However, a large body of data has accrued linking brain pathogens to enhanced
β-amyloid deposition (Miklossy, 2011). If an AD infection etiology is confirmed, patients could be given anti-infectives to slow or halt the diseases progression. Vaccination against AD-linked pathogens may also provide long-term protection. In any case, independent of the involvement of infection in AD etiology, the identification of an antimicrobial function for Aβ and emerging roles for innate immune pathways in β-amyloid generation seem poised to take the amyloid cascade hypothesis in new directions. Most importantly, these new findings seem likely to reveal much needed new therapeutic approaches for what has proven a highly intractable disease.

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Pramipexole in Treatment Resistant-Depression, Possible Role of Inflammatory Cytokines

Anhedonia is one of the most important predictors to developing treatment-resistant depression. The 'interest-activity' symptom dimension that includes loss of interest, diminished activity, and inability to make decisions has been shown to predict poor outcome of antidepressant treatment in large prospective clinical studies (Uher *et al*, 2012). Anhedonia symptoms can be induced experimentally in animals and humans by inflammatory cytokines, including interferon-alpha. Cytokines can affect dopamine function in the basal ganglia. Associations between altered dopamine function and impaired cortical-striatal reward circuitry are found in patients with major depression who display increased peripheral inflammatory markers and cytokines that include IL-6, TNF-alpha, and CRP (Felger and Miller, 2012). Anhedonia is not unique to depression. As a trans-diagnostic psychopathological domain that appears in various psychiatric and medical conditions, anhedonia may receive pathogenic contributions from common cellular immunity mechanisms that affect reward systems (Swardfager *et al*, 2016). SSRIs and other first-line antidepressants fail to alleviate IFN–induced anxiety and depressive symptoms. Traditional stimulants that increase dopamine release and methylphenidate that blocks its reuptake have minimal effects on fatigue and anhedonia in depressed patients with inflammation-associated medical conditions such as advanced cancer. These findings suggest potential roles for cellular inflammation in mediating the development of treatment resistance to traditional antidepressants and stimulants, specifically when fatigue and anhedonia persist. In Parkinson's disease, where depression is common and anhedonia is a prominent feature, L-Dopa and other non-receptor specific dopamine agonists display little efficacy in preventing
or treating depression. However, pramipexole, a relatively selective D3 dopamine agonist has shown to relieve depression in Parkinson's disease. Also, in chronic and severe treatment-resistant depressed patients, including bipolar disorder, pramipexole at high doses has shown promising response (Fawcett *et al*, 2016). The selective expression of D3 receptors in the mesolimbic projection areas including the nucleus accumbens makes this dopamine receptor a promising target to overcome treatment-resistant depression where anhedonia symptoms may be perpetuated by inflammatory cytokines, such as in severe medical conditions with known increased levels of inflammation. The effects of pramipexole on brain immunological mechanisms are not fully understood. However, recent data suggest potentially important roles. Pramipexole attenuates the development of experimental autoimmune encephalomyelitis in mice, an animal model for multiple sclerosis (Lieberknecht *et al*, 2016). D3 receptors can be found in CD4-positive T cells, which are involved in the modulation of peripheral immune responses and promote neuro-inflammation in a murine model of Parkinson's disease (Contreras *et al*, 2016). Future studies in treatment-resistant depression that use D3-preferring and other dopamine agonists should monitor inflammatory markers as well as specific measures of anhedonia to better understand the role of inflammation in anhedonia and treatment resistance.

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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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