Adolescent Binge Ethanol Exposure Accelerates Alzheimer’s Disease Neuropathology in the Basal Forebrain
Rachael Fisher

Cholinergic degeneration and neuroimmune system activation are hallmark features of many disease states, including alcohol use disorder (AUD) and Alzheimer’s disease (AD). Heavy alcohol use is an etiological factor associated with AD, but little is known about the interaction between adolescent binge alcohol exposure and AD pathology. Preclinical studies using the adolescent intermittent ethanol (AIE) paradigm that mimics weekend binge drinking behavior find basal forebrain cholinergic neuron degeneration and increased neuroimmune activation in brain, similar to observed pathology in AD. Using the 5xFamilial Alzheimer’s disease (5xFAD, Figure 1C) mouse model of AD, we tested the hypothesis that AIE treatment would accelerate onset of AD-associated pathology. We report AIE accelerated the loss of basal forebrain cholinergic neurons and hnRNP expression relative to age-matched 5xFAD CONs in female, but not male subjects. This was accompanied by accelerated accumulation of amyloid beta as well as upregulation of AD-related genes. In addition, AIE upregulated glial genes (e.g., Gfap and Iba1), increased microglial Iba-1+IR, and induced proinflammatory innate immune signaling genes in the basal forebrain, relative to 5xFAD CONs. In post-mortem human basal forebrain samples of individuals with AUD and an adolescent age of drinking onset, we found AUD increased amyloid beta expression in the basal forebrain and in ChAT+ neurons of AUD individuals, and decreased hnRNP expression that was negatively correlated with loss of cholinergic cell markers. These data reveal that adolescent binge ethanol exposure accelerates AD-associated neuropathology in the female adult basal forebrain and suggests that adolescent binge drinking may be an etiological factor contributing to AD neuropathology.