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Female rodents yield new insights into compulsive alcohol use and the impact of dependence:

Commentary on Xie et al. 2019, "Sex Differences in Ethanol Reward Seeking Under Conflict in Mice"

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The pursuit of alcohol in the face of adverse consequences is a central component of alcohol use disorder. Given this, it should not be surprising that criminalization-based approaches to addiction treatment are ineffective. Improving the clinical prognosis for people suffering from alcohol abuse disorder requires a fuller and more nuanced picture of the brain mechanisms that drive individuals to compulsive use, and to drink despite adverse health and social consequences. In rodents, we can model compulsive use or seeking of alcohol by studying aversion-resistant alcohol seeking and intake (Hopf and Lesscher, 2014). In these models, alcohol is either adulterated with increasing concentrations of a bitter tastant, quinine, or alcohol seeking is paired with footshock, or the threat of footshock. If rodents continue to seek alcohol despite the presence or threat of these aversive stimuli, we consider their alcohol use to be compulsive. Both long-term voluntary consumption of alcohol (Darevsky et al., 2019; Hopf et al., 2010; Seif et al., 2013), and chronic intermittent exposure to alcohol vapor (Radke et al., 2017; Vendruscolo et al., 2012) have been shown to promote aversion-resistant alcohol use in rodents.

While there is a growing literature characterizing the neural and behavioral mechanisms of compulsive alcohol use, the vast majority of these rodent studies have used only male subjects. This bias parallels the historical gender bias in research on alcohol use disorder in humans (Greenfield, 2002), as well as in biomedical research more generally. In rodents, this discrepancy can be traced, in part, to the inaccurate view that data from female rodents is more variable, due to the effect of circulating hormones across the cycle (Shansky, 2019). Yet, the available evidence indicates the data from female rodents is not more variable (Becker et al., 2016). The gender gap in human research has also been attributed to the difficulty in recruiting female subjects, given the higher prevalence of substance abuse in men versus women, but this historical gap has been rapidly closing (Becker and Koob, 2016). In addition to the alarming recent increase in the prevalence of substance abuse in women, some evidence suggests that women who develop addiction progress more rapidly from casual to compulsive use, and experience more severe negative health and social consequences (Hernandez-Avila et al., 2004). Given these trends, the lack of data on

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mechanisms of alcohol use and addiction in women, girls, and female animal subjects is particularly problematic. While research and treatment focused on women with addiction has been expanding, significant gaps remain. Additionally, many new studies and addiction treatment programs focus on understanding and combatting the peri- and postnatal effects of substance use, but fail to “treat women as persons who need treatment” (Meyer et al., 2019). Historical and existing biases in the human and animal research literature result in a frustratingly incomplete understanding of the neural and behavioral mechanisms that drive compulsive use.

The lack of research on compulsive alcohol use in female animals has likely obscured crucial neural and behavioral mechanisms driving alcohol abuse, limiting progression in the treatment of not only women and girls, but men and boys suffering from addiction as well. In a recent issue of *Alcoholism: Clinical and Experimental Research*, Xie and colleagues (2019) reveal important differences in compulsive alcohol seeking, and the impact of dependence, in male versus female mice. Thus far, questions of sex differences in aversion-resistant intake have focused on the pursuit and consumption of quinine-adulterated alcohol. Randall et al. (2017) examined motivation to pursue quinine-adulterated alcohol in female versus male rats in a progressive ratio test. They found no sex difference in the number of lever presses rats were willing to complete for quinine-adulterated quinine, though female rats consumed more alcohol for their body weight at every concentration of quinine tested (0.277mM – 2.5mM). Sneddon et al. (2018) found no difference in quinine-sensitive drinking (0.1 and 0.25 mM) in female versus male mice with binge-like alcohol consumption experience. But, like the previous study in rats, females consumed more alcohol than males, whether or not it was adulterated with quinine. In contrast, Fulenwinder et al. (2019) found that female mice are more resistant to quinine adulteration after continuous access to alcohol. Female mice only decreased their alcohol consumption at the highest concentration of quinine (0.3 mM), whereas male mice were sensitive to much lower concentrations (0.03 and 0.1 mM). Altogether these results suggest that female rodents may be more vulnerable to compulsive alcohol consumption, at least in some models of alcohol use and tests of compulsivity. Importantly, these previous studies examine consumption or seeking in the presence of the aversive consequence. That is, the negative outcome of quinine is present every time the animals consume the alcohol. In alcohol use disorder, the adverse consequences that result from alcohol use are frequently more remote. Rather than present at the time of alcohol use, these outcomes are predicted or threatened.

