Region-Specific Maintenance of the Blood Brain Barrier by Astrocytes: Implications for Involvement in Selective Vulnerability to Alzheimer's Disease

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Alzheimer's disease (AD) pathogenesis follows a pattern of selective vulnerability, defined by varying levels of neurodegeneration across brain regions and neuronal populations. While the mechanisms behind this pattern are not completely understood, neuronal support cells may play a critical role. Astrocytes are known to provide crucial support to the brain through maintenance of the blood–brain barrier (BBB), which if jeopardized, may lead to neuronal death and AD-related cognitive decline. This study utilized highly multiplexed immunofluorescence on human sourced neocortical tissues to detect inter-regional astrocyte associations with AD vulnerability by quantifying astrocytic-vasculature protein overlap as a measure of BBB integrity. A novel pipeline was implemented to compare astrocytic coverage of blood vessels across Clinical Dementia Rating, Braak, and Thal staging. Astrocytic coverage was additionally compared between the prefrontal and primary visual cortex (PFC and V1), susceptible and resilient regions of the brain, respectively. Results demonstrate stabilized astrocytic coverage of blood vessels across AD progression in the V1, suggesting astrocytic resilience to disease related changes. Additionally, significant increases in glial fibrillary acidic protein (GFAP)-specific astrocytic coverage of blood vessels across all measures of AD progression in layer IV of the V1 ($p = .026$; $p = .035$; $p = .043$) suggest the adoption of protective astrocytic phenotypes to maintain neuronal support and regional resilience to AD. Understanding the cellular contributions to differential AD susceptibility across regions and neuronal populations may provide key insights into biomarkers of resilience and vulnerability to AD, identifying possible targets for future AD treatments.

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