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Spatially-resolved gene expression patterns in Alzheimer's disease brain

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The human brain exhibits remarkable intra-tissue heterogeneity, which contributes to the complex mechanisms underlying neurodegenerative diseases such as Alzheimer's disease (AD). Spatial approaches are therefore essential to capture progressive and localized cellular changes that cannot be fully resolved by single-cell methods. In this study, we revealed that disease-associated gene expression and functions vary depending on cellular composition, with oligodendrocytes playing a central role in disease-specific hotspots within AD brains. To test this, we employed Multiplexed Error-Robust Fluorescence In Situ Hybridization (MERFISH) to profile the spatial transcriptome in the prefrontal cortex and hippocampus of both neurotypical individuals and AD patients. Specifically, we used a deep learning–based approach to integrate MERFISH spatial transcriptomics with matched single-nucleus RNA-seq and single-nucleus ATAC-seq datasets, enabling integrated analysis of intra-tissue heterogeneity in AD. Based on disease-associated gene expression patterns, we defined disease-specific regions as spatial clusters within AD tissues that exhibited high disease-associated gene scores. These regions were enriched in oligodendrocytes, which displayed diverse functional states, including cellular stress and immune responses. Furthermore, our analysis showed enriched chromatin accessibility at stress-related loci in glial cells, with AD oligodendrocytes exhibiting stronger peaks than those from neurotypical controls, indicating disease-associated remodeling. Collectively, these findings highlight spatially resolved gene expression and gene regulatory networks underlying intra-tissue heterogeneity. Our results underscore the importance of spatial context and multi-omic integration for understanding the cellular mechanisms driving neurodegenerative disease progression.