In their recent work, Xie et al. (2019) investigated compulsive alcohol seeking in female versus male mice using a model in which alcohol and the aversive outcome (electric footshock) are never experienced together, but the pursuit of alcohol still carries some conflict or risk. The procedure consists of a modified conditioned place preference paradigm (Barker et al., 2014, 2013). First, one chamber is associated with alcohol reward through multiple pairings, after which preference for the alcohol-paired chamber is assessed. Next, the mice were confined to the alcohol-paired chamber, where they received a single electric footshock. They were then retested for preference for the alcohol-paired chamber. Xie et al. used this second test to assess sex differences in alcohol-seeking at baseline versus under conflict (before and after footshock pairing). Xie et al. also examined the impact of an alcohol dependence induction, in the form of alcohol vapor exposure. Prior to conditioning,

some mice underwent four cycles of chronic intermittent exposure to alcohol vapor. This model of alcohol dependence has been shown to promote compulsive-like drinking in male rodents, including insensitivity to quinine adulteration of alcohol in male rats (Vendruscolo et al., 2012) and attenuated suppression of alcohol-seeking by footshock punishment in male mice (Radke et al., 2017).

Interestingly, Xie et al. report that the alcohol-seeking behavior of control females (i.e. those that were not exposed to alcohol vapor) was surprisingly insensitive to footshock. This suggests that their alcohol seeking is compulsive. Despite having a somewhat limited history of alcohol exposure, control females entered the alcohol-paired chamber just as quickly after they had experienced footshock in that chamber as they had before the footshock experience. In contrast, male control mice took longer to enter the alcohol-paired chamber and spent less time in this chamber after it had been associated with footshock. This sensitivity to footshock is consistent with previous reports of aversion-sensitive alcohol-seeking behavior in male rodents with limited alcohol exposure (Radke et al., 2017). These results are consistent with the possibility that female animals are more vulnerable than their male counterparts to compulsive alcohol use in models that involve limited prior alcohol exposure.

The impact of alcohol vapor exposure in this study reveals potentially important differences in 1) the impact of chronic alcohol exposure on alcohol seeking in male versus female rodents, and 2) the contributions of alcohol vapor exposure to compulsive alcohol seeking more generally. Surprisingly, alcohol vapor exposure had no significant impact on the compulsivity of alcohol-seeking in male mice. Given that the alcohol-seeking behavior of female control mice was relatively insensitive to the footshock pairing, it would be fair to expect that females exposed to chronic alcohol vapor would be just as, if not more, compulsive. Yet, the alcohol-seeking behavior of vapor-exposed female mice was *less* compulsive than in control females. In these subjects, footshock pairing reduced the time they spent in the alcohol-paired chamber and increased their latency to enter the chamber. These sex differences were observed despite no difference in overall sensitivity to footshock, as measured by paw retraction, and no differences in the extinction of preference for the alcohol-paired chamber in the absence of footshock. These unanticipated, sex-specific effects of vapor-exposure on compulsive alcohol seeking highlight the importance of characterizing the behavioral impact of these manipulations in both females and males.

While chronic intermittent exposure to alcohol vapor is a commonly used approach to the induction of alcohol dependence, very little research has been done on impact of this manipulation on the brains or behavior of female rodents, especially in relation to alcohol seeking and consumption behaviors. Emerging research suggests that females may react differently to vapor exposure in a variety of ways. In terms of alcohol consumption behavior, chronic alcohol vapor exposure may increase intake in adult male but not female Long Evans rats (Morales et al., 2015), though alcohol vapor exposure may be generally less effective in altering alcohol intake in Long Evans rats than in Wistar rats (Priddy et al., 2017). Whether there are important sex differences in the impact of alcohol vapor exposure on alcohol seeking in other models, or in mice, remains unclear. As more addiction research studies incorporate female subjects, we are bound to discover additional discrepancies in the

relationship between distinct aspects of addiction, drug and alcohol abuse, and dependence. The patterns of use and exposure that promote addiction-like behavior in male subjects may not be those that most strongly promote addiction in female subjects. This and other relevant studies should push us to examine whether the specific models we are using best capture addiction-relevant phenotypes in both males and females. Instead of seeing sex differences as an irritating complication, we should embrace them as an opportunity to improve upon our behavioral models of addiction and alcohol abuse, and to seek insight into the complex neural mechanisms that drive compulsive drug and alcohol use.

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