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Modeling the Impact of Social Contact on Substance Use

Substance-use disorders remain resistant to most forms of clinical treatment. Although preclinical studies have identified many interventions that reliably decrease drug-seeking behavior in laboratory animals, only occasionally have they predicted successful outcomes in clinical trials. One common criticism of preclinical models is that most do not capture the complex social environment in which substance use occurs. The predictive validity of these models might be improved by incorporating relevant features of the social environment known to influence substance use.

Several investigators have recently introduced new models, or refined existing models, to capture aspects of

the social environment that may influence drug-seeking behavior. Using the conditioned place preference procedure, a procedure in which a Pavlovian association is formed between a stimulus (eg, interoceptive drug cue, social partner) and a distinct environmental context, investigators have shown that drugs (eg, cocaine, nicotine) and social contact mutually enhance one another's rewarding effects when paired together (Thiel *et al*, 2009). Alternatively, social contact prevents and reverses a conditioned place preference for cocaine if the two are conditioned in separate contexts, and social contact reverses cocaine-induced increases in the transcription factor, *Zif268*, in the nucleus accumbens, amygdala, and ventral tegmental area (Fritz *et al*, 2011).

Advances in traditional drug self-administration procedures are also allowing investigators to determine how the presence of a social partner influences drug intake. For instance, research with prairie voles, a socially monogamous species, has shown that alcohol intake decreases in the presence of a low-consumption social partner (Anacker *et al*, 2011). Our laboratory recently developed custom-built, operant conditioning chambers that permit two rats to intravenously self-administer drugs simultaneously in the same chamber. We reported that the acquisition of cocaine self-administration is facilitated in the presence of a partner that is also self-administering cocaine (Smith *et al*, 2014) and the maintenance of cocaine self-administration is inhibited in the presence of a partner that does not have access to cocaine (Robinson *et al*, 2016). Interestingly, under conditions in which both partners have access to cocaine, individual patterns of cocaine intake become progressively more similar over time (Lacy *et al*, 2014). These studies suggest a number of behavioral mechanisms by which social contact may influence drug use. For instance, under conditions in which substance use is a group norm, group members may model drug use and selectively reinforce the drug use of others through social approval/

acceptance. In contrast, under conditions in which abstinence is a norm, drug use may be selectively punished through social rejection, and group members may model and differentially reinforce abstinence-related behaviors (see review by Strickland and Smith, 2014 for further examples and discussion).

The development of these animal models will significantly advance our understanding of the neurobiological mechanisms mediating the effects of social contact on substance use. Similar to the reinforcing effects of drugs, the reinforcing effects of social contact are dependent on dopamine transmission within the nucleus accumbens (Manduca *et al*, 2016), suggesting that this site may be a neuroanatomical locus in which information about social contact and drugs converge to mutually influence one another's rewarding effects. Consistent with this hypothesis, microinjection of the endogenous neuropeptide oxytocin into the nucleus accumbens increases social contact and affiliation (Yu *et al*, 2016), and reduces drug self-administration and other measures of drug-seeking behavior (Baracz *et al*, 2016).

The discovery that information about drugs and the social environment converge on a common neurobiological locus furthers our understanding of preclinical, human laboratory, and epidemiological research showing that social contact can modify the reinforcing effects of drugs. This knowledge may also explain the past failure of preclinical studies (which artificially constrain the social environment) to consistently predict clinical trial outcomes (which generally do not control the social environment). By incorporating relevant features of social contact into our preclinical models, we should be able to better identify which interventions will successfully translate into clinical practice.

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Impact on Cortical Function of Cocaine Abuse Co-Occurring with HIV

According to the USA Center for Disease Control (<http://www.cdc.gov/>) over 36 million humans are currently living with HIV infection, with 44 000 new infections diagnosed annually in

the USA, often reflecting risky sexual behavior. Substance use disorders (SUD) negatively influence every stage of the HIV/AIDS crisis, and SUD are a major obstacle in combating this global pandemic. Other than marijuana, cocaine is the most frequently abused illicit drug in HIV adults (eg, Martin *et al.*, 2016). Cocaine use is associated with increased likelihood of engaging in risky sex, accelerated disease progression, and non-adherence to antiretroviral treatment. An emerging explanation for this association relates to impulsive decision-making. While both cocaine-abusing and HIV-infected individuals often score higher on cognitive impulsivity tasks, those with the comorbidity tend to show the greatest impulsivity (eg, Martin *et al.*, 2016 and references therein). Human imaging studies point to impairments in prefrontal–subcortical networks in these deficits (eg, Meade *et al.*, 2011). To capture a more mechanistic view and to help identify potential therapeutic targets, my laboratory recently set out to evaluate neuropathophysiology within the medial prefrontal cortex (mPFC) in the context of HIV/AIDS comorbidity. We focused on the principal outputs, ie, pyramidal neurons. As we recently reviewed (Wayman *et al.*, 2015), our initial studies demonstrated that acute exposure to a prominent HIV-1 neurotoxic protein, Tat, induced an enduring mPFC astrogliosis and hyper excitability of mPFC pyramidal neurons that was exacerbated by chronic cocaine exposure. These effects were mediated by over-activation of high-voltage-activated L-type calcium channels and were associated with a Tat-induced increase expression of a calcium channel pore-forming protein, Cav1.2- α 1c. To better generalize the phenomenon to the chronic nature of brain exposure to HIV-1 proteins, we subsequently evaluated mPFC pathophysiology in HIV-1 transgenic rats following cocaine self-administration. As predicted by Tat-mediated excitotoxicity, the transgenic rats exhibited enhanced mPFC Cav1.2- α 1c expression, and a pyramidal cell hyper excitability and excitotoxicity (Wesley *et al.*, 2016).

This dysregulation was exacerbated following 2 weeks of withdrawal from cocaine self-administration (Wesley *et al.*, 2016).

These electrophysiological studies provide mechanistic support for a mPFC site of convergence for HIV-1 protein-mediated neurotoxicity and cocaine-induced dysregulation at the level of calcium channels within pyramidal neuronal outputs. Evidence for the behavioral consequences of such dysregulation is emerging, eg, in mice performing five-choice serial reaction-time tasks, DREADD-mediated stimulation of mPFC pyramidal neurons suppresses impulsivity (Warthen *et al.*, 2016), and nifedipine (a brain-penetrant Cav1.2/Cav1.3 calcium channel antagonist) reduces impulsivity (Dudley *et al.*, 2013). Thus, L-type calcium channel activity of mPFC pyramidal neurons may be an important regulator of impulsivity, with both ‘too much’ and ‘too little’ being detrimental. When viewed in the context of cognitive impulsivity in the HIV/AIDS cocaine-abuse co-morbid condition, these channels may be pharmacological targets for promoting healthy decision-making, and, in so doing, reduce HIV transmission and disease progression.

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