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Thesis abstract

Molecular, morphological, and functional profiling of human astrocytes in stress-related psychiatric disorders

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Severe stress is consistently one of the strongest risk factors for the development of psychiatric disorders, yet we still have a poor understanding of the cellular contributions to this risk in humans. Astrocytes are emergent players across brain functions, including regulation of the synaptic environment. However, the impact of stress on astrocytic functions, particularly in the context of human psychiatric disorders, is not yet well understood.

The primary goal of this thesis was to build a body of human-specific evidence on how astrocytes are shaped by stress at the cellular and molecular levels. This was conducted using a curated postmortem cohort consisting of psychiatric disorder cases stratified based on whether they had exposure to profound stress (deemed to have persisting ramifications) prior to diagnosis and at what life stage this primarily occurred. The work presented in Chapter 2 explores the transcriptome-wide changes underlying an association with a history of profound stress, using single-cell and spatial transcriptomics platforms to explore the transcriptional heterogeneity of cortical astrocytes. This approach highlighted that cortical astrocytes in the grey matter involved in synapse homeostasis particularly delineate the brains of people who lived with a psychiatric disorder and had a profound history of severe stress prior to diagnosis. This chapter also highlighted that these effects were largely driven by female cases. It also highlighted that the timing of stress exposure was important, as earlier exposures (i.e. during childhood) were associated with stronger transcriptional changes. The work described in Chapter 3 provides further cytoarchitectural support that grey matter astrocytes are disproportionately associated with profound early life stress. Astrocytes expressing the glutamate transporter excitatory amino acid transporter 2 were more dense and larger in size in cases that had a history of profound stress during childhood. These modifications were replicated at the bulk level via western blot and inversely correlated with synaptic structure density across the cohort, suggesting that these modifications are associated with changes to the synaptic environment. Finally, the work in Chapter 4 utilised human pluripotent stem cell-derived astrocytes (iAsts) to demonstrate that human astrocytes can be directly impacted by exposure to glucocorticoids. iAsts were highly responsive to the glucocorticoid receptor agonist dexamethasone and demonstrated changes to both neurotransmitter clearance and increases in calcium signalling in response to the neurotransmitters glutamate, N-methyl-D-aspartate (NMDA), and γ-aminobutyric

acid (GABA). This provides evidence that core functions of human astrocytes to regulate the synapse can be directly impacted by circulating stress hormones.

This body of work successfully identifies several human-relevant phenotypes in astrocytes related to stress. We identify that human astrocytes can be directly shaped by stress and that prior exposures to stress are also associated with both transcriptional and cytoarchitectural alterations to astrocytes in the human cortex. The evidence from this work indicates that functions of astrocytes in regulating synapses in the grey matter appear to be particularly associated with these stress histories. By focusing on astrocytes, we also highlight that the human brain is persistently impacted by profound stress, particularly during childhood, which has notable implications for treatment and diagnostic specificity.

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