Review of: "Predator odor (TMT) exposure potentiates interoceptive sensitivity to alcohol and increases GABAergic gene expression in the anterior insular cortex and nucleus accumbens in male rats"

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The authors model how an acute traumatic stressor (TMT, a synthetic predator odor) influences alcohol use in male Long Evans rats. Similar to what is reported in human subjects, exposure to a stressor increased sensitization to alcohol effects in male rats as shown by a leftward shift in ED_{50} of the dose-response curve compared to unstressed rats. Associated changes in neurobiology in the anterior insular cortex and nucleus accumbens are investigated as potential mechanisms. Findings show TMT-induced changes in neuronal activation and GABAergic signaling that may be modulating interoceptive sensitization effects to alcohol.

Overall, the paper is well-written and uses appropriate methods to model the effect of a stressor on alcohol use. It adds to the literature that investigates early experience as a predictor of lifetime behavioral trajectories, such as risk factors for substance use behavior. Animal models that recapitulate comorbid disorders are welcomed as they are needed for improved translation of findings. *The major limitation of the study is that it does not include female subjects.*This is considerably problematic as several studies have shown sex differences in both humans and animals in trauma response and alcohol use.

The paper has many strengths:

1. Modeling the interaction between exposure to stress and alcohol use behavior is significant as the comorbidity of post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) in humans is high.
2. Understanding the neurobiology associated with a traumatic stressor is useful knowledge for developing pharmacological targets for therapies treating PTSD.
3. The design allows for a comparison of the interaction of stress with alcohol-naïve and alcohol-experienced individuals. Thus, it is possible to descriptively compare changes in behavior due to alcohol.

Places for improvement:

1. Although the authors speak about modeling PTSD-AUD comorbidity, there is no assessment of PTSD-like behaviors following TMT (e.g., conditioned fear of re-exposure to TMT environment). Thus, it may be better to speak of the model in terms for modeling the effect of an acute stressor on alcohol use.

2. The authors acknowledge that despite uniform exposure, individuals do not all respond to trauma in the same way. Indeed, only a subset of individuals that are exposed to trauma develop PTSD. Thus, additional categorization of TMT-exposed rats for those that demonstrate PTSD-like vs. resilient behaviors would have allowed for more informative PTSD and AUD associations.
3. The lack of an alcohol-experienced group in the neurobiology experiments is a limitation which is discussed by the authors. This limitation is another reason why the model may be more appropriately discussed as an acute trauma and alcohol model (see #1 in places for improvement).
4. There are several other brain regions that are implicated in emotional processing and trauma memory that could have been examined and hypothesized to regulate alcohol sensitivity (e.g. amygdala) that would add to depth of findings. The circuitry and regions chosen in the current study are only briefly discussed and could use further background and rationale.