Full length article

**Frustration stress (unexpected loss of alternative reinforcement) increases opioid self-administration in a model of recovery**

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**Keywords:** Opioid addiction remains a persistent public health problem. For those in recovery who successfully reduce or eliminate opioid use, relapse remains a threat, though the likelihood of relapse declines as time in recovery increases (e.g., Gossop et al., 1990). Thus, preventing relapse is particularly crucial early in recovery before alternatives to drug use become habitual and less susceptible to disruption by precipitants of relapse (Ginsburg and Lamb, 2013a,b,c; Lamb et al., 2016; Lamb and Ginsburg, 2017). Psychosocial stress is thought to be an important precipitant of relapse (Dawes et al., 2000; Kosten et al., 1986; McLellan et al., 1983). It is believed that stress produces a dysphoric response which might prompt drug use and increase it to abnormally high levels (Koob, 2009). Although momentary stress exposure can produce reports of drug craving and increase attention to drug-associated cues, clinical evidence that stress exposure increases drug use is weak (Brown et al., 2015; Preston and Epstein, 2011). Yet such relationships are difficult to determine due to the complex nature of clinical studies, especially in naturalistic settings; thus, researchers have attempted to address this issue using preclinical techniques. Preclinical research on the role stress plays in relapse has largely involved studies using the reinstatement procedure in which drug-maintained responding is extinguished and then reinstated in extinction by exposing subjects to stressors including inescapable foot-shock or cold exposure (Crombag et al., 2008; Epstein et al., 2006; Mantsch et al., 2016). There is also some evidence that social isolation might precipitate reinstatement, though this has received relatively limited examination (Chauvet et al., 2009; Mantsch et al., 2016).

A limitation of the reinstatement procedure is the necessity of extinction and the lack of measures of drug-taking or alternative behavior after exposure to stressors (Katz and Higgins, 2003). Extinction is difficult to impose clinically, and its relevance to clinical situations has been challenged (Bouton et al., 2017). Instead, humans in recovery often reduce drug-seeking and consumption even in the presence of...
continuing drug availability – e.g., the dealer still lives down the block and has the same supply for sale at the same price as before recovery. Further, reinstatement is assessed under extinction, thus any effect on drug-taking is not possible to determine. As noted above, there is clinical evidence that stress exposure can increase self-reported craving, but the link between self-reported craving and resumption of drug use is, at best, weak (Furnari et al., 2015; Preston and Epstein, 2011; Wray et al., 2013). Therefore, it remains unclear whether reinstated drug use would rise to lower, greater, or similar levels as those observed before extinction. Finally, alternative behavior is neither reinforced nor measured in the reinstatement procedure, which prevents assessments of changes in other behavior upon exposure to relapse precipitants (Ginsburg and Lamb, 2013a).

While a case can be made for the clinical relevance of reinstated responding precipitated by exposure to drug-related stimuli, the relevance of the stressors typically used in this procedure is less apparent (Crombag et al., 2008; Epstein et al., 2006). Clinical studies linking stress exposure to relapse tend to identify psychosocial stress as the most important type of stress (Dawes et al., 2000; Kosten et al., 1986; McLellan et al., 1983; Pilowsky et al., 2013). Thus, the validity of exposure to inescapable foot-shock or cold, and the role such exposure might play in relapse in humans is not clear. Instead, relapse is more likely to follow from more common, daily life stressors, e.g., job loss, familial disruption, or financial difficulty (Gallo et al., 2001; Temple et al., 1991). These types of events have alternatively been classified as frustrations, where historical contingencies no longer produce expected reinforcement. Substance use and likelihood of relapse has been linked to diminished tolerance to this type of frustration stress in adolescents and adults (Baars et al., 2013; Miller, 1991).

Few preclinical studies have addressed the role frustration stress might play in relapse. In a study in mice, restricting access to an exercise wheel increased voluntary ethanol consumption in female mice with genetic manipulations that reduce β-endorphin levels (McGonigle et al., 2016). In rat studies, others have observed the resurgence of extinguished responding for ethanol or cocaine upon unsignaled extinction of food (Podlesnik et al., 2006; Pyszczynski and Shahan, 2013; Epstein et al., 2006). Clinical studies linking frustration stress exposure to relapse tend to identify psychosocial stress as the most important type of stress (Dawes et al., 2000; Kosten et al., 1986; McLellan et al., 1983; Pilowsky et al., 2013). Thus, the validity of exposure to inescapable foot-shock or cold, and the role such exposure might play in relapse in humans is not clear. Instead, relapse is more likely to follow from more common, daily life stressors, e.g., job loss, familial disruption, or financial difficulty (Gallo et al., 2001; Temple et al., 1991). These types of events have alternatively been classified as frustrations, where historical contingencies no longer produce expected reinforcement. Substance use and likelihood of relapse has been linked to diminished tolerance to this type of frustration stress in adolescents and adults (Baars et al., 2013; Miller, 1991).

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