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Decoding the Neural Mechanisms of Depression: Insights Through Ketamine's Pharmacological Lens

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Depression, a highly polygenic and heterogeneous disorder, has long eluded mechanistic understanding due to the limitations of traditional forward genetic approaches. Here, we propose a complementary strategy: leveraging the rapid, targeted action of ketamine—a potent NMDA receptor (NMDAR) antagonist with robust antidepressant effects—to reverse-engineer the primary neural mechanisms underlying depression.

Over the past decade, we have elucidated the mechanisms behind ketamine's rapid, sustained, and brain-region-specific action. By uncovering how ketamine works, we identified increased neuronal burst firing in the lateral habenula (LHb), the brain's "anti-reward" hub, as a core driver of depression etiology. Expanding this framework, our recent work extends beyond NMDARs, identifying two additional ion channels as critical mediators of LHb bursts and antidepressant efficacy. Through the characterization of one of these channels, the glia-specific potassium channel Kir4.1, we discovered a novel form of neuron-glia interaction, where astrocytic processes tightly envelop neuronal soma to regulate burst firing. I will present our ongoing work exploring how neurons and astrocytes dynamically interact in the LHb to modulate stress responses and depressive-like behaviors.