Craving and Neuroimmune Conditioned Response to Alcohol Cues and Consumption Associated with Future Drinking in Binge Drinkers

Sara K. Blaine, PhD[1], Clayton Ridner[1], Benjamin Campbell[1], Eric D. Claus, PhD[2], Emily B. Ansell, PhD[2], Jennifer L Robinson, PhD[1], Darren Beck, PhD[3]*

[1]Department of Psychological Sciences, Auburn University; Auburn, AL
[2]Department of Biobehavioral Health, Penn State University; State College, PA
[3]Edward Via College of Osteopathic Medicine, Auburn University; Auburn, AL

Preclinical and clinical studies suggest learned neuroimmune system responses to alcohol cues and consumption may contribute to alcohol's pharmacodynamic properties and/or Alcohol Use Disorder pathogenesis. These neuroimmune alterations may increase motivation to consume alcohol (craving) acutely and over time. We explored this possibility in a randomized, counter-balanced, crossover experiment.

Methods: Thirty-three binge drinkers (BD) and 31 non-binge, social drinkers (SD), matched for demographic and psychological variables, were exposed to alcohol cues and water cues in two separate 7T functional magnetic resonance imaging (fMRI) scans. Each scan was followed by the Alcohol Taste Test (ATT) of implicit motivation for alcohol and a post-experiment one-month prospective measurement of their "real world" drinking behavior. During each scan session, in addition to craving measures, blood plasma was collected repeatedly to examine the separate effects of alcohol cues and alcohol consumption on interleukin 6 (IL-6) levels. IL-6 and Analyses were performed on the difference scores between the change in IL-6, craving, neural cue reactivity, and IL-6 in response to alcohol cues minus the change in response to water cues.

Results: Initial craving for alcohol and baseline IL-6 levels were not difference between groups or across conditions. BD demonstrated significantly higher craving than SD in response to alcohol cues, while group differences in IL-6 cue responses were seen only at trend levels. All participants, BD and SD, showed greater Ventromedial Prefrontal Cortex (VmPFC) cue reactivity to alcohol than water, $p<0.001$whole brain corrected, $p<0.05$ cluster corrected. BD only consumed significantly more alcohol than SD during the ATT after exposure to alcohol cues, although breath alcohol levels did not exceed 0.03 g/210L. In BD, this greater ATT consumption was positively associated with alcohol cue induced craving, and IL-6 release post alcohol consumption. Greater VmPFC activation in the alcohol-water contrast in BD was also positively related IL-6 release post alcohol consumption and cue induced craving. Craving in response to alcohol consumption was related to the number of drinks consumed in the next month for BD only, as was IL-6 release ($R^2= 0.22$). Importantly, the VmPFC alcohol cue reactivity also was associated with the number of drinks consumed in the next month by BD, ($R^2= 0.17$). Tests of mediation were not significant.

Conclusions: Greater cue induced craving in BD was associated with greater VmPFC cue reactivity and greater IL-6 release post-acute consumption. Greater craving, neural cue reactivity, and IL-6 release were each associated with future alcohol consumption in the next 30 days. Although correlated, these effects on immediate and future drinking may be independent of one another. Further study with larger sample sizes is required to determine if these cue and acute consumption induced changes in neuroimmune function are be related to motivation (craving) to consume alcohol in the moment and in the "real world." *Funded by NIH grant R00-AA025401.*