University of Rochester School of Medicine and Dentistry
The Neuroscience Graduate Program

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In a Thesis Proposal

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Microglial and Dopaminergic Mechanisms of Psychosocial Stress in the Anterior Insular Cortex

Early-life stress is a significant risk factor for neuropsychiatric disorders. Microglia, the brain's resident immune cells, regulate neuroimmune signaling and are increasingly implicated in stress-related neuropathology. Prior work has proposed an intriguing model of microglial priming, in which an initial stressor induces lasting changes that render microglia hypersensitive to subsequent inflammatory insults. However, it is not yet known whether early-life psychosocial stressors also produce a primed microglial state that alters later psychological stress responses, nor are the neurobiological consequences of such priming well defined. The overall objective of this project is to investigate microglial mechanisms that may link early-life psychosocial stress to enduring stress vulnerability in brain circuits. Our lab previously demonstrated that microglia dynamically interact with dopaminergic axons in the medial frontal cortex, contributing to dopamine-dependent adolescent plasticity and cognitive functions. The anterior insular cortex (aIC), which also receives dense dopaminergic innervation and plays a key role in interoceptive and social-affective processing, represents a compelling region to examine stress-related priming mechanisms. Our preliminary data support this direction: juvenile social isolation in mice reduces dopamine release in the aIC, while transcriptomic analysis of adult-isolated mice reveals downregulation of microglial homeostatic genes. Building on these findings, we hypothesize that juvenile social isolation primes microglia and disrupts microglia–dopamine interactions in the aIC. Aim 1 will employ a two-hit psychological stress paradigm—juvenile social isolation (JSI) followed by adult restraint stress—to determine whether JSI establishes a primed microglial state in the aIC. Noninvasive in vivo two-photon imaging of microglial morphology and dynamics, paired with pharmacological manipulations and molecular and histological profiling, will identify mechanisms driving microglia priming. Aim 2 will probe how JSI alters microglia–dopamine interactions by integrating simultaneous in vivo imaging of microglia and dopamine axons with targeted pharmacological manipulations to assess circuit-level consequences and microglial contributions. Together, these studies will provide critical insight into how early-life psychosocial stress shapes neuroimmune and dopaminergic function in the aIC, advancing our understanding of the cellular mechanisms that confer vulnerability to stress-related neuropsychiatric disorders.

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