

Hannah Elkholy

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LSU Health Sciences Center, New Orleans, LA

Mentor: Dr. Michael Salling, PhD

LSUHSC New Orleans Department of Cell Biology and Anatomy

“Characterizing Latrophilin 3 in the Prefrontal Cortex in the context of ADHD”

Attention Deficit Hyperactivity Disorder (ADHD) is associated with delayed cortical maturation, prolonging the window of vulnerability for developing neuronal structures, particularly within the prefrontal cortex (PFC). Although ADHD is polygenic, there may be some implication of loss-of-function mutations in Latrophilin 3 (Lphn3), an adhesion G-protein-coupled receptor (aGPCR) that plays a role in the regulation of synaptic function, with ADHD. While Lphn3 has been identified on the postsynaptic spines of hippocampal glutamatergic neurons, its distribution and role within the PFC remain uncharacterized and a topic of interest in current literature. We hypothesize that in the prefrontal cortex, Lphn3 is located on postsynaptic dendritic spines extending from the prefrontal cortex to the mediodorsal thalamus (MdT), a circuit implicated in impulsivity and attention.

To investigate this hypothesis, we performed stereotaxic injections of a retrograde viral tracer (rgAAV-CAG-EGFP) into the MdT of male and female mice engineered to express HA tag-associated Lphn3, allowing for the selective visualization of neuronal projections of interest. Subsequent immunohistochemical analyses using antibodies against the HA tag and the presynaptic marker Bassoon determined the pre- or postsynaptic location of Lphn3.

These findings will inform future investigations into the intersection of Alcohol Use Disorder (AUD) and ADHD and their combined impact on behavior and neuronal morphology. By confirming the presence and synaptic localization of Lphn3 along the tract of interest, future studies can directly evaluate alterations in dendritic spine density and dimensions within prefrontal cortex projections. Furthermore, future investigations using conditional knockout of Lphn3 within the prefrontal cortex during early development may provide an optimized experimental model for elucidating the contribution of ADHD-associated mechanisms to PFC circuitry.