



## **ABSTRACT OF THE DISSERTATION**

### **Astrocyte Domain Disruption and Glutamate Dysregulation as Mechanisms of Demyelination-Induced Hippocampal Hyperexcitability and Cognitive Impairment**

**Friday, August 28, 10am - 1<sup>st</sup> Floor MRB Seminar Room & via Zoom**

Zoom Link: <https://ucr.zoom.us/j/98858251970>

**By**

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Multiple sclerosis (MS) is an autoimmune, demyelinating, and neurodegenerative disease associated with cognitive impairment and increased seizure susceptibility. Yet the mechanisms linking chronic demyelination to hippocampal dysfunction remain poorly understood. Here, I used the cuprizone (CPZ) model of chronic demyelination to investigate hippocampal pathology, astrocyte dysfunction, glutamate dysregulation, seizure activity, and cognitive impairment. In addition, I evaluated the restorative effects of remyelination generated either spontaneously or mediated by estrogen receptor- $\beta$  (ER $\beta$ ) ligand treatment. In these studies, I found that progressive demyelination leads to increased seizure incidence, impaired short-term recognition memory, persistent elevation of glutamate, reactive astrogliosis, reduced glutamate transporter expression, and CA1 neuronal degeneration. Chronic demyelination also disrupted astrocyte territory organization and genes associated with cell adhesion and neuroglial connectivity. Furthermore, remyelination partially restored the cellular and molecular abnormalities, but was limited in improving cognitive deficits. Together, these findings demonstrate chronic demyelination of the hippocampus produces systematic dysfunction involving neurons, glial, and glutamate homeostasis which contributes to epileptogenesis and cognitive impairment. However, the results indicate remyelination and ER $\beta$  ligand treatment can mitigate many consequences of demyelination and promote hippocampal recovery.