Amygdala-cortical circuit determinants of social isolation-induced alcohol consumption

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Background: An individual's standing in a social hierarchy is inversely related to alcohol consumption in rodents[1-4] and non-human primates[5-7] as well as problematic drinking in humans[8-10], highlighting the conserved impact of subordination on motivation for alcohol. Social rank also influences how individuals respond to challenges[11-13] such as social isolation, a particularly profound stressor with increasing human relevance. However, the neural circuit mechanisms by which social stress experiences engender aberrant alcohol drinking remain largely unknown.

Methods: In this study, we combined behavior, ex vivo whole-cell patch-clamp electrophysiology, *in vivo* cellular resolution calcium imaging, and machine learning to identify circuits underlying social rank and isolation effects on alcohol drinking. **Results:** We found that social rank of adult, male mice correlates with alcohol intake, and social isolation increases alcohol intake. Notably, we identified a previously unknown relationship between prior social rank and social isolation-induced escalated alcohol drinking, where subordinates display a greater magnitude increase in drinking compared to dominants. These data suggest behavioral factors, emerging from dominance hierarchies, can predict vulnerability to social isolation-induced escalated alcohol drinking. Using *ex vivo* whole-cell patch-clamp electrophysiology, we found that social isolation increases basolateral amygdala (BLA) excitability, highlighting the vulnerability of the BLA to social isolation. Unilateral photoactivation of ChR2-expressing BLA terminals in the mPFC increased alcohol, but not sucrose or water, drinking, suggesting that social isolation may escalate alcohol drinking through BLA projections to the mPFC. Indeed, using cellular resolution calcium imaging, we found that the BLA encodes alcohol, and the percentage of alcohol-encoding neurons is increased following social isolation. Using a SVM classifier, we found that population-level BLA activity preceding a drinking bout decodes whether alcohol or water was consumed, further supporting a role of the BLA in encoding alcohol.

Conclusion: Together, these findings suggest that low social rank may be a potent risk factor for increased alcohol drinking following a social isolation challenge, which may be mediated by amygdala-cortical circuits.

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