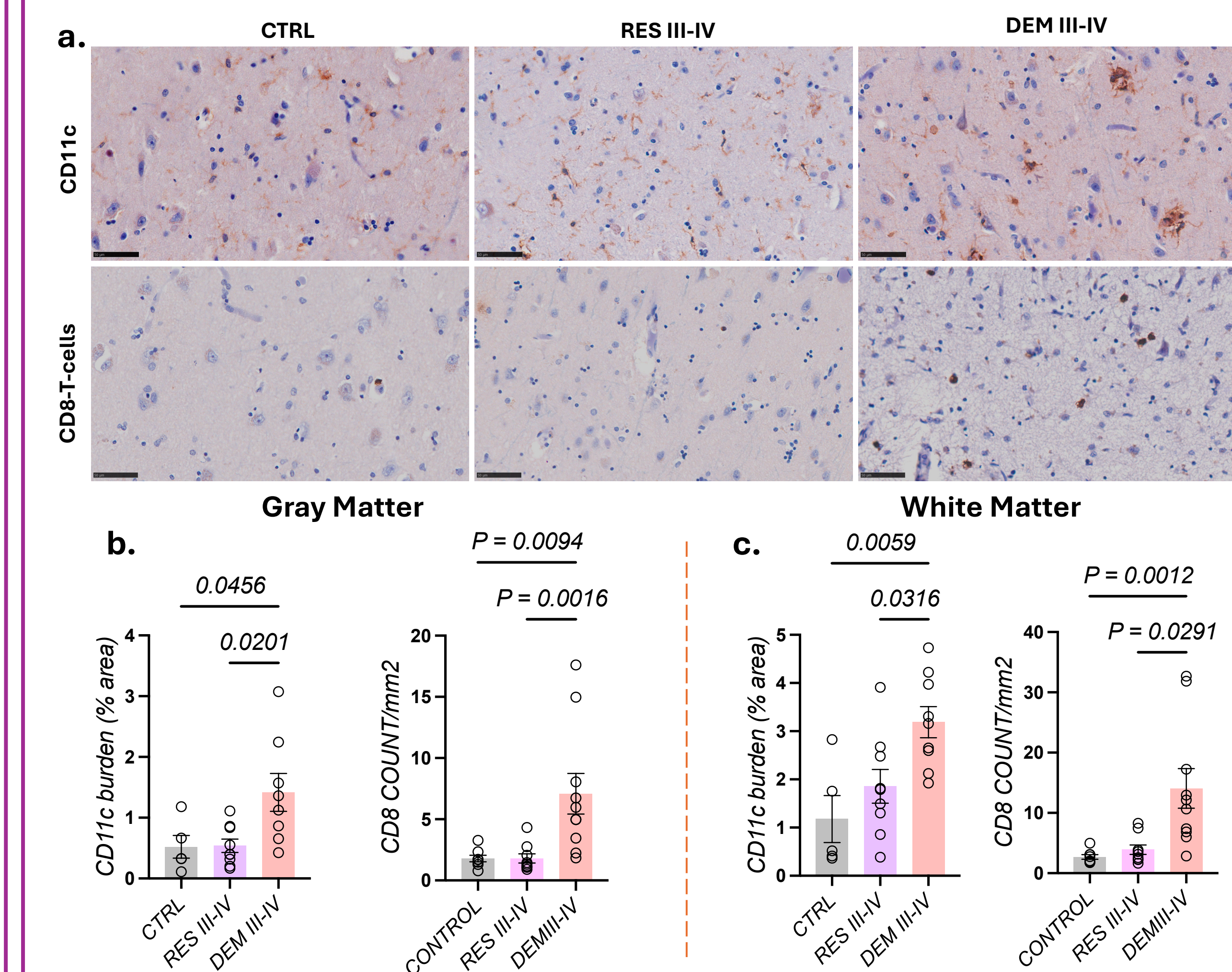


Fig. 4: Representative (a) images and datasets of CD11c and CD8 positive immunostaining in demented AD (Braak III-IV) and resilient (Braak III-IV) cases reveal significantly increased burdens of CD11c and CD8 positive T-cells in the entorhinal cortex (EC) of demented AD compared to controls. However, no significant increase is observed in resilient cases at the same Braak stages, indicating a potential protective mechanism that mitigates immune activation in resilience. Scale bar = 50  $\mu$ m.